FULL TITLE:

Giant Cell Arteritis: Ophthalmic Manifestations of a Systemic Disease

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ABSTRACT

Background: Giant Cell Arteritis (GCA) is a systemic granulomatous vasculitis, primarily affecting medium-large arteries. It has a predilection for the aorta and its major branches, including the carotid and vertebral arteries. Ophthalmic artery involvement frequently leads to irreversible visual loss and therefore GCA is one of the true ophthalmic emergencies. GCA, although classified as a large vessel vasculitis, is known to affect smaller-sized vessels, resulting in a multiplicity of signs in the eye, some of which are often missed.

Purpose: We set out to highlight some of the less frequently observed clinical signs, which may provide clues to clinically diagnosing GCA in patients presenting with non-classical features and inconclusive inflammatory markers.

Methods: We review the literature and describe the diverse ocular and some of the systemic findings that can be associated with GCA.

Results: Although the most common ocular manifestation of GCA is anterior ischaemic optic neuropathy, the clinical presentation of GCA can vary dramatically. In the absence of obvious ocular involvement, more subtle ophthalmic signs of anterior segment ischaemia, such as hypotony and anisocoria, may be present at the time of initial clinical examination.

Conclusion: There are no specific biomarkers for disease to date, therefore pertinent history and clinical examination can guide towards diagnosis in the acute setting. The diagnostic process is not always straightforward yet appropriate and prompt diagnosis is critical to enable timely intervention and prevent significant morbidity.

KEY WORDS:

Temporal arteritis, ocular features, systemic manifestations, vasculitis, clinical signs.

Introduction

Giant Cell Arteritis (GCA) is one of the few true ophthalmic emergencies. It is a systemic granulomatous vasculitis that primarily affects large arteries. It has a predilection for the aorta and its major branches, including the carotid and vertebral arteries [1]. It commonly involves the ophthalmic artery compromising blood supply to the eye and as such has the potential to cause irreversible visual loss.

GCA is the most common form of vasculitis affecting people over 50 years of age, with the incidence peaking between ages 70-80 years [10]. It predominantly affects populations of Northern European ancestry with the highest reported incidence rate being in Norway affecting 32.4/100,000 over the age of 50 [2]. Women are more commonly affected than men [3]. To date, the patho-aetiology of GCA remains incompletely understood but is likely that a combination of genetic and environmental risk factors are involved. Support for a predominant genetic cause arises from the variance in racial predisposition and the fact that GCA predominantly affects European-derived populations [3]. To date, the *HLA-DRB1*04* gene has been consistently implicated in GCA [4-6]. In addition a study genotyping 1,651 GCA subjects from six countries revealed that in addition to the HLA region, the *PTPN22* and *REL* loci encoding for key proteins involved in T cell and antigen presenting function were associated with an increased susceptibility to GCA [7]. There have been no robust or consistent associations identified between either environmental or infective risk factors [8, 9]. Studies have suggested a possible link between GCA and viral infections including Varicella Zoster virus, Human Herpes Virus, Cytomegalovirus and parvovirus B19, but none have conclusively demonstrated a link between the two [9-11].

In view of the potential ophthalmic complications, patients with suspected GCA are often referred to an ophthalmologist for clinical diagnosis and management. Making a clinical diagnosis in the acute setting can be challenging because there is still no quick and simple test. GCA can manifest itself in the eye in many ways. Although GCA is primarily a large vessel vasculitis, the 2012 Revised International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides concluded that GCA can affect arteries of any size [1]. This revised definition states that GCA can affect different anatomical structures within the eye, including small vessels, and thus cause a diversity of signs suggestive of disease.

To date, many of the clinical reviews on GCA concentrate on the common ophthalmic presentations, predominantly arteritic anterior ischaemic optic neuropathy, central

retinal artery occlusions and cranial nerve palsies. By reviewing the diverse range of clinical presentations of GCA and describing its multiple, often atypical, ocular manifestations, we hope to heighten clinicians' awareness of the condition. This work also illustrates some of the potential non-ocular manifestations of GCA and describes the complications associated with large vessel involvement. We discuss the initial investigations commonly used in the acute setting that may assist in clinical diagnosis. Early clinical diagnosis of CGA, followed by appropriate management can minimize vision loss.

Methods

A review of publications up to December 2015 was performed using the PubMed and ISI Web of Science databases. The search criteria included: "giant cell arteritis OR temporal arteritis OR Horton's disease" AND "Clinical Manifestations OR Ocular Manifestations". For more detailed review of specific clinical features associated with GCA, the precise terminology was entered into the search engine. Articles written in English, French or Dutch, were reviewed.

We reviewed studies and case reports stating that a diagnosis of GCA was defined as either having positive temporal artery biopsy, a clearly established clinical definition or meeting the American College of Rheumatology (ACR) classification clinical criteria *for* GCA. Articles were excluded if they did not distinguish between GCA and polymyalgia rheumatic (PMR).

We summarise the various clinical features associated with GCA; we describe the symptoms and signs of the disease as well as its ocular and systemic manifestations. The ocular signs are categorised based on the anatomical distribution affected and the systemic features by the system of the body involved.

Results: Clinical Presentation - Guiding towards GCA Diagnosis

Symptoms

As a systemic inflammatory vasculitis, GCA can produce a wide range of ischaemic symptoms including headaches, scalp tenderness, jaw claudication, diplopia and loss of vision (Table 1) [12]. Scalp tenderness, jaw or tongue claudication and neck pain are symptoms strongly suggestive of this disease. The odds of having a temporal artery biopsy (TAB)-positive result have been reported to be nine times greater when a patient

experiences jaw claudication and 3.3 times greater when they have neck pain. Jaw claudication is also found more commonly in patients with ocular involvement than those without ocular involvement and thus should raise alarm bells for ophthalmologists [13].

As part of a generalised inflammatory state, patients with GCA may experience constitutional symptoms including fatigue, general malaise, fever, anorexia, and weight loss. In the absence of ischaemic symptoms, the non-specific nature of these constitutional symptoms often causes delay in diagnosis.

