TAKAYASU ARTERITIS

BOTTOM LINE

Takayasu arteritis (TAK) is a large-vessel vasculitis affecting the aorta and its primary branches occurring more often in women <40 years-old and Asian (but all ethnicities affected). Patients usually present sub-acutely with prodromal systemic symptoms followed by arm/leg claudication and abnormal blood pressures, pulses, and bruits on exam. Other involvement including renal, mesentery, coronary or carotid arteries present with hypertension, abdominal or chest pain, and carotidynia respectively. ESR or CRP may sometimes be elevated though ultrasound or angiography is necessary to establish diagnosis. Treatment starts with steroids; steroid-sparing therapies are added, though little evidence exists to guide therapy

EPIDEMIOLOGY

- Prevalence 1-40/1,000,000 (higher prevalence reported in Japan); Annual Incidence 1-2/1,000,000
- Age 10-40 years, median age 25
- Sex F > M, (1.5:1 to 8:1)
  - Females may have more supradiaphragmatic vessel involvement, men may have more abdominal vessel involvement
- Genetics
  - HLA loci: HLA-B*52 (an HLA-B serotype more prevalent in Asian populations)
  - Non-HLA loci: SVEP1, CFL2, VPS8, chr13q2

CLINICAL MANIFESTATIONS

Presentation in the early phase is characterized by a chronic waxing/waning course dominated by nonspecific systemic symptoms leading to delayed recognition and diagnosis by months-years until the consequences of arterial compromise are evident.

CLINICAL PHENOTYPES

Clinical Phases	Early phase	• Systemic symptoms: subacute fever, arthralgias/myalgias, weight loss
	Later phase	• Vascular inflammation: vessel pain, tenderness • Fibrosis: bruits, ischemia
Angiographic clusters	Cluster 1	Abdominal predominant vascular disease • Hypertension, lower limb claudication, mesenteric ischemia, childhood onset of disease
	Cluster 2	Aortic arch predominant vascular disease • Carotidynia, stroke, upper limb claudication, lightheadedness, less treatment responsive
	Cluster 3	Focal vascular disease • Asymmetrical arterial involvement, fewer involved arteries, less likely to have arterial occlusion

SYSTEMIC MANIFESTATIONS

Systemic	• Weight loss, low-grade fever, fatigue
Head/neck, ocular	• Carotidynia (10-30%), bruits • Retinal involvement, transient visual changes or visual loss (4-8%) due to carotid involvement • Subclavian steal: subclavian stenosis proximal to origin of vertebral artery decreases posterior cerebral blood flow, especially with upper limb exercise; syncope and neuro symptoms
Extremity	• Arm claudication from subclavian involvement or leg claudication from abdominal involvement common • Unequal blood pressures, weak/asymmetric distal pulses, bruits, rarely causes digital gangrene
Cardiac	• Aortic root dilatation, aortic regurgitation and murmur • Angina due to coronary artery ostial narrowing or coronary arteritis
Respiratory	• Chest pain, dyspnea, hemoptysis, pulmonary arteritis in ~55% which can lead to pulmonary hypertension
Renal	• Renovascular hypertension from renal artery involvement
GI	• Abdominal pain, ischemic colitis; bruits
MSK	• Arthralgias/myalgias (13-41%), peripheral inflammatory arthritis and sacroiliitis is reported in up to 10-20%
Derm	• Erythema nodosum, pyoderma gangrenosum, erythema induratum and ulcerative lesions
Comorbidities	• Associations with IBD (2.6%), psoriasis, and ankylosing spondylitis

Physical exam should include 4 extremity BP, auscultation for cardiac murmurs and bruits (carotid, subclavian, renal, abdominal, femoral arteries), palpation of temporal, carotid, brachial, femoral and dorsal pedal arteries

INVESTIGATIONS		
CBC	• May show normochromic normocytic anemia of chronic inflammation as well as leukocytosis and/or thrombocytosis	
ESR/CRP	• May be elevated in active disease, though not reliably so.	
Serology	• No associated antibodies	
Imaging	• Stenotic lesions in >90% of patients; aneurysms in 25%	
	Ultrasound with colour Doppler	• Sensitivity 81%, Specificity 100% for diagnosis • May show common carotid and proximal subclavian circumferential vessel wall thickening and luminal narrowing, wall elasticity measures, calcium/plaque imaging • Limited imaging of aorta/proximal subclavian, no direct measure of inflammation, technician dependent
	MR angiogram (MRA)	• Sensitivity 92%, Specificity 92% (1.5T MRI) for diagnosis • Smoothly tapered circumferential luminal narrowing, dilation, stenosis, occlusion; vessel wall thickening, edema, or wall enhancement • Limited resolution for distal aortic branches, may not discriminate versus atherosclerotic plaque
	CT angiogram (CTA)	• Sensitivity 95%, Specificity 100% for diagnosis • Smoothly tapered circumferential luminal narrowing, dilation, stenosis, occlusion; vessel wall thickening, enhancement and "low attenuation ring" on delayed phase images. • More ability to image calcification and plaque • Limited resolution for distal aortic branches, risk from radiation and IV contrast
	^{18}FDG-PET ± CT/CTA	• Increased metabolic activity in arterial wall suggests disease activity • PET scan alone provides no information of arterial wall morphology • Atherosclerosis can cause some degree of inflammation on PET, access may be limited
Biopsy	• Not practical, rarely done, not needed for diagnosis. Tissue sometimes obtained after surgery • Lymphohistiocytic infiltration of vessel wall with activated dendritic cells, T /B lymphocytes, macrophages and multinucleated giant cells. Intimal hyperplasia, fibrosis of media and intima causing stenosis or occlusion.	

