Giant Cell Arteritis: A cause lurking behind several common ocular diagnoses

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Giant Cell Arteritis: Natural History

Ocular involvement:
- Thirty percent of giant cell arteritis patients have ocular manifestations
- Ocular involvement typically presents within two weeks of the onset of systemic symptoms

Between 20-50% will have bilateral involvement

When second eye involved:
- Within one day: 36%
- Within 2-7 days: 36%
- Within 8-30 days: 28%

Giant Cell Arteritis: Epidemiology

Incidence increases with age especially in individuals over age 70
- Disease extremely rare under the age of 50
- Affects women 2.5x more commonly than men

Incidence highest in white individuals, particularly those of Scandinavian descent
- ~20/100,000
- Lower in Hispanics, Asian, Middle Eastern and Black populations
Increased risk of development in patients with polymyalgia rheumatica

20% of isolated polymyalgia rheumatica have TAB-confirmed GCA

- Pain involving:
  - Shoulder and upper arms bilaterally
  - Neck
  - Hip, gluteal and upper thighs

- Morning stiffness lasting >45-60 min

- Low grade fever, fatigue, anorexia, weight loss

- Causes elevated ESR (>30mm/hr) and CRP (>6mg/L)

Symptoms of Giant Cell Arteritis

- Headache
  - Persistent severe head pain, usually in temporal area
  - Most common complaint, present in about 75% of patients with GCA
  - Often associated with localized or diffuse scalp tenderness

- Scalp tenderness
  - Noted when combing hair, wearing hat or eyeglasses

- Jaw claudication
  - Pain associated with chewing - ischemia of the masticatory muscles
  - More common with ocular involvement
  - Odds of positive TAB 9x greater when present

De Smit et al., Graefes Arch Clin Exp Ophthal 2016; 254:2291-2306

- Temporal headache
- Scalp tenderness
- Eye claudication
- Neck pain
- Unexplained weight loss
- Malaise
- Sudden vision loss in one eye
- Diplopia

De Smit et al., Graefes Arch Clin Exp Ophthal 2016; 254:2291-2306

- Tab positive GCA 72% vs 43%
- Tab negative GCA 18% vs 13%

VZV antigen in:

PCR(+)

TA positive GCA 100%
Normal TA/control 100%

TA negative GCA 0% vs 0%

Normal TA/control 0%


Nagel et al. JAMA Neurology 2015;72:1281-1287
**Symptoms of Giant Cell Arteritis**

**Sudden Vision Loss in One Eye**
- Most common ocular symptom
-Transient visual symptoms may precede permanent vision loss

**Diplopia**
- About 10% of patients with GCA experience diplopia
- Consider GCA in patients over 50 with transient or persistent diplopia

**Giant Cell Arteritis: Ocular Involvement**

1/3 to 1/2 of patients with giant cell arteritis will have ocular involvement

**Ocular involvement / visual manifestations:**
- Anterior ischemic optic neuropathy (81%)
- Amaurosis fugax (30%)
- Cilioretinal artery occlusion (22%)
- Central retinal artery occlusion (14%)
- Diplopia (6%)
- Posterior ischemic optic neuropathy (3%)

**Sudden Vision Loss in One Eye**
- Consider GCA in patients over 50 with transient or persistent diplopia

**Diplopia**
- Symptoms of Giant Cell Arteritis

De Smit et al., Graefes Arch Clin Exp Ophthalmol 2016; 254:2291-2306

**Giant Cell Arteritis: Systemic Symptoms**

Be aware of “occult ” GCA!!

Not all GCA patients have systemic symptoms
One in five experience no systemic symptoms

**Occult Giant Cell Arteritis**

Occult Giant Cell Arteritis: Ocular Manifestations

Extensively questioned about systemic symptoms and signs during or before onset of visual symptoms

**Occult Giant Cell Arteritis**

Occult Giant Cell Arteritis: Ocular Manifestations

22.2% of GCA patients with ocular involvement had no systemic symptoms!

No significant difference in age or gender between symptomatic and asymptomatic groups

Serologic markers were statistically lower in the asymptomatic group:

- Erythrocyte sedimentation rate 80.0 vs. 92.0 mm/hr  P=0.001
- C-reactive protein 4.0 vs. 10.0 mg/dL  p=0.013

**Giant Cell Arteritis Diagnosis**

High clinical suspicion:
- Suggestive clinical presentations / diagnoses
- At risk populations
- Associated systemic symptoms

- Treatment may be initiated prior to tissue confirmation if clinical suspicion is high enough!