Patients may also describe a past medical history or symptoms of Polymyalgia rheumatica (PMR). There is considerable clinical and some immunogenetic overlap between GCA and PMR, with co-occurrence being almost 40 times more likely than would be expected if they were truly separate syndromes [14, 15]. The precise nature of their relationship remains to be clarified and although there are distinct differences [16, 17], the presence of PMR should alert clinicians to the possibility of GCA.

Approximately one in five patients present with ocular symptoms or signs only, experiencing no constitutional symptoms, and are diagnosed with occult GCA [18]. These patients tend to be older and have lower circulating inflammatory marker values than patients with systemic symptoms [19].

The prevalence of visual manifestations amongst patients with GCA varies, but studies suggest about one in three patients with GCA will experience visual symptoms [12]. The visual obscurations resulting from GCA can be transient or permanent. Amaurosis fugax has been reported to affect between 10-30% of patients with GCA and is associated with poor visual prognosis [13, 20]. Transient visual symptoms preceding permanent visual loss has been reported to affect as many as 50-65% of patients and occurs within an average of 8.5 days [19].

In one study, almost half of patients who experienced visual complications had bilateral ocular involvement [13]. A more recent study reported 9% of patients had bilateral involvement at presentation, but then the second eye was involved in a further 9% after treatment was initiated [21]. Generally the second eye is affected within 7 days of the first eye [22]. With improvement in recognizing GCA and prompt treatment by clinicians, permanent visual loss has reduced in more recent cohorts and is said to affect ~15% of patients [12, 23].

Signs: The Ocular Manifestations

GCA is a very heterogeneous disease. Despite the frequently non-specific presentations of GCA, the eye is most consistently affected. Therefore, the ophthalmologist needs to be aware of the numerous ocular signs associated with this disease (Table 2). Here we describe the ocular manifestations reported in the literature and some of their underlying anatomical processes.

Anterior and Posterior Ischaemic Optic Neuropathy

GCA most commonly affects the eye by causing ischaemia of the optic nerve, known as ischaemic optic neuropathy (ION). ION is classified according to the anatomical site of the ischaemia within the optic nerve. Anterior ischaemic optic neuropathy (AION) occurs when the optic nerve head loses blood supply whereas posterior ischaemic optic neuropathy (PION) represents ischaemia of the optic nerve within its intraorbital, intracanalicular or intracranial tract [24]. ION is further classified by aetiology. When it is caused by arteritis, of which GCA is by far the most common, the ION is referred to as arteritic-ION. However, the most common form of ION is non-arteritic, caused by microvascular disease. In clinical practice, differentiating between non-arteritic versus arteritic ION will determine the management pathway for a patient.

Arteritic - Anterior ischaemic optic neuropathy (A-AION) is the most common ocular manifestation of GCA, affecting 80% of patients with ocular GCA [13]. A-AION is caused by ischaemia of the posterior ciliary arteries (PCAs), branches of the ophthalmic artery that supply the optic nerve head. Individuals may have between 1 and 5 PCAs though the majority have 2 PCAs [24]. The medial branch is the most important as together with its short branches, it supplies all or most of the ONH in 96% of eyes. The medial PCA appears to be more commonly involved in GCA [13]. However there is marked inter-ocular variation in the supply by the PCAs and their branches. These arteries act as end arteries without collateral supply. As such, the site of infarction along the PCA determines the distribution of ischaemia and explains the specific field loss [13].

In the acute stage of A-AION, the disc is typically described as swollen and having a chalky white pallor [13] (Figure 1). A-AION usually affects the whole disc, but in one-third of patients the anatomical site of the ischaemic lesion results in only a segment of the disc being affected. Patients commonly experience sudden visual loss and have an altitudinal visual field defect. Optic atrophy normally develops within 6 to 8 weeks, with either generalised pallor or segmental pallor of the optic disc. It is often very difficult to

distinguish it from glaucomatous cupping [13]. Optical Coherence Tomography (OCT) may be useful in differentiating GCA optic disc changes from glaucoma [25] but this is not applicable for the acute stage.

Arteritic – Posterior Ischaemic Optic Neuropathy (A-PION) is a rare presentation of GCA. Because of the site of ischaemia in PION, damage to the nerve is not fundoscopically visible and therefore is a diagnosis of exclusion. There are often few clinical signs at the time of visual loss, but patients subsequently develop optic atrophy. However other clues such as reduction in visual acuity and colour vision, abnormal pupil function tests and visual field defects may suggest in the acute stage that optic nerve damage has occurred [13, 26]. Diffusion-weighted Magnetic Resonance Imaging may be of help in the acute phase of PION when no signs are visible fundoscopically [27]. Both patients with AION and PION warrant urgent work-up to determine whether their underlying pathology is likely arteritic or non-arteritic in nature.

Choroidal Ischaemia

Choroidal ischaemia is caused by occlusive disease at the level of the PCAs and their choroidal branches. In a minority of patients, findings can be similar to chorio-retinal degeneration with pigmentary changes and small haemorrhages near the macula [28] or peripherally [13]. However, often no signs are evident until later in the disease process. Fundus Fluorescein Angiogram (FFA) and indocyanine green angiography can aid diagnosis by demonstrating choroidal filling defects in patients with choroidal non-perfusion secondary to GCA [29, 30]. Electro-diagnostic testing might help locate the site of the ischaemia when visual acuity does not match clinical features. This would suggest pathology at the level of the photoreceptors, retinal pigment epithelium or optic nerve. Choroidal infarction in a patient over the age of 50 years justifies baseline investigations for GCA.

Retinal Ischaemia: Central and Cilio-retinal artery occlusions and Cotton Wool Spots

Retinal arteries affected by GCA include the central or cilioretinal arteries.

The central retinal artery (CRA) is a branch of the ophthalmic artery. In a *central retinal artery occlusion (CRAO)*, fundoscopic appearance consists of a pale fundus, grossly narrowed arteries, segmentation of the blood in veins and a cherry red spot at the macula. In a prospective study CRAO occurred in 14% of patients with GCA [13]. Many of these patients also had PCA involvement. This can be explained by the fact that in

60% of people the CRA arises from the ophthalmic artery by a common trunk with one or more of the PCAs [31]. Although there is anastomosis of capillaries between the CRA and the PCA circulation, the blood flow is not sufficient to prevent blindness resulting from occlusion of either one of them [28].

