Recent Advances in Giant Cell Arteritis

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Objectives

• Describe giant cell arteritis (GCA)
• Review the criteria for the classification of GCA
• Consider results of a recent, phase 2 trial of Tocilizumab
Describe GCA
Historical Perspective

- First described by Hutchinson in 1890\(^1\)
- Later by Horton *et al* in 1932\(^2\)
Pathophysiology

• Activation of dendritic cells in adventitia of arteries by unknown antigen produces chemokines that recruit CD4\(^+\) T helper cells

• Activated CD4\(^+\) T helper cells polarize into:
  • Th1 cells and produce interferon gamma
  • Th17 cells and produce interleukin 17

• Interferon gamma causes endothelial cells and vascular smooth muscle to recruit more Th1 cells, CD8\(^+\) T cells, and monocytes

• Monocytes differentiate into macrophages and giant cells and produce:
  • Growth factors
  • Other interleukins
  • Proteolytic enzymes\(^3\)
Pathophysiology, continued

• Platelet-derived growth factor (PDGF) is important in stimulating intimal hyperplasia
• Vascular endothelial growth factor (VEGF) also promotes intimal proliferation
• Interleukin-6 (IL-6) augments the inflammatory response
• Metalloproteinases lead to the destruction of vascular elements, including the internal elastic lamina$^3$
Etiology

• The initial event that triggers the cascade remains uncertain
• Genetic, environmental, and autoimmune factors have been identified
• Familial aggregation, association with the HLA-DR4 haplotype, and an apparent higher frequency in northern Europe and in people in the US with similar ethnic backgrounds suggest genetic predisposition
• GCA is less common among African Americans
• A possible association between Toll-like receptor 4 gene polymorphism and susceptibility to biopsy-proven GCA
• *Chlamydia pneumoniae, Mycoplasma pneumoniae, parvovirus B19,* and recently *varicella zoster* have been implicated as the impetus for the destructive inflammation
• The granulomatous histopathology of GCA may begin as a foreign body giant cell attack on calcified internal elastic membrane in the arteries and on calcified atrophic parts of the aortic media
Etiology, continued

• Elastin as the inciting antigen?
  • Disease severity has been shown to correlate with the amount of elastic tissue within the vessels\(^3\)
Epidemiology

- Annual incidence rates for GCA in the US range from 0.5 to 27/100,000 people aged 50 years and older\(^4\)
- A review from Olmsted County, Minnesota identified 125 cases over 42 years, representing an average annual incidence rate of 17.8 cases per 100,000 population aged 50 years and older and a prevalence of persons with active or remitted GCA of 200 cases per 100,000 population aged 50 years or older. A regular cyclical pattern in incidence over 20 years was noted.
- F:M preponderance of about 3-4:1
- Most prevalent in the white population of European origin
- Age is the most important risk factor for GCA, and the incidence increases with age
  - Peaking in the seventh to eighth decade. The age range in one series of 166 biopsy-proven cases was 55-92 years. The median age of onset is 75 years
The most commonly reported symptoms in patients with GCA are as follows:

1. Headache (initial symptom in 33%, present in 72%)
2. Neck, torso, shoulder, and pelvic girdle pain that is consistent with polymyalgia rheumatica (PMR; initial in 25%, present in 58%)
3. Fatigue and malaise (initial in 20%, present in 56%)
4. Jaw claudication (initial in 4%, present in 40%)
5. Fever (initial in 11%, present in 35%)
History, continued

- Around 50% of patients with GCA experience visual symptoms over the course of the disease
  - Transient and intermittent unilateral visual blurring or vision loss
  - Diplopia
  - Partial field defect that may progress to complete blindness over days
  - Patients may experience visual hallucinations, which may precede permanent loss of vision
- If GCA remains untreated in patients with unilateral vision loss, the second eye may become affected within 1-2 weeks
Physical Exam

- Approximately half of patients have signs of superficial temporal artery inflammation, including erythema, pain on palpation, nodularity, thickening, or reduced pulsation on the affected side. The examiner may be able to roll an affected temporal artery between the fingers and the skull.