- Potential role less non-invasive tests:
  - Positron emission tomography (PET)
  - Computed tomography angiography (CTA)
  - Magnetic resonance angiography (MRA)
  - Color duplex ultrasonography (CDUS)

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  - Computed tomography angiography (CTA)
  - Magnetic resonance angiography (MRA)
  - Color duplex ultrasonography (CDUS)
**Giant Cell Arteritis: Serologic Markers**

- Erythrocyte sedimentation rate: Greater than 47 mm/hr
- C-reactive protein: Greater than 2.45 mg/dL
- Platelet count: Greater than 400,000/μL

**Gold Standard: Temporal Artery Biopsy**

- Inflammatory infiltrate seen in the arterial wall, primarily composed of lymphocytes and macrophages
- Commonly seen, but not diagnostic signs include fragmentation of internal elastic lamina and intimal hyperplasia with partial or complete lumen occlusion
- Sensitivities of 70 – 90%, specificity is 100%
- Up to 30% of patients with a clinical diagnosis of GCA have negative biopsies
- Biopsy lengths of >0.5 cm and bilateral sampling improves sensitivity

**Gold Standard: Temporal Artery Biopsy**

- Giant cell arteritis
- The name “Giant Cell Arteritis” comes from the histologic appearance of the inflamed arterial wall
- Giant cells are a coalescence of several macrophages
- These coalescences are not required for the diagnosis of giant cell arteritis
- Granulomatous inflammation with macrophages is the diagnostic hallmark of giant cell arteritis

**Gold Standard: Temporal Artery Biopsy**

- Granulomatous inflammation
- Inflamed arterial wall
- Macrophages
- Lymphocytes
- Vessel wall

**Gold Standard: Temporal Artery Biopsy**

- Intimal hyperplasia
- Near complete occlusion of the lumen

**Gold Standard: Temporal Artery Biopsy**

- Intimal hyperplasia
- Near complete occlusion of the lumen
- Giant cell
Giant Cell Arteritis: Imaging Technologies

Gold Standard: Temporal Artery Biopsy

- Fragmentation of internal elastic lamina
- Giant cell

Giant Cell Arteritis: Imaging Technologies

- Computed tomography angiography (CTA)
- Magnetic resonance angiography (MRA)
- Positron emission tomography (PET)
- Color duplex ultrasonography (CDUS)

Giant Cell Arteritis: Computed Tomography Angiography

- Circumferential wall thickening (left) and late enhancement (right) of descending thoracic aorta

CTA is currently primarily used in the diagnosis of large vessel GCA.

To date, there is limited reporting of the use of CTA for the imaging of superficial cranial arteries such as the temporal artery.

Giant Cell Arteritis: Magnetic Resonance Angiography

- Contrast enhanced MRA showing stenosis of the axillary arteries
- MRA is highly valued in the diagnosis of large-vessel GCA

Multi-center study of MRA imaging of temporal artery showed sensitivities of 78.4% and specificity of 90.4% for detecting GCA.

Despite promising diagnostic accuracy in studies, MRA has not replaced temporal artery biopsy in the diagnosis of cranial giant cell arteritis.

Giant Cell Arteritis: Positron Emission Tomography (PET)

- PET image demonstrating uptake in the vessel wall of the aortic arch
- High-intensity signal from brain and narrow caliber make temporal arteries difficult to image with PET

PET allows imaging of increased metabolic activity in inflamed tissues.

Meta-analysis reported good sensitivity (89.5%) and specificity (97.7%) for large-vessel GCA.

Despite promising study results, CDUS has not replaced TAB in the diagnosis of GCA.

Some debate for using CDUS to identify best section of temporal artery to biopsy.

Giant Cell Arteritis: Color Duplex Ultrasonography

- "Halo sign" in a patient with giant cell arteritis
- Hypoechoic area around temporal artery:
  - Longitudinal view of temporal artery before (top) and two days into steroid therapy (bottom)

PET allows imaging of increased metabolic activity in inflamed tissues. Despite promising study results, CDUS has not replaced TAB in the diagnosis of GCA. Some debate for using CDUS to identify best section of temporal artery to biopsy.
The Important Diagnostic Role Systemic Symptoms Play

A good case history and availability of lab testing remains key!