DIAGNOSIS

Suspect TAK in young patient, typically under 40 years and more often female, presenting with subacute systemic features of aortic main-branch claudication — particularly carotidynia, extremity claudication, hypertension, unequal blood pressures/pulses, anginal chest pain, and bruits. ESR or CRP may be elevated, but is not sensitive. Vessel imaging should show smooth circumferential narrowing of the aorta and major branches with wall thickening. If "aortitis" was discovered incidentally on CT, seek supportive evidence of vasculitis by imaging other regions of aorta and primary branches with MRA or CTA; carefully consider differential or comorbid atherosclerosis to explain imaging findings. Recognition and diagnosis can be delayed by months to years due to subacute presentation; often consequences of arterial disease is the first sign noticed at presentation.

DIFFERENTIAL DIAGNOSIS	
Rheum	• GCA (affects older patients, higher predilection for cranial branches of aorta) • Behcets: commonly has mucosal ulcers, skin rash, uveitis • IgG4-related disease: may IgG4-RD involving other organs (ex: retroperitoneal fibrosis, peri-aortitis) and atopy • Cogan's syndrome: typically presents with vestibuloauditory dysfunction and keratitis
Infectious	• Syphilis, Salmonella, Staph/strep, tuberculosis
Genetic	• Collagen disorders: Marfan, Ehlers-Danlos syndrome, Loeys-Dietz • Turner syndrome • Fibromuscular dysplasia
Other	• Atherosclerosis: can cause degree of vessel wall edema on MR or PET, but usually with shorter segment non-circumferential vessel wall narrowing

CLASSIFICATION CRITERIA: 2022 ACR/EULAR CRITERIA

Takayasu arteritis is a ***clinical diagnosis***. 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.

- Criteria should be applied to classify Takayasu arteritis after a diagnosis of medium or large vessel vasculitis has been made
- Alternate diagnoses mimicking vasculitis should first be excluded

Absolute Requirement	Age ≤60 years at time of diagnosis	
	Evidence of vasculitis on imaging[1]	
Additional Clinical Criteria	Female Sex	+1
	Angina or ischemic cardiac pain	+2
	Arm or leg claudication	+2
	Vascular bruit[2]	+2
	Reduce pulse in upper extremity[3]	+2
	Carotid artery abnormality[4]	+2
	Systolic blood pressure difference in arms ≥20mmHg	+1
Additional Imaging Criteria	Number of affected arteries[5] • One arterial territory • Two arterial territories • Three or more arterial territories	 +1 +2 +3
	Symmetric involvement of paired arteries[6]	+1
	Abdominal aorta involvement with renal or mesenteric involvement[7]	+3

Sum scores for 10 items, if present. Classification criteria met if total score ≥5

1. Evidence of vasculitis in the aorta or brach arteries must be confirmed by vascular imaging (ex: CTA, MRA, Ultrasound, PET)
2. Bruit detected by auscultation of large artery including aorta, carotid, subclavian, axillary, brachial, renal, or iliofemoral
3. Reduction or absence of pulse by physical exam of axiallary, brachial, or radial arteries
4. Reduction or absence of pulse of the carotid artery or tenderness of the carotid artery
5. Number of arterial territories with luminal damage (ex: stenosis, occlusion, aneurysm) detected by angiography or ultrasonography from the following 9 territories: thoracic aorta, abdominal aorta, mesenteric, left/right carotid, left/right subclavian, left or right renal arteries.
6. Bilateral luminal damage (stenosis, occlusion, or aneurysm) detected by angiography or ultrasonography involving the abdominal aorta and either the renal or mesenteric arteries
7. Luminal damage (stenosis, occlusion, aneurysm) detected by angiography or ultrasonography involving the abdominal aorta and either the renal or mesenteric arteries

TREATMENT

Little evidence exists to guide therapy. Steroids and steroid-sparing cs/b-DMARDs are typically used.
Treatment response is monitored with serial clinical assessments; repeat ESR/CRP and ultrasound or angiography may help

Steroids	Prednisone 0.5-1.0mg/kg/d for 2-4 weeks tapering with similar schedule to GCA.
Steroid sparing	Drug-free remission is uncommon; steroid sparing agents usually used • Methotrexate 20-25mg/week • Azathioprine 2mg/kg/d • Leflunomide 20mg/d • Mycophenolate mofetil 1.5-3g/d • Cyclophosphamide — reports for use is severe life/organ-threatening disease (ex: lung, retinal or stroke)
	• Advanced DMARDs: TNF-inhibitors (Infliximab), Tocilizumab, tofactinib, ustekinumab, abatacept, rituximab
Surgery	• Revascularization should be avoided during active disease; may be considered in chronic fibrotic stage • Endovascular stenting may help for short segment stenoses; open surgery with bypass grafting may be necessary for long segment and extensive disease.

PROGNOSIS

- Minority may have self-limited course; majority have progressive or relapsing disease requiring long term immunomodulation
- Morbidity substantial: 74% have decreased functional daily activities and 23% unable to work.
- Mortality:
  - US: 94-95% 10-year survival
  - South Korea: 87% 10-year survival
  - Japan: 96.5% 15-year survival

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