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ABOUT THE AUTHOR

Laura Donaldson, MD, PhD

Dr. Donaldson is a graduate of the MD/PhD program at the University of Toronto. She completed ophthalmology residency at McMaster University and neuro-ophthalmology fellowship at the University of Toronto. She is currently practicing neuro-ophthalmology and general ophthalmology in Niagara Falls and Hamilton and maintains interests in teaching and research.

Author Affiliations: Department of Surgery, Division of Ophthalmology, McMaster University, Hamilton, Ontario

Update on Giant Cell Arteritis: Essential Information for Ophthalmologists

Laura Donaldson, MD, PhD

Introduction

Giant cell arteritis (GCA) is an important cause of irreversible vision loss in the elderly population. For any physician, making this diagnosis can be difficult due to the highly variable clinical presentation of this large-vessel vasculitis. The 1990 American College of Rheumatology (ACR) classification criteria for GCA[1] are frequently used, however, they were developed to classify GCA patients vs those with other forms of vasculitis and are not true diagnostic criteria. Despite the high predilection of GCA for ocular circulations, the original 1990 criteria did not include any signs or symptoms related to vision. The classification criteria were updated by the ACR and European Alliance of Associations for Rheumatology (EULAR) in 2022[2] with the significant inclusion of "Sudden vision loss" (**Table 1**).

The Importance of the Ophthalmologist in Diagnosis and Management of Giant Cell Arteritis

Sudden vision loss has a broad differential and as ophthalmologists, we provide the expertise to assess these patients and determine whether vision changes are related to vasculitis. Patients with a suspected or known diagnosis of GCA are often referred for evaluation of undifferentiated vision changes. Ocular findings can confirm a diagnosis or recurrence and guide therapy including corticosteroid dose and duration. This review will focus primarily on the scenario where the ophthalmologist makes the initial diagnosis of GCA. Approximately 20% of GCA cases with ocular involvement are classified as occult,[3,4] where patients do not present with any systemic symptoms but still have elevated erythrocyte sedimentation rate (ESR) and C-reactive protein

ACR 1990	ACR/EULAR 2022	
Presence of 3 criteria classifies as GCA	Score ≥ 6 classifies as GCA Age ≥ 50 not a criterion but an absolute requirement for classification	
Clinical Criteria		
• Age at onset ≥ 50 • New headache • Abnormal temporal artery	• Morning stiffness in shoulders/neck • Sudden vision loss • Jaw or tongue claudication • New temporal headache • Scalp tenderness • Abnormal temporal artery	**+2** **+3** **+2** **+2** **+2** **+2**
Laboratory, Imaging, and Biopsy Criteria		
• ESR ≥ 50 mm/hr • Positive TAB	• Max ESR ≥50 mm/hr or CRP ≥10 mg/L • Positive TAB or TAUS • Bilateral axillary artery involvement • FDG-PET activity throughout aorta	**+3** **+5** **+2** **+2**

Table 1. Classification criteria for giant cell arteritis; *courtesy of Laura Donaldson, MD, PhD.*

Abbreviations: ACR: American College of Rheumatology, **CRP:** C-reactive protein, **ESR:** Erythrocyte sedimentation rate, **EULAR:** European Alliance of Associations for Rheumatology, **FDG-PET:** fluorodeoxyglucose positron emission tomography, **GCA:** giant cell arteritis, **TAB:** temporal artery biopsy, **TAUS:** temporal artery ultrasound

(CRP). In these cases, the ophthalmologist is likely the first or only provider seen and has the responsibility to recognize GCA and prevent further permanent vision loss and other serious sequelae of this disease.

Diagnostic key: Involvement of multiple circulations should immediately cause concern for giant cell arteritis.

- Bilateral, simultaneous, or immediately sequential anterior ischemic optic neuropathy
- Anterior ischemic optic neuropathy in combination with CRAO, cilioretinal artery occlusion, or cotton wool spots outside of the peripapillary region
- Ischemic vision loss in combination with cranial nerve palsy

Ocular Manifestations of Giant Cell Arteritis

Permanent ischemic vision loss occurs most commonly through one of three mechanisms.[3,5-9]

1. Anterior ischemic optic neuropathy (70–90%)
2. Central retinal artery or cilioretinal artery occlusion (~15%)
3. Posterior ischemic optic neuropathy (~5%)

1. Anterior ischemic optic neuropathy

Anterior ischemic optic neuropathy (AION) results from non-perfusion of the short posterior ciliary arteries supplying the optic nerve head. Approximately 90% of cases of AION neuropathy are non-arteritic (NAION), with the arteritic form (AAION) comprising the minority of cases. Ophthalmologists assessing a patient with AION

cannot consider a negative inquiry for GCA symptoms and the presence of vascular risk factors including diabetes and hypertension to be sufficient to rule out GCA. All cases of AION in a patient over age 50 must have urgent ESR and CRP measured, regardless of whether or not any GCA symptoms are reported. Other clinical features affect the pre-test probability for AAION versus NAION, however, they do not negate the need for this testing.