Although only a quarter of the population have a cilioretinal artery [31], when present it is occluded in the majority of patients (>80%) with ophthalmic GCA [13]. *Cilioretinal artery occlusions*, even more so than CRAO, have been found to be associated with A-AION in approximately 85% of cases [13]. The reason for this is that they arise directly or indirectly from the PCA circulation [32]. Findings on examination include interpapillomacular retinal pallor with whitish edges. OCT may reveal oedema at macular level in the acute phase and FFA may confirm the diagnosis.

Whilst involvement of smaller vessels such as the retinal branch arteries is uncommon in GCA in view of the calibre of the vessels, the literature has described cases where the nasal branches of the CRA were directly affected by GCA [28]. Inflammation of the CRAs can also reduce blood flow to mimic branch retinal artery occlusion [13].

Cotton wool spots (CWS) have been observed in approximately 30% of GCA patients who suffer visual loss during the early stages of their disease (Figure 2) [13]. They may represent focal inner retinal ischaemic lesions caused by platelet microembolisation [13] or localised accumulations of axoplasmic debris within the retinal ganglion cell axons [33]. Some studies have described that the CWS pattern or distribution may help determine the underlying pathology to a certain degree [34]. For example a CWS pattern secondary to panretinal hypoperfusion from CRAO is disseminated in an irregular circle or oval at a variable distance from, and centred just temporal to the optic disc. These CWS tend to vary in morphology as compared to CWS caused by diabetic retinopathy [34, 35].

In daily clinical practice, the presence of CWS, irrespective of the distribution or mechanism of their underlying formation, CRAO and/or cilioretinal artery occlusion should alert the clinician of possible GCA diagnosis [36].

Anterior Segment Ischaemia: including Ocular Hypotony

Anterior segment ischaemia is considered rare in GCA. It can be seen as pure anterior segment ischaemia but more often in conjunction with a generalised ocular ischaemic syndrome. Anterior segment ischaemia primarily occurs when the anterior ciliary

arteries (ACA) become compromised. Approximately two thirds of the anterior segment is supplied by seven of these arteries, which travel in the recti muscles and are branches of the muscular arteries originating from the ophthalmic artery. As a result ACA ischaemia may also result in ocular motility defects as described in the section on ophthalmoplegia [37].

The other third of the blood supply to the anterior segment of the eye is supplied by the medial and lateral long branches of the PCAs [35]. Interruption of either of these long branch PCAs or ACAs can render the iris and ciliary body ischaemic. In the case of anterior segment ischaemia caused by PCAs involvement itself, before these branch into long and short PCAs, the optic nerve head and choroid may also be affected.

Isolated anterior segment ischaemia, if detected early and treated promptly, has better prognosis than posterior involvement. In the case of co-existent anterior and posterior segment ischaemia, improvement in acuity and anterior segment findings with steroid treatment suggests that anterior segment is the main contributor to the patient's visual reduction [38]. Winter et al. classified clinical signs of anterior segment ischaemia into early and late features. Corneal oedema, striate keratopathy, anterior uveitis and Keratic precipitates and conjunctival oedema are early signs (Figure 3a) [39-41]. Tonic pupils, hypotony and rubeosis iridis are late signs (Figure 3b). Unfortunately, as the early signs often do not produce visual symptoms and are non-specific clinical features, GCA is often overlooked as a diagnosis.

Low intraocular pressure (IOP), or *ocular hypotony*, is an uncommon presentation of GCA but a degree of hypotony, often unnoticed, is probably more prevalent than recognised. In 1973, Horven measured the IOP of 22 patients with GCA and found statistically significant reduction in IOP in eyes affected by GCA compared to unaffected eyes. In his study, 22% of eyes affected by GCA had an IOP of <10mmHg. [42]. In a study looking at 16 patients with GCA, the mean IOP in the eye affected by GCA was 11.9 mm Hg, significantly lower than the 15.1 mm Hg in affected eyes of age-matched NAION patients and 15.8 mm Hg in control patients. In this study, 5 GCA patients had IOP < 10 mm Hg (mean 6.8 mm Hg) at presentation, without other signs of anterior segment ischaemia [43].

Hypotony probably results from occlusion of the long PCAs or the ACAs and subsequent reduced production of aqueous humour caused by ciliary body ischaemia. This pattern of inflammation and occlusion to the ciliary body has been described at post-mortem

[44]. Hypotony can reduce anterior chamber depth and affect corneal appearance. The wrinkling effect of Descemet's membrane causes striate keratopathy (Figure 3a). Very low IOP results in corneal oedema [45, 46]. This causes abnormal fluorescein staining of the cornea and raised pachymetry measurements can be observed. Occasionally anterior chamber inflammation is seen [38]. Corticosteroids can improve ocular hypotony [45].

In the absence of the more common posterior signs, the clinician should look out for signs of anterior segment ischaemia in a patient with suspected GCA. These may provide vital clues that posterior involvement, and hence risk of permanent visual loss, is imminent hence requiring urgent treatment.

Scleritis and Peripheral Ulcerative Keratitis

Scleritis is uncommon in GCA but cases have been described in the literature [47]. It is most commonly associated with autoimmune diseases such as rheumatoid arthritis, ANCA-vasculitis, systemic lupus erythematosus, relapsing polychondritis and sarcoidosis. It causes dull eye pain, characteristically worse at night, associated with decreased visual acuity and depending on the location of the inflammation, patients may also have a red eye. Peripheral ulcerative keratitis (PUK) is commonly associated with small vessel vasculitides such as ANCA-vasculitis. However PUK has been described in GCA in the absence of other vasculitides [48]. A description of corneal ulceration has also been reported in a fatal case of GCA [37]. As with anterior segment ischaemia, thorough examination of the sclera, episclera and cornea can avoid diagnosis being missed.

Anisocoria

Pupil abnormalities in GCA are often associated with 3rd cranial nerve palsies. However GCA-related anisocoria without motility deficits can also occur [49]. *Parasympathetic pupillary mydriasis* is generally presumed to be secondary to microvascular ischaemia of the ciliary ganglion or post-ganglionic short ciliary nerves and parasympathetic fibres of the iris sphincter [50]. Anisocoria can also result from iris ischaemia and atrophy [45]. This can present as either a mydriatic or miosed pupil.