- Gentle pressure on the scalp may elicit focal or generalized tenderness. This differs from the hypersensitivity or hyperesthesia (unusual discomfort from a very mild stimulus, such as gently stroking the patient's hair) that is commonly found with migraine.³
The most common cause of vision loss in GCA is anterior ischemic optic neuropathy (AION), which is caused by vasculitis of the posterior ciliary artery. Vision loss may precede the funduscopic changes of optic nerve infarction by roughly 36 hours. Other important vascular ophthalmic presentations of GCA include the following:

- Posterior ischemic (retrobulbar) optic neuropathy
- Central retinal artery occlusion
- Branch retinal artery occlusion
- Choroidal ischemia
Physical Exam, continued

- Neuro-ophthalmic manifestations\(^3\) of GCA include the following:
  - Diplopia (less than 6%)
  - Ptosis
  - Nystagmus
  - Internuclear ophthalmoplegia (INO)
  - Pupillary abnormalities
Diagnosis: Temporal Artery Biopsy

- H&E stain with predominance of mononuclear cell infiltration or granulomatous inflammation, usually with mononuclear giant cells
- Verhoeff-Van Gieson stain shows breaks in elastic lamina
- Masson’s Trichrome stain highlights complete loss of smooth muscle fibers of the tunica media
- Intimal proliferation with resulting luminal stenosis
- Invasion and necrosis of the media progressing to involvement of the entire vessel wall (ie, panarteritis) with an inflammatory infiltrate consisting predominantly of mononuclear cells
- Giant cell formation with granulomata within the mononuclear cell infiltrate
- Intravascular thrombosis (less consistently found)
Diagnosis: Ultrasound (US)

- November 2016, Health Technology Assessment
  - The Role of US Compared to Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis
  - Prospective multicenter cohort study
  - 381 patients

- Results
  - Sensitivity and specificity were similar with biopsy and US
    - Biopsy: 91%, 81%
    - US: 93%, 77%

- Cost
  - 485 L per patient
Classification of GCA

GIANT CELL (TEMPORAL) ARTERITIS
Classification Tree

Sens: 95.3%
Spec: 90.7%

Abnormal temporal arteries (tender scalp)

Age at onset, yr
<50
≥50

No GCA
GCA

Claudication

Artery biopsy (headache)

No GCA
GCA

Age at onset, yr
<50
≥50

No GCA
GCA

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ACR 1990 Criteria

• Compared 214 patients with GCA with 593 patients who had other forms of vasculitis
• 33 variables were selected as potentially important discriminators against other forms of vasculitis
• 2 single and 8 combined items were selected as having the greatest potential to separate cases of GCA from controls
• Sensitivity and specificity were calculated
ACR 1990 Criteria

- Traditional format

<table>
<thead>
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<th>Definition</th>
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<tbody>
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<td>1. Age at disease onset ≥50 years</td>
<td>Development of symptoms or findings beginning at age 50 or older</td>
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<td>2. New headache</td>
<td>New onset of or new type of localized pain in the head</td>
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<td>3. Temporal artery abnormality</td>
<td>Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries</td>
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<td>4. Elevated erythrocyte sedimentation rate</td>
<td>Erythrocyte sedimentation rate ≥50 mm/hour by the Westergren method</td>
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<td>5. Abnormal artery biopsy</td>
<td>Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells</td>
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* For purposes of classification, a patient shall be said to have giant cell (temporal) arteritis if at least 3 of these 5 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 93.5% and a specificity of 91.2%.
ACR 1990 Criteria

- Tree format

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<td>3. Claudication of jaw, tongue, or on deglutition</td>
<td>Development or worsening of fatigue or discomfort in muscles of mastication, tongue, or swallowing muscles while eating</td>
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<td>4. Temporal artery abnormality</td>
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<td>5. Scalp tenderness or nodules*</td>
<td>Development of tender areas or nodules over the scalp, away from the temporal artery or other cranial arteries</td>
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* Used as a surrogate if artery biopsy is not available (criterion 2) or if temporal artery abnormality is not present (criterion 5).
Figure 1. Classification tree for giant cell (temporal) arteritis (GCA). The circles and boxes contain the number of patients with GCA (top number) and the number of control patients with other forms of vasculitis (bottom number). The bottom half of the boxes shows the percentage of patients with GCA (out of all GCA cases) (left number) and the percentage of controls (out of all controls) (right number). Boxes specify whether patients are classified as having GCA or not having GCA (No GCA). The numbers under these specifications are the subset numbers (see Table 4 for definitions of criteria and Table 5 for explanations of subsets). Parentheses indicate the surrogate variable to be used when the first variable is not defined.
Nomenclature and classification of vasculitis – update on the ACR/EULAR Diagnosis and Classification of Vasculitis Study (DCVAS)