Giant Cell Arteritis: Validity and Reliability of Various Diagnostic Criteria

Odds of positive temporal artery biopsy:
- 9.0x greater with symptom of jaw claudication
- 3.4x greater with symptom of neck pain
- 3.2x greater with CRP above 2.45 mg/dL
- 2.0x greater with erythrocyte sedimentation rate of 47 mm/hr
- 2.0x greater with age 75 years or greater

Prior to more fully obstructing blood flow in the vessels that lead to the above ocular diagnoses, patients often experience transient symptoms

Vast majority of amaurosis fugax has an embolic cause:
- 74% carotid pathology
- 11% cardiac source

GCA is the cause of 1% of amaurosis fugax

Amaurosis fugax occurs in 15% of patients with GCA overall and 30% of those with ocular involvement

Amaurosis Fugax

Pathophysiology:
- Transient decreased blood flow within the ophthalmic, posterior ciliary, central retinal, branch retinal, or cilioretinal arteries
- Results in transient “graying-out” of vision

Most of amaurosis fugax has an embolic cause:
- 74% carotid pathology
- 11% cardiac source

GCA is the cause of 1% of amaurosis fugax

Amaurosis fugax occurs in 15% of patients with GCA overall and 30% of those with ocular involvement

ABCD2 Score: Risk Factor Assessment of Stroke After TIA:

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 years</td>
<td>1 point</td>
</tr>
<tr>
<td>BP &gt; 140/90</td>
<td>1 point</td>
</tr>
<tr>
<td>Duration of TIA &lt; 60 min</td>
<td>1 point</td>
</tr>
<tr>
<td>Unilateral weakness</td>
<td>2 points</td>
</tr>
<tr>
<td>Speech/his weakness</td>
<td>1 point</td>
</tr>
<tr>
<td>Cataract</td>
<td>1 point</td>
</tr>
</tbody>
</table>

High Risk: > 5 points
Moderate Risk: 3–5 points
Low Risk: < 3 points

ABCD2 Score:

Low Risk: < 4
Moderate Risk: 4–5
High Risk: > 5

2-Day Stroke Risk:

- Low Risk: 0.1%
- Moderate Risk: 4.1%
- High Risk: 8.1%

All high-risk patients with acute amaurosis require urgent evaluation with focus on embolic sources

In Caucasians over the age of 50, or anyone with suggestive systemic symptoms, this work-up must include ruling out giant cell arteritis

All patients with non-acute amaurosis fugax (greater than 30-days) and low-risk amaurosis fugax (ABCD2 < 4) require outpatient evaluation for embolic sources

Patients with non-acute amaurosis fugax who are at risk for GCA need urgent work-up:
- Caucasians over the age of 50
- Patients of any race with GCA systemic symptoms or strong clinical suspicion
- Patients with polymyalgia rheumatica
- Absence of significant vasculopathic and embolic risk factors

Giant cell arteritis can result in the symptom of amaurosis fugax!!
Anterior Ischemic Optic Neuropathy

Classification:
- Non-arteritic anterior ischemic optic neuropathy (NA-AION)
- Arteritic anterior ischemic optic neuropathy (A-AION)

90% of AION cases
- Predisposing factors: Diabetes, hypertension, blood loss, atherosclerosis, sleep apnea, cardiovascular disease, migraine, disc drusen, high IOP
- Precipitating factors: Nocturnal arterial hypotension

10% of AION cases
- 80-85% of vision loss due to GCA
- 6.9% of newly diagnosed GCA patients
- Vasculitis of the short posterior ciliary arteries or posterior ciliary arteries
- Visual acuity better than 20/64 in 50%
- Presence of associated microvascular risk factors
- Rare to present simultaneously in both eyes

Differing features of NA-AION:
- Onset of symptoms noticed upon awakening (73%)
- Disc at risk: Smaller than average cup-disc ratio (75% ratio < 0.25)
- Disc swelling is hyperemic with dilation of surface capillaries and peripapillary splinter hemorrhages
- Edema can be sectoral, affecting only the top or bottom half of the nerve
- Visual acuity better than 20/64 in 50%
- Presence of associated microvascular risk factors
- Rare to present simultaneously in both eyes
Differencing features of A-AION:
• Fluorescein angiography may show delayed choroidal filling and areas of choroidal non-perfusion
• Concurrent cilioretinal artery occlusion (arise from posterior ciliary artery circulation)
• Lower IOP