Tonic pupils are a rare complication of GCA as the ciliary ganglion usually has an anastomotic blood supply from between one and four arteries and is based on a network of capillaries (Figure 3b) [51, 52]. Tonic pupils in GCA are characterised by

poor pupillary reactivity to light, slow and tonic constriction to a near target (disproportionately better than response to light) and accommodative paresis [53]. Diagnosis may be confirmed by topical dilute pilocarpine, which causes a hypersensitivity reaction as a result of disrupted parasympathetic innervations [53]. However, when the iris muscle itself has become ischaemic from GCA, there may be no response to 0.125% pilocarpine testing [50].

Another form of anisocoria in GCA is miosis from *Horner's syndrome* or sympathetic denervation of the dilator pupillae muscle. This is less common in GCA than a tonic pupil [22]. In GCA, Horner's syndrome is usually caused by central involvement. Pre-ganglionic infarctions are rare and post-ganglionic infarctions are very difficult to distinguish due to the likely involvement of other neighbouring structures [22]. Detecting subtle signs such as anisocoria, can not only alert the ophthalmologist to the possibility of GCA diagnosis, but it can also provide clues to the location of ischaemia.

Ophthalmoplegia

While up to 15% of patients with GCA have been reported to experience diplopia [54], the bulk of the literature suggests that 6% of GCA patients experience diplopia and for most it is transient symptom [13, 55]. There are numerous causes for diplopia in GCA, with cranial nerve palsy the most common, but direct extraocular muscle ischaemia and orbital pseudotumour have been reported.

Ophthalmoplegia in GCA is most commonly attributed to palsies of the 3rd, 4th and 6th cranial nerves. In GCA, *cranial nerve palsies* are often incomplete and temporary [55]. In the event of a 3rd cranial nerve palsy, patients may also exhibit ptosis. Transient diplopia is a poor prognostic feature; patients with ischaemic complications more frequently experience transient diplopia compared to those who did not suffer irreversible ischaemic complications (15.6% versus 3.6%) [56]. Within the orbit, active arteritis of the small arteries supplying the individual ocular motor nerves likely explains the underlying transient ocular paralysis [28] rather than minute discrete brain stem ischaemic events in the absence of long tract signs or disconjugate eye movements [57]. However, internuclear ophthalmoplegia has been described, suggesting the possibility of brainstem involvement albeit rare [58].

An alternative explanation for ophthalmoplegia in GCA is that vascular lesions directly affect the muscles, and hence cause *extraocular muscle ischaemia* (Figure 4). GCA has been described to cause ischaemic necrosis of the extraocular muscles [59] and

ophthalmoplegia resulting from direct muscle involvement [60]. In these cases, it is not uncommon for diplopia to be transient. This has been attributed to the temporary reduction of blood supply to the muscles and is analogous to intermittent claudication of the jaw muscles [61]. The infrequent nature of extraocular muscle ischaemia in GCA is largely accounted for by the rich anastomotic vasculature of the extraocular muscles. The arteries supplying the extraocular muscles are branches of the ophthalmic artery, leaving from its proximal intra-orbital course. These muscular branches anastomose with branches of the external carotid system, including the temporal and facial arteries. Because of these anastomotic links, for ischaemic changes to occur in the extraocular muscles, the arteritic process must affect both the ophthalmic artery and branches of the external carotid, which include the temporal, facial, ascending pharyngeal and middle meningeal arteries [59]. These patients commonly experience symptoms in anatomical relation to branches of the external carotid artery such as jaw and tongue claudication and scalp necrosis. However, should a patient present with an unusual form of ophthalmoplegia that does not quite fit the pattern of a cranial nerve palsy, this ischaemic mechanism should be considered.

Orbital Pseudotumour is rare in GCA but can cause diplopia in GCA. Although more commonly described in polyarteritis nodosa and granulomatosis with polyangiitis, painful proptosis and mechanical restriction of extraocular movements has been described in GCA [62]. Perivascular oedema accompanying vasculitis leads to varying degrees of inflammation of the orbital soft tissue. When this affects extraocular muscle, orbital myositis and restrictive painful diplopia may occur. When the inflammation is more extensive it may cause proptosis and ophthalmoparesis known as orbital pseudotumour [63].

Ocular Ischaemic Syndrome: full eye involvement from GCA

The definition of ocular ischaemic syndrome (OIS) remains contentious. It implies general ischaemia of the eye involving both the anterior and posterior segments. Signs associated with visual loss may include hypotony, corneal oedema, iris ischaemia, pupillary abnormalities, rubeosis, uveitis, CWS, retinal haemorrhages and optic nerve head ischaemia [64-68]. Further proposed criteria include pupillary abnormality and rubeosis. OIS secondary to GCA is rare with only a few cases described [13] [68], and points towards a malignant course of GCA as it usually indicates multiple vessel involvement [66]. Early recognition and prompt treatment is essential.

Other Organ Involvement

The Central Nervous System

Headache occurs in 76% of patients and is the first symptom in 40% of GCA cases [69, 70]. Although it is a common symptom and often the reason for investigation, it is usually caused by inflammation of the extra-cranial arteries and their branches. The central nervous system (CNS) itself is not commonly involved in GCA. However, when it is, it forms part of the spectrum of “cranial GCA”.

GCA can affect different areas of the cerebral circulation. Usually when the CNS is affected it is as a result of thrombosis of the carotid or vertebral arteries rather than primary intracranial arteritis [71]. This is most likely because both contain an internal elastic lamina from the aortic arc to their point of entry into the dura mater [72]. However, intracranial involvement of the basilar arteries, the posterior cerebral arteries, the anterior inferior cerebellar arteries, the circle of Willis, and the intracranial segments of the carotid and vertebral arteries have been described [72]. Direct extension of thrombus from the site of arteritis, or embolization from arteritic-thrombosed vessels may also account for cerebrovascular ischemic events [73, 74].

