GIANT CELL ARTERITIS (GCA)

BOTTOM LINE

GCA is a large-medium vessel vasculitis affecting patients (more often female) typically over 70 years old. GCA affects the aorta and its major cranial (less often appendicular) branches; thus, patients commonly present with cranial claudication symptoms including new temporal headache, scalp tenderness, vision changes/blindness, and jaw claudication. Appendicular features include arm/leg claudication, decrease pulsation, and unequal blood pressures. ESR should be elevated in virtually all patients, usually over 40-50mm/h. Temporal artery biopsies are helpful, specific, but insensitive; imaging modalities like Doppler ultrasound can be supportive in experienced hands. Treatment requires prompt glucocorticoid (prednisone) to avoid complication of permanent vision loss, then tapered over 52 weeks. Many patients benefit from tocilizumab for steroid sparing and decreasing flare rates; with tocilizumab, prednisone can be tapered more rapidly over 26 weeks. Relapses are common.

EPIDEMIOLOGY

- Most common idiopathic vasculitis; prevalence and incidence (crude estimates in the >50 year-old population):
  - Prevalence: 500-7500/1,000,000 population
  - Annual Incidence: 80-300/1,000,000 population
- Risk
  - Age: peak incidence age 70-79 years; virtually never occurs <50 years old
  - Ethnicity: Scandinavian, northern European most common; less common Latino, Asian, Arabic, African
  - Sex: F>M, ~3:1
  - Genetic variant associations:
    - HLA region: HLA-DRB1, HLA-DQA1
    - Non-HLA region: PTPN22, LRRC32, REL, PLG and P4HA2

CLINICAL FEATURES

Patients present with subacute constellation of symptoms representing a systemic inflammatory process causing claudication of aorta and major cranial and/or appendicular branches.

Systemic	• Fever, fatigue, weight loss. Consider GCA on differential for elderly patient with fever of unknown origin	
Headache ~66%	• New headache, classically temporal, but also frontal, occipital, unilateral, or generalized • Associated scalp tenderness (ex: scalp pain when washing/brushing hair, sleeping on pillow)	
Jaw claudication ~50%	• Mandibular pain/fatigue onset with mastication and relieved with stopping ("jaw angina") • Associated with positive temporal artery biopsy results	
Ocular	Vision loss 15-20%	• Transient ("amaurosis fugax") or permanent vision loss, usually monocular • Cause: anterior ischemic optic neuropathy (AION, 85%), central or branch retinal artery occlusion (CRAO/BRAO), posterior ischemic optic neuropathy (PION), rarely cerebral ischemia
	Diplopia 5%	• Due to ischemia of any portion oculomotor system (including brainstem) • More specific for GCA versus vision loss
PMR 40-50%	• Polymyalgia rheumatica (see PMR chapter) • GCA with PMR = 40-50% | PMR patients with GCA = 10% • Symmetrical morning stiffness in shoulders and hip girdle sparing body distal to elbow and knees	
Large vessel (LV-GCA)	• LV-GCA: vasculitis of aorta and "appendicular" branches, usually in the upper extremity • Vessels include: aorta, brachiocephalic trunk, subclavian or femoral artery; • Aortic aneurysm ~10%, aortic dissection 1-6% • Patients with LV-GCA ***may lack cranial symptoms altogether*** • Compared to cranial-GCA, LV-GCA more likely: Younger, less headache, more arm claudication	
Less common	• Stroke, TIA • Dementia, hallucinations • Non-productive cough, URTI symptoms (perhaps activation of cough receptors along aorta) • Head/neck: maxillary/dental pain, face swelling, throat pain, tongue pain/macroglossia/necrosis	
Exam findings	• A full cardiovascular exam is required • Signs of vascular compromise: unequal brachial blood pressures, abnormal distal pulses, temporal artery abnormalities ("ropey" enlargement, decrease pulsation), bruits (axillary, carotid, abdominal), cardiac murmurs • Signs of PMR: symmetrical shoulder impingement/tendinitis	