Summary
Classification of vasculitis remains unsatisfactory. This is largely because the pathogenetic mechanisms of this family of related disorders have not been fully understood. Existing classification criteria are useful but limited. This has become more apparent with the advent of more effective and more specific therapies. A rational basis for classification could significantly improve our approach to treatment. The development of diagnostic criteria in vasculitis is an even greater challenge but may ultimately provide more useful for the non-specialist clinician. International efforts are underway to provide more effective classification and diagnostic criteria.

Keywords: classification, vasculitis, ANCA
2012 validity study

- Retrospective chart review of all patients undergoing biopsy at a single institution from 10/2001 to 5/2006
- 112 patients were identified
- Charts were reviewed:
  - ACR criteria
  - Biopsy results
  - Progression of visual loss after diagnosis
- Results:
  - 9 of 35 patients (25.7%) with positive biopsies would not have been diagnosed with GCA
  - An additional 16 patients (45.7%) met only 2 criteria and required the positive biopsy to establish the diagnosis of GCA
  - 11 of 39 patients (28.2%) with negative biopsies met the criteria and would have been diagnosed with GCA
- Conclusion:
  - The current American College of Rheumatology criteria should not be used to diagnose GCA and all patients suspected of having GCA should undergo a temporal artery biopsy
Recent Clinical Trial
2016 clinical trial, background

- Single center, phase 2, randomized, double-blind, placebo-controlled trial from March 3, 2012 and Sept 9, 2014
- Patients aged 50 years and older from University Hospital Bern, Switzerland, who met 1990 ACR criteria for GCA
- Patients with new-onset or relapsing disease were randomly assigned (2:1) to receive either tocilizumab (8 mg/kg) or placebo intravenously
- 13 infusions were given in 4 week intervals until week 52, and both groups received oral prednisolone, starting at 1 mg/kg per day and tapered down to 0 mg according to a standard reduction scheme defined in the study protocol
- The primary outcome was the proportion of patients who achieved complete remission of disease at a prednisolone dose of 0.1 mg/kg per day at week 12
2016 clinical trial, methods

- 20 patients were randomly assigned to receive tocilizumab and prednisolone and 10 patients to receive placebo and glucocorticoid
- 16 (80%) and seven (70%) patients, respectively, had new-onset giant cell arteritis
2016 clinical trial, results

• 17 (85%) of 20 patients given tocilizumab and four (40%) of ten patients given placebo reached complete remission by week 12 (risk difference 45%, 95% CI 11-79; p=0.0301)

• Relapse-free survival was achieved in 17 (85%) patients in the tocilizumab group and two (20%) in the placebo group by week 52 (risk difference 65%, 95% CI 36-94; p=0.0010)

• The mean survival-time difference to stop glucocorticoids was 12 weeks in favor of tocilizumab (95% CI 7-17; p<0.0001), leading to a cumulative prednisolone dose of 43 mg/kg in the tocilizumab group versus 110 mg/kg in the placebo group (p=0.0005) after 52 weeks

• Seven (35%) patients in the tocilizumab group and five (50%) in the placebo group had serious adverse events
2016 clinical trial, conclusions

• For the first time in a trial setting, efficacy of tocilizumab has been demonstrated in the induction and maintenance of remission in patients with giant cell arteritis.

• In May 2017, the United States Food and Drug Administration has expanded approved use of subcutaneous tocilizumab to include treatment of adults with giant cell arteritis.
Summary

• GCA remains with an unknown etiology
• It is common in northern Europe and in persons in the US with similar ethnic backgrounds, and less common in African Americans
• Age is the most important risk factor; incidence increases with age
• Most common symptoms is HA
• Around 50% of patients experience visual symptoms
• The most common cause of vision loss is anterior ischemic optic neuropathy (AION)
• Biopsy can be positive without evidence of giant cells
• US may be more cost effective at making the diagnosis
• The 1990 ACR criteria for GCA may both underestimate and overestimate the disease as often as 1 in 4 patients
• Tocilizumab is effective in the induction and maintenance of remission in patients with GCA
References