Inflammatory involvement of the carotid, vertebral arteries and or their branches causes transient ischaemic attack (TIA), ischaemic stroke causing potential unilateral weakness, and multi-infarct dementia in 3-6% of GCA patients [75-77]. Arteritis of the vertebrobasilar system on the other hand may cause ischaemia of the cerebellum, occipital lobe, and brainstem. This leads to dysphagia, ataxia, unsteady gait, vertigo, confusion and compromise of vital functions possibly in the absence of the classical GCA symptoms [73, 74, 77, 78]. Small infarcts of the vertebrobasilar arteries may also result in higher cortical dysfunction [77]. These arteries have a narrower caliber and hence a greater vulnerability to high-grade stenosis and occlusion from GCA [79].

Although a patient may have no direct ocular damage, CNS involvement may cause visual complaints. GCA related infarcts in the pons, cerebellum and occipital lobes, can result in visual symptoms, including double vision, visual fields defects or even cortical blindness [28]. Chiasmal vessels can be affected and lead to either monocular visual loss or bilateral visual field defects. Ischaemic changes in the lateral geniculate nucleus are extremely rare probably because of its dual blood supply [28]. The occipital cortex is also thought to be protected by its dual circulation of internal carotid and vertebral arteries [28] and as such cortical blindness is rare.

The reason why some patients with GCA develop cerebrovascular attacks (CVAs) whilst others do not is not understood [77]. CVAs have been described as being more common in patients who present with visual loss and jaw claudication [69]. One study found a significant association between transient visual loss and CVA development [77]. Although CNS events do occur as a result of GCA, these remain rare. A recent study showed that cerebrovascular diseases including TIAs, ischaemic strokes, subarachnoid haemorrhages and intracerebral haemorrhages were no more common in GCA compared to age-matched controls [80].

The Cardiovascular System

The cardiovascular system can be affected by GCA at many different levels. Involvement of the aorta and/or its major branches is often referred to as large vessel (LV) involvement GCA, or LV-GCA. Anatomy damaged by GCA may include the ascending aorta and its main tributaries (brachiocephalic, left common carotid, and left proximal subclavian arteries) as well as the descending aorta. Involvement of the aorta may be in the form of aortitis, aortic aneurysm, aortic dissection, aortic stenosis. Occasionally, GCA may involve more distal vessels and cause inflammation of the major upper and lower limb arteries, such as the subclavian, brachial, axillary, iliac or femoral arteries. GCA can also affect coronary vessels. The anatomy and the pathological process involved at its site will determine the symptoms experienced by the patient.

LV-GCA has been defined as large-artery stenosis or aortic aneurysm/dissection that develops in the one year leading up to GCA diagnosis or at any time thereafter [81]. LV-GCA has serious complications. In a long-term follow up study (median 7.6 years), 27% patients with GCA experienced large-artery complications from GCA [82, 83]. Some patients had more than one complication: 18% had thoracic or abdominal aortic aneurysm or dissection, 13% large-artery stenosis including cervical, subclavian, axillary, brachial, Lower-extremity artery stenosis [82, 83]. These numbers are very similar to a more recent study in which the cumulative incidence of any LV manifestation at 10 years was close to 25% [81].

There is a definite increased mortality risk if a patient has LV involvement in the form of aortic dissection [82]. Although there is no increased mortality risk in patients with aortic aneurysms or artery stenosis compared to patients without LV involvement, there is a significant increased morbidity risk; 61.9% of patients with large-artery stenosis experience a stroke, compared to 19% of patients who don't have LV involvement [82].

Interestingly, in regards to predicting risk of LV involvement at the time of presentation, patients with headache, scalp tenderness, abnormal temporal arteries and high ESR are less likely to have LV involvement [83]. Indeed only about 40% of patients with LV involvement will have cranial symptoms. So although GCA patients with LV involvement may have visual symptoms, vision loss is less common than in patients without LV involvement [84]. On average, patients with LV involvement also tend to be about 6 years younger [84, 85].

Presentations of aortitis specifically may include inflammatory dorsal and lower back pain, signs of vascular disease of the upper limbs, and higher level of acute phase reactants [85]. As aortitis is associated to arteritis of the supra-aortic vessels, the clinical picture in these patients is commonly that of aortic arch syndrome; claudication of the arms and absence or asymmetry of upper extremity pulses [86, 87]. Factors predictive of large-artery stenosis on the other hand are said to include diminished pulse or blood pressure and/or claudication of an arm, TIA or stroke, and diplopia. An aortic insufficiency murmur has been found to be predictive of aortic aneurysm and/or aortic dissection [83]. Although these symptoms and signs can help risk stratify patients, there are no consistent clinical predictors across studies that allow clinicians to identify the patients at risk of aortic dilation and aneurysm formation [84]. As such, the BSR guidelines suggest that large-vessel GCA should be suspected in patients with prominent systemic symptoms, limb claudication or persistently high-inflammatory markers despite adequate glucocorticosteroid therapy [88].

Today, it is not fully understood as to why some patients develop aortic involvement whilst others do not. Interestingly in a recent study looking at predictors of dissection in aortic aneurysms attributed to GCA, older age and later calendar year at time of diagnosis of aortic aneurysm have been associated with decreased risk of dissection and rupture [89]. No association between size of aneurysm and risk of dissection/rupture was identified. Active aortitis was noted in some patients with aortic dissection and aneurysm but not in subjects with aneurysms alone, suggesting that active inflammation may cause dissection and rupture risk in some patients with GCA [89].

Limb Restricted (LR)-GCA has also been described in the literature in a recent case series of 79 patients [90]. The median age was 66. Limb claudication was reported in 87% of these patients, and cranial symptoms and polymyalgia rheumatica in 20%. Interestingly, constitutional symptoms were not reported. Upper and lower limb arteries were involved in 86% and 9% of the patients respectively, and the remaining

5% had simultaneous upper and lower limb vessel involvement. The results of this paper suggested that in the event of a patient older than 50 years of age presenting with bilateral limb claudication, elevated ESR, and suggestive vascular radiological findings despite a negative temporal artery biopsy and non-suggestive aortic imaging, LR-GCA should be suspected. However since constitutional symptoms are typically absent in LR-GCA, differential diagnosis on imaging with atherosclerosis may be challenging [90].