Factors that could lead to a delay in diagnosis of GCA in patients with AION:
• NA-AION is the much more prevalent subtype of AION
• Onset of ocular signs and symptoms over hours to days
• No ocular treatment for NA-AION leading to routine follow-up intervals
• Standard of care for NA-AION is non-urgent assessment of modifiable microvascular risk factors
• Up to 21% of patients with GCA do not have systemic symptoms
• Logistic difficulties in obtaining urgent laboratory testing

Factors that must ALL be present to not urgently rule-out GCA in AION:
• Black, Hispanic, or Asian Race
• Associated systemic risk factors present
• No GCA-associated systemic symptoms
• No polymyalgia rheumatica
• Vision loss noticed upon awakening
• Vision better than 20/200
• Disc at risk in involved or fellow eye
• Unilateral presentation

Any Caucasian over the age of 50, any person with GCA-associated systemic symptoms, and any bilateral presentations of AION should be urgently evaluated for GCA!

Central Retinal Artery Occlusion

Occlusion/hypo-perfusion of the central retinal artery

Optic Presentation:
• Regional retinal whitening involving all quadrants obscuring some superficial vessels
• Whitening most dense in central macula and surrounding optic nerve where retinal nerve fiber layer is most thick
• Retinal whitening absent in foveal area resulting in "cherry red spot"
• Patchy filling / narrowing of retinal arteries
• Emboli possibly clinically visible

Central Retinal Artery Occlusion

Cases of GCA-associated CRAO where fluorescein angiography is performed show occlusion of the central retinal artery and one of the posterior ciliary arteries even if the disc was not swollen

Relevant Anatomy:
In 40% of individuals, the central retinal artery arises from the ophthalmic
In 60% of individuals, the central retinal artery arises from the ophthalmic artery by a common trunk with one or more of the posterior ciliary arteries
Cilioretinal artery found in 25% of individuals
The cilioretinal artery arises from one of the posterior ciliary arteries

Central Retinal Artery Occlusion

CRAO occurs in 7% of GCA patients and 14% of patients with ocular involvement
The ciliary arterial artery arises from one of the posterior ciliary arteries. Ciliary arterial artery occlusion is seen in 7% of GCA patients and 21% of those with ocular involvement. Ciliary arterial artery occlusion in GCA is usually seen in conjunction with arteritic anterior ischemic optic neuropathy (92%) and rarely in isolation.


Ciliary arterial occlusion in GCA is usually seen in conjunction with arteritic anterior ischemic optic neuropathy (92%) and rarely in isolation.


Webeye.ophth.uiowa.edu When present in patients with GCA-associated CRAO, the ciliary arterial artery is occluded in 80% of cases.


Ciliary Artery Occlusion

Ciliary artery occlusions seen over a 10-year period:

Three distinct groups:

• Isolated ciliary arterial artery occlusion: 61%
• Combined with central retinal vein occlusion: 27%
• Combined with anterior ischemic optic neuropathy: 12%

All patients with combined ciliary arterial artery occlusion and AION had GCA.

Choroidal Ischemic Lesions

Occlusion of the posterior ciliary arteries can lead to patchy choroidal ischemia. Over weeks, they appear as midperipheral choroidal degenerative lesions. Typically triangular in shape with base toward equator and apex toward disc. Seen in 3% of GCA patients.

Ophthalmology 2015;122;2336-43

Branch Retinal Artery Occlusion and Cotton Wool Spots

Branch retinal artery occlusion:

• Branch retinal artery occlusion from GCA is exceedingly rare
• Reduced flow in the central retinal artery can mimic branch retinal artery occlusion

Cotton Wool Spots:

• Seen in ~30% of GCA patients with ocular involvement
• May be caused by platelet microembolism
• May be caused by anisometric stasis within ganglion cell axons in response to reduced blood due to an upstream location of stenosis
• Predilection for circular area a short distance from the nerve.