1. Features Supporting a Diagnosis of AAION:

a) Preceding transient monocular vision loss

Transient monocular vision loss (TMVL) is often a precursor to AAION. One case series reported 32% of patients with AAION had a preceding history of TMVL, vs 2.5% of NAION patients.[10] Partial occlusion of posterior ciliary arteries by inflammatory infiltrates decreases optic nerve head perfusion and can result in TMVL with minor increases in intraocular pressure.

b) Bilateral simultaneous or closely sequential AION

Bilateral simultaneous NAION is rare, and usually occurs in the setting of severe arterial hypotension such as in shock or during hemodialysis.[11] In AAION, bilateral involvement is common[12] and the risk of closely sequential AION increases with the interval between the time of first eye involvement and initiation of steroid treatment.

c) Absence of a crowded "disc at risk" in the fellow, unaffected eye.

The pathophysiology of NAION is thought to involve development of a compartment syndrome at the optic nerve head, where ganglion cell axons travel through small fenestrations in the rigid lamina cribrosa. Eyes that develop NAION almost always have minimal or no cupping of the optic nerve producing significant crowding of axons.[13,14] Absence of this feature should strongly raise suspicion for AAION.

d) Pallid optic disc edema

Waxy pallor of the optic disc in the acute phase is seen in approximately half to two-thirds of AAION.[12,15] In NAION, typically there is diffuse or segmental disc hyperemia evolving to pallor over weeks with resolution of disc swelling.

e) Severe central vision loss

Central visual acuity at presentation is usually worse in AAION than in NAION, with a higher proportion of arteritic cases presenting with vision of hand motions or worse. This cannot be used as a reliable predictor of AAION, however, as a minority of cases are consistently reported with vision 20/50 or better in affected eyes.[5,15]

2. Central Retinal or Cilioretinal Artery Occlusion

Approximately 5% of central retinal artery occlusion (CRAO) is arteritic and all patients over age 50 without a visible retinal embolus require urgent measurement of ESR and CRP. Reperfusion and spontaneous vision improvement may occur in embolic CRAO but this is very rare in the arteritic form.[16]

3. Posterior Ischemic Optic Neuropathy

Posterior ischemic optic neuropathy (PION) is due to vasculitic involvement of pial vessel and ophthalmic artery branches supplying the retrobulbar optic nerve.[17] The optic nerve head appears normal in the acute phase. PION is rare and almost exclusively occurs in one of three scenarios: severe systemic hypotension, in the peri-operative setting (most frequently with spinal surgery) and in GCA.

Other Ocular Manifestations of Giant Cell Arteritis

Focal Retinal Ischemia

Cotton wool spots, or focal areas of inner retinal ischemia, are common in patients with ocular involvement of GCA and may be an early sign of vasculitis.[12,18] Cotton wool spots at the optic nerve head may be seen in other causes of ischemic optic neuropathy, but if seen outside of the peripapillary region they indicate involvement of the retinal circulation. Focal middle and outer retinal ischemic changes, paracentral acute middle maculopathy or acute macular neuroretinopathy are also increasingly being recognized in GCA due to widespread availability of spectral domain and swept-source optical coherence tomography (OCT).[19]

Optic Perineuritis

GCA is an important cause of optic perineuritis in older individuals. These patients often present with evidence of optic neuropathy but relatively spared central acuity, as ischemic

changes primarily affect peripheral optic nerve axons supplied by small pial branches.[20,21] The hallmark of optic perineuritis is optic nerve sheath enhancement on MRI of the orbits with contrast.

Diplopia

Diplopia in GCA is usually caused by 3rd, 4th, or 6th nerve palsies. More rarely, brainstem ischemia can affect these cranial nerve nuclei, their fascicles or other central pathways controlling vision. Approximately 6–10% of patients with ocular involvement have diplopia and older patients with ischemic vision loss and acute oculomotor nerve palsy should be presumed to have GCA until proven otherwise.[12,22,23]

Uncommon Ocular Signs of GCA

- Hemianopia secondary to posterior circulation stroke
- Horner's syndrome
- Anterior segment ischemia and ocular ischemic syndrome
- Orbital inflammatory syndrome

Work-up of GCA: To Biopsy or Not

Temporal artery biopsy (TAB) is considered the gold standard for diagnosis of GCA and is still the first choice of neuro-ophthalmologists, particularly in North America.[24] Biopsy also has the advantage of identifying other pathology that can mimic GCA,[25] including small vessel vasculitis, amyloidosis, lymphoma, and sarcoidosis.