GCA can involve the coronary arteries through granulomatous inflammation and as such has been associated with increased cardiac risk [91]. A literature review described 31 cases of myocardial infarction with confirmed coronary involvement of GCA [92, 93]. Pericarditis has also been reported [94]. However a recent large population-based cohort study in the UK analysing data on patients with GCA and/or PMR, showed that they were not at an increased risk of coronary diseases (stable angina, unstable angina, myocardial infarction, unheralded coronary death) and cardiac diseases, (heart failure and cardiac arrest) in comparison to age matched controls, regardless of PMR/GCA duration [80].

The Respiratory System

Lung involvement in GCA is less common than in other vasculitides although granulomatous vasculitis of pulmonary arterioles and reticulonodular pulmonary infiltrates may occur [95]. Respiratory and ear-nose-throat signs and symptoms such as tongue infarction, trismus, hearing loss and facial swelling are rare presentations of GCA [96]. Cough is commonly reported by 10% of patients with GCA, possibly owing to ischaemia of the cough receptors [97].

The Gastrointestinal & Renal systems

Hepatic dysfunction with deranged liver enzymes has been reported in GCA as a result of non-specific hepatitis [60]. Elevated serum alkaline phosphatase and transaminases, suggesting liver involvement in GCA have been reported. These normalised with corticosteroid treatment suggesting inflammatory involvement [98, 99]. Gallbladder involvement has also been documented [100]. The gastrointestinal tract can also be affected; reports of GCA causing small bowel infarction have been reported [101, 102]. In addition mesenteric ischaemia, potentially resulting in bowel ischaemia, has been described in the literature causing symptoms such as chronic postprandial symptoms and acute abdominal pain [103].

Renal involvement in GCA is rare though cases of GCA causing small vessel vasculitis and necrotising glomerulonephritis with resulting renal failure have been described [104]. Bladder involvement is also exceedingly rare. However cases such as bladder neuropathies as a result of GCA vasculitis have been reported [105].

The Reproductive System

Both breast and female genital tract (FGT) involvement in GCA have been reported in the literature. Twenty cases of classic GCA involving medium to small-sized arteries of the breast have been described with bilateral mammary involvement in 50% of the cases and constitutional symptoms in 65% [106]. It is felt that GCA of the breast should be considered as a potential diagnosis in the case of elderly women presenting with PMR-like symptoms and tenderness, lumps, or pain in the breast. GCA of the breast occasionally mimics carcinoma, and its initial manifestations may be similar to those of other forms of vasculitis involving the breast. As such biopsy is crucial for establishing a definitive diagnosis [106].

A recent article reviewed 32 case reports of patients with female genital tract (FGT) GCA [107]. Most the patients were symptomatic and had constitutional symptoms suggestive of GCA. Eleven patients (34.4%) were asymptomatic at presentation and were diagnosed with GCA of the FGT incidentally when the genital organs were dissected out for unrelated gynaecologic conditions. ESR was elevated in 69% cases and was mostly associated with generalized constitutional symptoms. TAB was performed in 50% of reported patients of which 75% had histologically confirmed temporal arteritis. [107]. Histological examination of the FGT specimens revealed that medium and small-sized arteries of the myometrium, the most commonly involved site among the genital organs, were involved in 72% cases. This was followed by the ovaries and fallopian tube (each 47%), cervix (37.5%), and parametrium and vaginal cuff (each 3%) [107]. GCA of the FGT was associated with malignancy in 18.8% of cases [107].

Reported cases of male genital involvement are far less common. There are however cases of scrotum, testicular as well as prostate involvement resulting from GCA [108-110].

The Orofacial Region

The orofacial region is commonly involved in GCA. In addition to jaw claudication, considered a pathopneumonic sign of GCA [70], and pain of the masticatory muscles on

chewing (occurring in approximately 40% of patients with GCA), other symptoms described include trismus (a reduction in the ability to open the mouth occurring in close to 7% of patients) [111]. Additional features include facial swelling, odontogenic pain dysphagia, dysarthria, submandibular mass, chin numbness, glossitis, and lip or tongue necrosis [23].

The Skin and Peripheral Nervous System

Cutaneous manifestations of GCA are rare, comprising <1% of cutaneous vasculitis [112]. Findings include scalp necrosis and ulceration that can mimic shingles [113, 114], oedema, erythema, hyperpigmentation, pallor and alopecia [115].

Single or multiple peripheral neuropathies have been described in 5-14% of patients with GCA, including facial nerve palsy, cervical radiculopathies and sciatic neuropathy [71, 116]. This could be attributed to vasculitis of a nutrient artery but smaller vessel ischaemia could also be responsible.

Classifying GCA: are there different types?

The 1990 American College of Rheumatology (ACR) criteria, although merely implemented for the classification of GCA, are still broadly used today to guide clinicians towards diagnosis: 1. Age > 50 years, 2. New onset headache, 3. Abnormal temporal artery examination, 4. Elevated ESR, 5. Positive temporal artery biopsy (TAB). The presence of three or more of these five criteria was found to be strongly associated to GCA with a sensitivity of 93.5% and a specificity of 91.2% [117]. Although these ACR criteria may guide towards a clinical diagnosis of GCA, they do not necessarily predict the course, the extent of organ involvement, the severity or the duration of the disease. Recognition of involvement of vessels beyond the cranial arteries has created challenges in the disease classification of GCA [118].

As described in this review, there is large variety of manifestations associated with GCA and the potential anatomy affected by this disease is extensive. GCA predominantly targets the head and neck arteries. However by definition being a systemic vasculitis, this disease is able to affect any artery in the body [1]. However to date, there is no real defined “sub-classification” system to describe the level of vasculature damaged by GCA; i.e. whether a patient has ocular versus non-ocular disease, occult versus constitutional GCA, cranial versus extra-cranial disease, systemic inflammatory syndrome versus focal or localised ischaemic disease, relapsing versus remitting disease, masked or silent GCA

etc. Even though such sub-classification does not formally exist, these terms have all been employed in published literature. Some terminology has become quite murky; the use of extra-cranial and large vessel GCA seem to have been used interchangeably yet depending on the context they do not necessarily have the same meaning. Extra-cranial involvement by definition includes peripheral neuropathies and skin lesions which may be secondary to smaller calibre vessel disease.