GCA and Retinal Artery Occlusion

Risk and Risk Periods for Stroke and Acute Myocardial Infarction in Patients with Central Retinal Artery Occlusion

In the one year following the incidence of CRAO:
• 9.0% had an ischemic stroke
• 0.90% had an acute myocardial infarction

Risk of stroke or myocardial infarction after a CRAO compared to control groups:
• 14x higher in first 30 days post-CRAO
• Greatest risk in the first 7 days post-CRAO
• 7x in the 30 days before CRAO

The window for stroke prevention after CRAO is very short. Therefore these patients require IMMEDIATE evaluation and preventative intervention to reduce mortality and morbidity.
**GCA and Retinal Artery Occlusion**

All patients with acute central, branch, and cilioretinal retinal artery occlusion require urgent evaluation with focus on finding embolic sources.

In Caucasians over the age of 50, anyone with systemic symptoms, or when the cilioretinal artery is involved this work-up should include ruling out GCA.

All patients with non-acute (10+ days) central, and cilioretinal retinal artery occlusion require outpatient evaluation for embolic sources.

All patients with non-acute (10+ days), central, and cilioretinal retinal artery occlusion also are at risk for GCA and urgent work-ups.

- Caucasians over the age of 50
- Patients of any race reporting GCA-associated systemic symptoms
- Patients with polymyalgia rheumatica
- Absence of embolic risk factors (carotid, heart, aortic disease)
- Associated cotton wool spots in temporal distribution
- When the cilioretinal artery is involved (usually with associated AION)

**Posterior Ischemic Optic Neuropathy**

Pathophysiology:
- Hypoperfusion within the pial vascular plexus
- Blood supply to the posterior optic nerve is supplied by the pial plexus

Pial plexus is derived from:
- Ophtalmic artery
- Central retinal artery
- Other orbital arteries
- Circle of Haller-Zinn
- Peripapillary choroid

**Classification:**
- **Non-arteritic (53-66%)**
  - Age over 50 years
  - No underlying structural risk factors
  - Same underlying vascular risk factors as NA-AION
- **Arteritic (8-26%)**
  - Age under 50 years
  - Younger 50 vs. 68 years (NA-PION vs. A-PION)
- **Post-surgical (7-39%)**
  - 30% after orbital surgery
  - Younger 50 vs. 68 years (NA-PION vs. NA-AION)

**Baseline visual acuity according to PION subtype**

<table>
<thead>
<tr>
<th>Percentage of eyes</th>
<th>Nonarteritic (n=46)</th>
<th>Arteritic (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF or worse vision</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>Non-arteritic (n=46)</td>
<td>Perioperative (n=34)</td>
<td>Arteritic (n=6)</td>
</tr>
<tr>
<td>Baseline visual acuity</td>
<td>CF, LP, NLP</td>
<td>Visual acuity</td>
</tr>
</tbody>
</table>

**Percentage of eyes with visual improvement in all subtypes**

- 30% chance of improvement in VA in all subtypes

Note: Younger patients are at higher risk for A-PION.

10/12/17
Factors that could lead to a delay in diagnosis of GCA in patients with PION:

- Failure to diagnose PION
- Failure to recognize GCA as a cause of PION

**Posterior Ischemic Optic Neuropathy (PION)**

PION is a diagnosis of exclusion!

**Differential diagnoses:**
- Compressive, infiltrative, or inflammatory optic neuropathy
- Urgent contrast-enhanced MRI required to rule-out compressive or infiltrative optic neuropathy

**Patients who are at risk for GCA need work-up:**
- Caucasians over the age of 50 years
- Patients of any race reporting GCA-associated systemic symptoms
- Patients with polymyalgia rheumatica
- Microvascular ischemic risk factors

**Requires evaluation for systemic vascular disease**

**Giant Cell Arteritis and Diplopia: The Other Ophthalmic Symptom**

Diplopia reported in 6 – 20% of patients with ophthalmic complications
- Most as a transient symptom

**Prospecive evaluation of newly diagnosed GCA (Rheumatology Clinic)**
- Enrolled 37 patients from Jan 2010 to May 2013
- Nine (27%) presented with diplopia at diagnosis
  - All nine + TAB

**Nine patients with diplopia:**
- Characteristics
  - Eight patients with diplopia at diagnosis complained of preceding temporary diplopia
  - Only one patient had persistent diplopia
  - More often had extracranial vessel inflammation
  - Tendency to higher incidence of vision impairment at Dx

**Examination:**
- Confluent abduction deficit (5)
  - 1 presented initially with vertical diplopia followed by ptosis (III)
  - His consistent with abduction deficit (I)
  - Decompensated exophoria (I)
  - Resolved ON IV deficit (1)
  - Undetermined cause (I)