The sensitivity of unilateral TAB is likely around 77–87%[26,27] with very high specificity. The ACR recommends TAB performed within two weeks of corticosteroid initiation and with a specimen at least 1 cm in length, with TAB preferred over temporal artery ultrasound (TAUS) and other imaging modalities.[28]

The use of imaging as an alternative to TAB for diagnosis of GCA is becoming increasingly common. Updated EULAR guidelines for imaging in GCA were published in 2023[29] and recommend consideration of TAUS, high resolution MRI, and fluorodeoxyglucose positron emission tomography (FDG-PET) as first-line options over TAB. FDG-PET has more limited availability and is used more often in suspected extracranial GCA.

TAUS, looking for a "halo sign" and temporal artery compressibility, has advantages of being non-invasive and inexpensive. The bilateral temporal arteries and axillary arteries can also be simultaneously assessed for evidence of vasculitis. TAUS sensitivity in the hands of an experienced ultrasonographer is likely similar to TAB, but with lower specificity.[30,31] A major limitation is that false negatives occur quickly after steroid initiation, in as little as 2 days.[32]

MRI angiography also has the advantage of being less invasive, and allows for simultaneous assessment of all major cranial vessels. Alternate pathology including stroke, sinusitis and TMJ disease can also be identified.[33] Standardized imaging protocols on high resolution (at least 3T) machines read by radiologists experienced with this specific procedure can give high sensitivity,[34] but currently this is difficult to achieve outside of tertiary centres. Like TAUS, MRI findings of GCA can also normalize quickly following administration of corticosteroids.[35]

If TAUS or MRI with vasculitis protocol can be performed quickly and by experienced operators, these modalities are good options to rule in GCA when pre-test probability is high.

Treatment of GCA

The mainstay of GCA treatment is high-dose corticosteroids to prevent onset or worsening of permanent vision loss and to induce remission. Vision loss from GCA is a true ophthalmologic emergency and initiating treatment immediately is key. In the pre-steroid era, the prevalence of permanent vision loss from giant cell arteritis was probably around 40%.[36] Currently, the rate of irreversible ischemic vision loss in at least one eye is approximately 8–17%, with longer time to treatment associated with higher risk.[5,37-39]

Most patients with bilateral ischemic vision loss from GCA lose vision simultaneously, or sequentially before the diagnosis of GCA is made.[40] After initiation of corticosteroids the risk of vision loss in a fellow, unaffected eye is highest within the first two days, with the longest interval in a recent systematic review reported to be 12 days.[41] Progression of vision loss in an already affected eye is similarly rare with highest risk in the first few days of treatment.[42]

There is ongoing debate about whether to treat new onset GCA with intravenous (IV) or oral corticosteroids. In a recent survey of neuro-ophthalmologists, 52% routinely

treat GCA patients with vision loss with IV methylprednisolone, and only 3% routinely initiate IV treatment in GCA patients without vision loss.[43] Both the ACR and EULAR do conditionally recommend IV corticosteroids for patients with ischemic vision loss.[28,44] However, the quality of evidence guiding this decision is low and there are no randomized trials to determine whether or not IV corticosteroids can prevent further deterioration or increase the likelihood of vision improvement in these patients.[45] High-dose oral prednisone at a dosage of approximately 1 mg/kg/day can be an acceptable option for patients with ischemic vision loss from GCA, particularly if organizing IV corticosteroids would delay treatment.

Early referral to rheumatology should be made for consideration of adjuvant therapies. Tocilizumab has shown clear benefit in reducing total corticosteroid requirement in GCA[46] and is now routinely used early in the disease course.[28] Methotrexate is also a common option as a steroid-sparing agent.[44]

Conclusion

Approximately 20% of patients with ocular GCA lack systemic symptoms and a result usually present first to ophthalmology. Recognition of how GCA manifests differently than other causes of ocular ischemia is key for early diagnosis and immediate initiation of high-dose systemic corticosteroids. TAB remains the gold standard for confirming a diagnosis; TAUS and MRI are likely to play greater roles in the future as standardized protocols are adopted and expertise in interpretation becomes more widespread.

Correspondence

Laura Donaldson, MD, PhD
Email: Laura.donaldson@medportal.ca

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None declared.

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