Recently, guidelines have placed importance at determining and describing whether a patient has GCA with or without large vessel (LV) involvement GCA, or LV-GCA. As highlighted in the cardiovascular section, LV involvement has serious implications. Overall, patients with GCA and aortic manifestations have a greater morbidity and also have higher than expected number of deaths from cardiovascular and pulmonary causes than the general population [81].

The observed increase in LV involvement occurring in GCA cases over the last 20-30 years is unlikely caused by a true increase in the LV incidence or change in disease expression, but rather due to greater physician awareness of the extra-cranial manifestations of GCA as well as improvement in imaging technologies which have led to increased utilization of imaging studies to evaluate for LV disease [81]. Recent imaging studies suggest that prevalence of aortitis in GCA was historically underestimated; infra-clinical aortitis is present in 20 to 65% of cases at diagnosis. [86].

A delay in diagnosis can perpetuate the risk of LV involvement. In a study by Kermani et al, the rate of occurrence of any LV disease was high within the first year of GCA diagnosis (5 events per 100 person-years), suggesting that disease may be present well before clinical detection [81]. This is in keeping with previous imaging studies detecting a significant proportion of patients with newly diagnosed GCA to have involvement of the aorta (45 to 65%) and its branches (29% to 74%) [119-122]. While the rate of large-artery stenosis does not significantly increase after five years, the rate of aortic aneurysms/dissections increases even beyond five years after diagnosis of GCA [81].

Considering the complications associated with LV involvement, the increased mortality risk associated with aortic dissection, and the fact that patients with LV-GCA exhibit a more chronic or relapsing disease course [123], it has been suggested that screening for aortic aneurysms should be considered in all patients with GCA 5 years after incidence [89]. Although these are merely suggestions, the British Society of Rheumatology (BSR) guidelines recommend a baseline chest radiograph and a subsequent X-ray every 2

years to monitor for aortic aneurysm [88]. The validity of X-ray in detecting aortic involvement has been debated. The BSR guidelines add that imaging through positron emission tomography (PET) and magnetic resonance imaging (MRI) scanning can assist in the assessment of suspected LV involvement [88]. 18 fluorodeoxyglucose (18F-FDG)-PET scanning has shown qualitative ability at confirming or excluding presence of GCA related vascular inflammation [124].

As highlighted, the spread of manifestations and anatomical distribution affected by GCA is extensive. It's a clinically heterogenous disease and although it has no formal sub-classification, it's important for the clinician to determine the extent of disease involvement as this has implications for management and prognosis.

Investigations: Assisting in GCA Diagnosis

Together with a patient's first presentation, the initial baseline investigations can help assist in making a diagnosis in the acute setting. A patient is classified as having GCA if three or more of the five ACR criteria are met. Nevertheless there are flaws to the ACR criteria. In a 2012 retrospective cases series, Murchison et al found that close to 26% of their TAB positive cases would not have been diagnoses with GCA by using the ACR criteria alone [125]. There was significant disagreement between the ACR criteria and biopsy results. As such today, the gold standard for diagnosis remains a positive TAB. It is useful in confirming the diagnosis but does not exclude it if negative as histological specimens may have skip lesions.

In the acute stage, treatment with high dose corticosteroids should be started empirically when the symptoms and/or inflammatory markers suggest a diagnosis of GCA is likely, and should not depend on TAB results becoming available [88] [126]. The BSR guidelines recommend a TAB being performed within a week of steroid initiation however histology can be positive up to 6 weeks after [88]. A TAB is a relatively safe and simple operation, nevertheless it remains an invasive surgical procedure and complications have been reported. Up to 16% of patients undergoing a TAB suffer facial nerve damage, with over half fully recovering [127].

There are currently no specific biochemical markers to identify GCA. Commonly performed blood tests to identify this inflammatory state include erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Although recent studies supports that CRP might be slightly more sensitive in predicting GCA compared to ESR [128], neither are specific inflammatory makers and may be elevated in other

inflammatory or infective diagnoses. In an observational GCA study of 764 patients, 13.6% of patients had a normal CRP. Elevated CRP and elevated ESR provided a sensitivity of 86.9% and 84.1% respectively, for a positive TAB; specificity of both was as low as 30% [128]. Misleadingly, ESR and CRP values can be normal in patients with GCA [129, 130]. In this large observational study ESR and CRP were normal in 10.2% at time of diagnosis [128]. In another study, 21% of patients with GCA had a normal ESR and CRP at time of relapse whilst on corticosteroids [131]. Hence both markers need to be interpreted within clinical context.

To decide whether a patient's ESR is raised, many clinicians use the empiric formula created by Miller et al. in 1983. Miller's formula states that a normal ESR value is age in years divided by 2 for men and age in years + 10 divided by 2 for women [132]. An alternative formula suggested by Hayreh states that the top normal ESR is $17.3 + (0.18 \times \text{age})$ mm/hour for men, and $22.1 + (0.18 \times \text{age})$ mm/hour for women [133]. In a retrospective study comparing both formulae, Hayreh's formula had greater sensitivity (85.5% vs 76.5%) at predicting GCA TAB-positive patients [133].

In addition to a raised ESR and a CRP > 2.45 mg/dL, an elevated platelet count >400,000/ μ L has shown to be beneficial at predicting a positive biopsy result [134]. Hence, the combination of ESR, CRP, and platelet count, is likely to provide most useful biochemical information to predict GCA probability [135]. Full blood count in patients with GCA may also show normochromic normocytic anaemia and lymphocytosis [117].

The role of imaging techniques to diagnose GCA have been studied with the aim of mitigating the need to perform an invasive TAB procedure as well as delineating both the extent of cranial and extracranial involvement [136]. Although imaging may play a role in follow-up, particularly in distinguishing those with and without LV involvement, and in relapsing and non-responding patients, each of the imaging modalities has its limitations and has not replaced the need for a TAB nor has a substantial role yet in the acute setting. The Temporal Artery Biopsy –v Ultrasound in diagnosis of GCA (TABUL) study is currently being performed in the UK to test diagnostic accuracy (sensitivity and specificity) of ultrasound as an alternative to TAB [137].