**Suggests that diplopia may be more common symptom of GCA**

**Diplopia in GCA setting may be warning sign for subsequent vision loss**

**Etiology of Diplopia in GCA**

**Numerous causes have been suggested**
- Cranial nerve palsies (most common)
- Direct muscle ischemia
- Orbital pseudotumor
- Internuclear ophthalmoplegia (rare)

**GCA-associated diplopia**
- Often incomplete or temporary
- Active arteritis of small arteries to muscle is postulated to explain transient ocular paralysis

**Transient diplopia is a poor prognostic feature**

**Patients with irreversible ischemic complications more frequently experience transient diplopia**
Etiology of III Palsy

**Compression**
- **Aneurysm**
  - Posterior communicating artery
- Brain tumor
- Sphenoid wing meningioma
- Pituitary: lateral spread to cavernous sinus

**Ischemia (most common)**
- Atherosclerosis
- Diabetes
- Hypertension
- Smoking
- Giant Cell Arteritis over age 50

**Inflammation**
- Multiple sclerosis (rare)
- Infection
  - Viral or post-viral

**Trauma**
- Severe open or closed head injuries

Management of III Palsy

- Recommend DO NOT apply Pupil Rule – Don’t forget footnotes if you do
- Recommend urgent work-up of ALL III palsies regardless of pupil function

Urgent imaging looking for aneurysm
- MRI of brain with and without contrast
  - Plus MRA

**DO NOT FORGET GIANT CELL ARTERITIS**
- Patients over 50 screen for symptoms and get ESR, CRP, platelets

GCA in III, IV, and VI Palsy

Factors that could lead to a delay in diagnosis of GCA in patients with CN Palsy:
- Failure to recognize GCA as a cause of cranial nerve palsies
- The most common cause of IV and VI palsies is microvascular ischemia that is not always worked-up and often monitored for three months before further work-up is considered

Giant cell arteritis has been found to be the cause of 4% of isolated III, IV, and VI palsies in individuals over age of 50

We Know GCA is a Blinding Disease, but Does it Kill?

Risk of mortality in patients with giant cell arteritis: A systematic review and meta-analysis

Long-term mortality, at a population level, is not increased by GCA.

Slightly increased risk of death in first two years after diagnosis with initiation of high-dose steroids.

Mortality in Patients with Biopsy-proven Giant Cell Arteritis: A South Australian Population-based Study

In the population-based cohort study, no observed increase in mortality risk.

Risk of death from infection within the first year was increased with GCA.


Risk of death in first two years after diagnosis with initiation of high-dose steroids.


GCA Pathophysiology: Important Role of IL-6 and Interferon-γ

IL-6 secreted by activated macrophages in the vessel wall stimulates the liver to produce:

- Active phase proteins:
  - Fibrinogen (main driver of elevated ESR)
  - C-reactive protein

- Thrombopoietin (TPO) that works on megakaryocytes in bone marrow resulting in platelet formation

Interferon-γ and Th1 cells that produce it along with activated macrophages are less responsive to steroids.

Release partially responsible for chronicity of disease despite steroid treatment.


GCA BRIEF Pathophysiologic Overview

Antigenic stimulation via Toll-like receptors on dendritic cells within vessel adventitia.

Macrophages produce IL-6 that induces conversion of T cells into highly active Th17 cells.

Dendritic cells produce cytokines that attract lymphocytes (especially T cells) into the vessel wall and that lead to differentiation of peripheral blood monocytes into macrophages.

Note: IL-6 and interferon-γ repeatedly are involved in the erroneous autoreactivity of GCA.


GCA Treatment Overview

Major inflammatory pathways:

- IL-6 / Th17 Axis
- Interferon-γ / Th1 Axis

Proven Effective Therapies:

- Steroids
- Tocilizumab

Anecdotal and Limited Benefit:

- Aspirin
- Statins

GCA Treatment: Steroids

Steroids remain the mainstay of treatment.

Starting Dose:

- 40-60 mg / day oral prednisone
- 1 gm / day IV methyl-prednisolone if immediate risk of vision loss x 3 days, then oral prednisolone
- High doses maintained for ~3-4 weeks

Once activity suppressed (serologic markers), long taper commences.

Taper:

- Decrease by 10 mg / 2 weeks until dose is 20 mg/day
- Decrease by 2.5 mg / month until dose is 10 – 15 mg/day
- Decrease by 1.5 mg / month with goal of discontinuation by 18-24 months.