INVESTIGATIONS		
CBC	• Hb: normocytic anemia due to chronic inflammation; improves with steroids • PTL: Thrombocytosis, reactive • WBC: usually normal or minimally elevated	
ESR, CRP	• ESR and CRP are elevated; ESR usually at least >40-50mm/h	
	Variable affecting ESR	• Increases ESR: Age, Anemia, ESRD, paraproteinemia, Obesity, infection, cancer • Decreases ESR: RBC-opathies (ex sickle cell), cachexia, CHF, CLL
	Correcting ESR for age	• Men: Age/2 • Women: (Age + 10)/2
ALT	• Normal, measure baseline in case need to start tocilizumab	
SPEP	• Elevated alpha2 fraction due to systemic inflammation, consider testing for paraproteinemia for high ESR differential	
Antibodies	• No antibody associations; may have positive ANA or RF by chance.	
Temporal artery Biopsy (TAB)	• Unilateral temporal artery biopsy at least 1cm in length • Sensitivity may be as low as 40-60%; do not delay treatment of GCA to obtain biopsy	
	Classic Findings	• Transmural infiltration of lymphocytes and macrophages; giant cells in 75% of positive biopsies
	Less Specific	• Inflammation sparing media, restricted to periadventitial small vessels and vasa vasorum
	Non specific	• "Healed" arteritis (no inflammation but structural changes like intimal hyperplasia, fragmented internal elastic lamina, adventitial fibrosis)
	Unlikely	• Fibrinoid necrosis suggests alternative diagnosis (ex GPA, MPA)
Temporal artery U/S (CDUS)	• Color Doppler Ultrasound (CDUS) should only be sought in centers with experienced sonographers • "Halo sign": circumferential dark area (mural edema) around vascular lumen of temporal artery • "Compression sign": persisting visibility of halo during compression • Sensitivity 68-88%, Specificity 77-91%; but ***requires skilled and experienced sonographer***	
Other	Other temporal artery imaging	• MR-angiography: Most MR machines typically lack resolution to image temporal artery • High-power 3-Tesla MRI, correctly protocoled, has high negative predictive value • CT-angiography: typically lacks resolution to image temporal artery • PET scanning: typically not accessible modality, uptake in vessels suggests active vasculitis (ddx atherosclerosis)
	Large vessel imaging	• Image aorta and first-order branches (usually subclavian) if high clinical suspicion LV-GCA (compatible history or extremity claudication, abnormal peripheral vascular exam, high ESR), and temporal artery tests not helpful • MR-angiogram and CT-angiogram may show circumferential vessel narrowing; MR may show circumferential vessel enhancement. Finding may be non-specific, confused with atherosclerosis

DIAGNOSIS		
Suspect GCA in patient, usually Caucasian >70 years-old, with subacute claudication in the cranial arteries (new headache, scalp tenderness, vision change, jaw claudication, abnormal temporal artery) or appendicular arteries (arm/leg claudication, faint pulses, unequal blood pressures). ESR should be elevated, usually at least >40mm/h. Treatment with steroids should be initiated promptly if high clinical suspicion, and then temporal artery testing sought. If accessible, a reliable high-quality CDUS +/- axillary arteries can be the first diagnostic test. Large vessel imaging can be done based upon clinical suspicion as indicated.		
High quality CDUS available	CDUS +	• High pre-test probability: treat empirically for GCA • Mod/low pre-test probability: temporal artery biopsy or MR-angiography to rule in or out GCA
	CDUS -	• High pre-test probability: temporal artery biopsy or MR angiography rule in or out GCA • Low pre-test probability: not GCA
High quality CDUS not available	TAB +	• Treat as GCA
	TAB -	• High pre-test probability: treat as GCA if confirmatory CDUS or MR-angiography unavailable • Moderate pre-test: shared decision to treat or monitor clinically with close serial re-assessments • Low-pretest probability: not GCA (*do not pursue a TAB if low or very low pre-test probability*)
Be wary of empiric or "diagnostic trials" of prednisone: prednisone tends to improve many headache etiologies other than GCA		

DIFFERENTIAL DIAGNOSIS CRANIAL GCA	
Rheum	• GPA, MPA, EGPA (temporal artery and other cranial involvement of an ANCA-associated vasculitis) • Polyarteritis nodosa, IgG4-RD (described) • Juvenile temporal arteritis
Heme	• Amyloidosis (amyloid deposition in temporal artery) • Non-Hodgkin lymphoma (intravascular lymphoma)
Tumour	• Local neoplasm around temporal artery • Metastases to skull, occipital condyle syndrome • Angiolymphoid hyperplasia with eosinophilia (rare benign intravascular tumour)
Infection	• Bacterial: bacterial sinusitis (headache, inflammation); infectious endocarditis (with septic emboli to eye) • Viral: varicella zoster affecting cranial arteries • Fungal: Aspergillus (invasive into sinuses) • Atypical: Syphilis (acute ischemic optic neuropathy, aortitis), nocardia (isolated ocular manifestations)
Other	• Migraines, Atherosclerosis, Neurosarcoid, Tolosa-Hunt, Calciphylaxis, CPPD, Moeckenberg's medial sclerosis
DIFFERENTIAL DIAGNOSIS "HALO SIGN" ON TEMPORAL ARTERY ULTRASOUND	
Rheum	• MPA, GPA, EGPA, PAN, juvenile temporal arteritis
Malignant	• Non-Hodgkin lymphoma
Other	• Amyloidosis, angiolymphoid hyperplasia with eosinophilia (ALHE), atherosclerosis, Migraine, infection
DIFFERENTIAL DIAGNOSIS AORTITIS	
Rheum	• Takayasu arteritis, Cogan's, Behcets, Rheumatoid vasculitis, relapsing polychondritis, IgG4 periaortitis, sarcoid, spondyloarthropathy, relapsing polychondritis. ANCA vasculitis affect aortic branches
Infectious	• Syphilis, Salmonella, Staph/strep, tuberculosis
Metabolic	• Atherosclerosis
Idiopathic	• Retroperitoneal fibrosis
Other	• Non-inflammatory aortic aneurysm due to atherosclerosis (hypertension, diabetes, etc) or collagen disorders like Marfan's and Ehlers-Danlos