In practice, in the emergency or out-of-hours setting, clinicians use inflammatory marker values in the presence of symptoms and signs to predict clinical risk and decide whether immediate high-dose glucocorticosteroids is necessary [88]. The chance of visual improvement is greater with early diagnosis and immediate steroid therapy. In

the unfortunate event of already established monocular vision loss, the main goal of high-dose glucocorticosteroids is the preservation of vision in the fellow eye [138]. Treatment with high dose glucocorticosteroids is effective but can be associated with serious adverse events [139]. Side effects are almost universal, affecting up to 90% of those with GCA [140]. As such deciding which patient likely has GCA based on symptoms, signs and biochemical results is critical in order to mitigate steroid treatment to those that do not need it.

Conclusion

GCA is a complex disease, which causes significant morbidity and mortality. It has serious complications including blindness, stroke and aortic dissection. With an ageing worldwide population, the incidence rates of GCA are rising and hence visual loss and burden attributed to this disease is set to increase [3]. The spectrum of ophthalmic presentations for GCA is diverse. This work reviews the numerous ophthalmic signs with which GCA can present, many of which are atypical and as such easily and often missed. We highlight that GCA is truly a systemic disease, potentially involving many organ systems. Although it is a vasculitis which predominantly affects medium and large vessels, smaller calibre vessels can be affected.

There is no formal classification system to further sub-categorise a patient's GCA status. However as described, it is important for clinicians to determine the likely anatomy affected by GCA. Information about prognosis and extent of disease involvement may be gained from a patient's initial signs, symptoms and acute inflammatory markers. As such this initial clinical assessment is crucial. Determining whether a patient will likely develop ocular or LV involvement has significant implications on their management.

Despite advancements in diagnostic tools and medical technology, signs and symptoms remain key to making the diagnosis of a clinical condition where no single test is 100% sensitive not specific. Given that ophthalmologists are often the front-line diagnosticians of GCA and that laboratory tests have their limitations, timely recognition of its clinical features is essential in making a prompt diagnosis, avoiding delay in prompt corticosteroid treatment and therefore preventing morbidity associated with this disease.

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No author has any competing interests related to this research. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

INFORMATION ABOUT PARTICIPANTS:

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article (figures).

Table 1. Rates of reported symptoms amongst GCA patients

Symptoms	Rates amongst GCA patients (%)	Reference
Jaw claudication	34 - 50	[20, 23]
Headache	67 - 75	[12, 20]
Scalp tenderness	31 - 50	[12, 20]
Constitutional symptoms: Fever, fatigue, weight loss, anorexia	35 - 50	[12, 141]
PMR	34 - 50	[12, 142]
Visual symptoms	20 - 50	[13, 141]
Transient	10 - 30	[12, 141]
Permanent	5 - 19	[143, 144]
Diplopia	5 - 15	[54, 145]

Box 1. Ocular Manifestations from GCA, their potential associated signs and the rate at which they are seen in GCA patients with ocular involvement.

Ocular Manifestations	Signs on examination	Reported Rates %	(Ref)
Optic Nerve Ischaemia			
Anterior Ischaemic Optic Neuropathy	Swollen, chalky white pale optic nerve head	88 - 92.3	[143, 146]
Posterior Ischaemic Optic Neuropathy	Often no signs. May have RAPD	7.1	[13]
Retinal Ischaemia			
Central Retinal Artery Occlusion	Pale fundus, narrowed arteries, cherry red spot	4 - 14.1	[13, 147]
Cilio-retinal Artery Occlusion	Interpapillomacular retinal pallor with white edges	10 - 21.8	[13, 148]
Cotton wool spots	CWS - isolated or multiple	Up to 33	[13]
Choroidal Ischaemia	May show pigmentary changes in fundus & small haemorrhages	rare	[30]
Anterior Segment Ischaemia	Hypotony, corneal oedema, striate keratopathy, uveitis, rubeosis iridis, pupil abnormality	Rare (likely under-reported): Degree of Hypotony in all GCA affected eyes; 31% < 10mmHg	[43]
Pupil involvement	Anisocoria: Tonic pupils, ischaemic mydriasis, Horner's syndrome	rare	[22]
Ophthalmoplegia		5.9 - 15	[13, 54]
Cranial Nerve palsy	Features of 3 rd , 4 th & 6 th CN palsies	-	-
Extra-ocular muscle ischaemia	Isolated rectus or oblique muscle palsy	-	-
Orbital Pseudotumour	Restrictive painful diplopia and proptosis	Very rare	[62]
Scleritis	Tender globe, scleral injection or discolouration	Very rare	[47]
Peripheral Ulcerative Keratitis	Ulceration or thinning of cornea & injection	Very rare	[48]
Ocular ischaemic syndrome	Signs of Anterior Segment Ischaemia + Posterior Segment Ischaemia (including optic nerve, retinal or choroidal ischaemia)	rare	[149]

Figure Legends:

Figure 1. *Arteritic Anterior Ischaemic Optic Neuropathy secondary to GCA.* A chalky white disc on fundus examination of the right eye of a patient presenting with sudden visual loss, jaw claudication, headache and scalp tenderness.

Figure 2. *Retinal ischaemia secondary to GCA.* Cotton wool spots on fundus examination of the right eye of a patient presenting with visual loss, jaw claudication and headache.

Figure 3. Anterior Segment Ischaemia secondary to GCA. Patient presenting with bilateral visual loss, fever, general malaise, weight loss, anorexia and bilateral reduction in vision. Examination revealed bilateral anterior segment ischaemia. **3a.** Corneal photographs (slit and co-axial views) of the left eye demonstrating corneal oedema and Descemet' folds secondary to ocular hypotony (IOPs 4mmHg and 2mmHg in the right and left eye respectively). **3b.** Anisocoria secondary to bilateral tonic pupils and iris ischaemia.

Figure 4. Ophthalmoplegia secondary to GCA. Patient presenting with classical symptoms of GCA and diplopia from isolated right medial rectus palsy in the absence of other features suggestive of 3rd cranial nerve palsy.

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