Adverse events in 86%:

- Two or more in 58%

Highlights the need for steroid sparing agents.


GCA Treatment: Steroids

High dose glucocorticosteroids associated with high rate of complications:

Table 1. Major adverse events that occurred in 100 of 118 patients with giant cell arteritis.

<table>
<thead>
<tr>
<th>Type of adverse event</th>
<th>Patients with the event, member (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophthalmic outcomes</td>
<td></td>
</tr>
<tr>
<td>Visual loss</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Bilateral blindness</td>
<td>66 (56)</td>
</tr>
<tr>
<td>Slit Lamp features</td>
<td>54 (46)</td>
</tr>
<tr>
<td>Ocular Ultrasound</td>
<td>22 (19)</td>
</tr>
<tr>
<td>Other outcomes</td>
<td></td>
</tr>
<tr>
<td>High Blood Pressure</td>
<td>22 (19)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>9 (8)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>27 (23)</td>
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<td>High Blood Pressure</td>
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<td>27 (23)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

GCA Treatment: Interleukin-6 Receptor Blockade

Once weekly by subcutaneous or intravenous injection in combination with steroid taper

Humanized monoclonal antibody

Binds to both soluble and membrane-bound IL-6 receptors

IL-6 is a pro-inflammatory cytokine produced by inflammatory cells involved in the pathophysiology of GCA

IL-6 involved in diverse physiologic processes including T-cell activation, acute-phase protein synthesis, and cell proliferation

www.acetemra.com

Outcome measures:

Sustained Remission Rate:

- Absence of a flare
- Normalization of C-reactive protein to less than 1 mg/dL
- Occurring from week 10 through 52 while adhering to steroid taper

Cumulative Steroid Dose:

- Total steroid dose over 52-week trial

The percentage of subjects with adverse events were similar in all groups

Sustained Remission rate:

- Weekly tocilizumab + 26 week steroid taper 56%
- Every other week tocilizumab + 26 week steroid taper 53%
- Weekly placebo + 26 week steroid taper 18%
- Weekly placebo + 52 week steroid taper 18%

1-Year cumulative steroid dose:

- Weekly tocilizumab + 26 week steroid taper 1862 mg
- Every other week tocilizumab + 26 week steroid taper 1862 mg
- Weekly placebo + 26 week steroid taper 3296 mg
- Weekly placebo + 52 week steroid taper 3818 mg

Ten percent of anterior ischemic optic neuropathies are arteritic!
Back to the Cases: Diplopia

68-year old Caucasian male

4+ limitation of abduction of the left eye

What is the chance that giant cell arteritis is the cause of the EOM deficit?

Four percent of isolated cranial nerve palsies are caused by GCA!

Back to the Cases: Central Retinal Artery Occlusion

82-year old Caucasian male

Inner retinal thickening and hyperreflectivity

No embolus

Unilateral inner retinal whitening

What is the chance that giant cell arteritis caused this CRAO?

Approximately 4% of CRAOs are caused by GCA!

Conclusions

About a third of patients with giant cell arteritis will have ocular involvement

Diagnoses made that require consideration of GCA as an underlying cause:

- Anterior ischemic optic neuropathy
- Amaurosis fugax
- Cilioretinal artery occlusion
- Central retinal artery occlusion
- Posterior ischemic optic neuropathy
- Diplopia

Patient characteristics that require urgently ruling-out GCA as a cause of above:

- Caucasians over the age of 50 years
- Patients of any race reporting GCA-associated systemic symptoms
- Patients with polymyalgia rheumatica
- Patients that do not meet criteria typical of non-GCA causes of the diagnosis

When in doubt, rule it out!!!

We could not have said it better ourselves!

Occult Giant Cell Arteritis: Ocular Manifestations

Sohan Hayreh, MD, MS, PhD

“Any patient over the age of 50 years who presents with a history of amaurosis fugax, diplopia, or vision loss and who has clinical findings of arteritic ischemic optic neuropathy, central retinal artery occlusion, cilioretinal artery occlusion, or posterior ischemic optic neuropathy should be suspected of having giant cell arteritis regardless of whether he or she has systemic symptoms.”

Giant Cell Arteritis:
A cause lurking behind several common ocular diagnoses

Thank you for your attention