CLASSIFICATION CRITERIA: 2022 ACR/EULAR

Classification criteria are not meant as diagnostic criteria to diagnose disease in a single specific patient. Classification criteria are a standardized way of recruiting a well-defined homogenous population of patients in research studies in order to ensure comparability across studies of a heterogenous disease.

Absolute requirement	Age ≥50 years at diagnosis	
Additional criteria	Morning stiffness in shoulders/neck	+2
	Sudden visual loss	+3
	Jaw or tongue claudication	+2
	New temporal headache	+2
	Scalp tenderness	+2
	Abnormal exam of temporal artery[1]	+2
Lab, imaging, biopsy criteria	Max ESR ≥50mm/hour or max CRP ≥10 mg/L[2]	+3
	Positive temporal artery biopsy or halo sign on temporal artery ultrasound	+5
	Bilateral axillary involvement[3]	+2
	FDG-PT activity throughout aorta[4]	+2

If the sum of scores ≥6, then classification criteria for GCA is met. Sensitivity 87.0%, Specificity 94.8%

1. Diminished pulse, tenderness, "cord-like" appearance
2. ESR, CRP measured before treatment for GCA
3. Luminal damage (stenosis, occlusion, aneurysm) on angiography (CT, MR, catheter-based), halo sign on ultrasound, PET uptake
4. Abnormal FDG uptake in arterial wall on PET scan

TREATMENT		

First line steroids	• Initiate steroid therapy promptly if mod-high suspicion of GCA without delay for biopsy/CDUS
	• Initial dose
	  • Prednisone 1mg/kg/day, maximum 60mg/d
	  • Methylprednisolone 500-1000mg IV daily x 3 then prednisone 1mg/kg/d if vision loss at diagnosis; Consider IV steroids, but not proven to make difference in recovery of vision loss.	

	"Traditional" steroid taper	• Prednisone 1mg/kg/day (up to 60mg/d) x 2-4 weeks, then taper 5mg weekly until 20mg/d, then taper 5mg every 2 weeks until 10mg/d, then taper daily dose by 1mg monthly until off
	"Expedited" steroid taper	• If on background tocilizumab • Prednisone 1mg/kg/day (up to 60mg/d) x 2-4 weeks, then taper 5mg weekly until 10mg/d, then taper 1mg weekly until 5mg/d, then consider tapering off completely based on disease activity
Steroid sparing	• Consider adding early if significant steroid side-effects, comorbidity (ex diabetes), or relapsing GCA • Some may start tocilizumab up front routinely for all GCA patients, though discussion on this topic is evolving	
	Tocilizumab	• Tocilizumab 162mg SC weekly • Patients on tocilizumab may taper prednisone more quickly (as above) • Tocilizumab will normalize ESR and CRP via IL6 blockade, which may make disease monitoring more difficult — solely on clinical assessment (and serial imaging for LV-GCA) • Duration: unknown, at least 12-18 months
	Methotrexate	• Methotrexate 20-25mg weekly • Steroid sparing benefits of Methotrexate in GCA are modest
Relapses	Major relapse	• Ex: new visual ischemia (diplopia, transient/permanent vision loss), limb claudication, aortitis) • May require increase prednisone to 1 mg/kg/day (≤60 mg/day)
	Minor relapse	• Ex: recurrent polymyalgia rheumatica, headache, scalp tenderness • May only require increase to most recent asymptomatic prednisone dosage
Target	• Remission: absence of clinical signs/symptoms attributable to active GCA, normalization of inflammatory markers	
LV-GCA	• Generally treated the same as Cranial GCA as above • Optimal role for repeat imaging to monitor disease is unclear; perhaps repeat CTA/MRA at 6 mo then yearly if stable • Aortic Aneurysms: if 3-5cm and enlarging with concordant ESR rise, consider increasing treatment • Limb ischemia: stabilizes/improves with steroids & collateralization; revascularization surgery rare	
Adjunctive Treatment	• Aspirin 81mg/d: conflicting evidence for stroke prevention in GCA. Consider adding if other significant risk factors or if critical/flow-limiting involvement of vertebral or carotid arteries • Osteoporosis: Vitamin D, Order BMD, consider empiric bisphosphonate therapy	
PROGNOSIS		
• Disease course variable, 1-2 years of treatment in some, chronic steroid required in others for several years • GCA does not adversely affect overall survival, perhaps except for patients with aortic aneurysm/dissection		

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