Giant Cell Arteritis: 2018 Review

by Anne Winkler MD & David True, DO

Giant cell arteritis is the most common large vessel vasculitis. When suspected, patients should be urgently treated.

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Abstract

Giant cell arteritis is the most common large vessel vasculitis. Classic symptoms include headaches, scalp tenderness, visual loss and muscle stiffness and pain. First line treatment is with high dose steroids but methotrexate may be of some help in decreasing steroid use. Tocilizumab has been shown to significantly decrease relapse rate and lower steroid cumulative dose.

Introduction

Giant cell arteritis (GCA) (previously called temporal arteritis) is a large vessel vasculitis usually seen in older adults over the age of 50. It is the most common vasculitis in North America and Western Europe. GCA classically targets large vessels with predominance for the aorta and its Branches.[1] Arterial inflammation may lead to vascular damage which can result in stenosis, occlusions and even aneurysms. Additionally, the arterial inflammation may lead to serious loss of function including visual loss, limb anoxia and stroke. Suspicion of giant cell arteritis is a medical emergency and patients need to be quickly diagnosed and treated to prevent irreversible consequences of vessel inflammation.

Clinical Features

Giant cell arteritis (GCA) typically occurs in individuals over the age of 50. Mean age is approximately 70.[2] GCA is 2 .5 more likely to occur in women than men with lifetime risk at 1% for women and 0.5% for men.[3] It is also more likely to occur in Northern Europe countries and those of northern Europe ancestry with incidence rate of 20 per 100 ,000. The incidence of GCA is much lower in southern Europe and Mediterranean and quite rare in patients of African and Asian descent. [4,5,6]

HLA genes that have been identified through GWAS (genome wide association studies) that are associated with the development of GCA as well as increased complications. The HLA gene most commonly associated with GCA in Caucasians is HLA Br1*04. Those with this gene are at higher risk for developing GCA and also at higher risk for complications of GCA such as visual loss and also at higher risk of resistance to glucocorticoids. [7,8,9] There are also non-HLA genes associated with GCA – including PTPN22, LRRC32, IL17A, IL33. Most of the genes that have been identified are involved in endothelial function, innate immunity system, cytokines and cytokine receptors. [10]

2GCA

The onset of GCA may be acute or insidious. Typical symptoms of giant cell arteritis (Table 1) include headaches, scalp tenderness and jaw claudication but constitutional symptoms are common including malaise, fatigue, weight loss and anorexia and low-grade fever. Eighty to 90% of individuals have symptoms involving the extracranial arteries of the aorta, including headaches and scalp tenderness and jaw claudication and visual loss. Headaches occur at least 70-80% of the time, but not universally, and are typically severe and

may be unilateral or bilateral and are usually located in the temporal area.[1] Patients usually describe the pain as sharp and burning and severe. Scalp tenderness usually presages the headaches by a few weeks. Headaches and scalp tenderness tend to occur prior to the onset of visual loss. The visual loss occurs in about 30% of patients and is permanent in about 10-15%. [11] This is considered a medical emergency and patients need to be treated with high dose prednisone or pulse solumedrol as quickly as possible. More than 50% of patients will present with polymyalgia rheumatic which is usually manifested with significant muscle and morning stiffness classically in the proximal girdle locations. Jaw claudication occurs in about 40% of patients and again is usually early finding but tongue claudication is rare. Temporal artery tenderness or bulging of the artery may occur and on physical exam one may find the artery to be nodular or indurated. Aortic arch syndrome is not common nor is lower or upper extremity claudication but may be present due to involvement of the large arteries such as the femoral or brachial arteries. Fever of unknown origin or failure to thrive is a rare but possible presentation of quite elderly patients.

Table 1. Clinical Features of Giant Cell Arteritis

FREQUENT
- Headaches
- Scalp tenderness
- Polymyalgia rheumatic
- Elevated ESR/ CRP
- Anemia

COMMON
- Ocular symptoms
- Jaw claudication
- Malaise
- Weight loss
- Anorexia

UNCOMMON
- Cerebrovascular accidents
- Myocardial infarctions
- Limb claudication
- High fever

Comorbid conditions include myocardial infarctions and patients with GCA are at 4 times more risk of MI than age matched controls.[12] Cerebrovascular accidents are usually a later phenomenon and are increased 2.5 times compared to those without GCA.[13] Other vascular conditions including aneurysms and dissections are also 2.5 times more common to happen in patients with GCA.[14]

Pathogenesis

Immunopathology is not clearly understood as yet but it appears that dendrocytes within the adventitial layer activate T cells – Th1 which produce gamma interferon and Th17 which produce IL (interleukin) 17 and Th21 which produce IL21. Interestingly, Th1 and gamma interferon (IFN) seem to persist throughout the disease process and do not decrease with steroid treatment but Th17 and IL17 does. Other major cytokines detected include IL2, IL17, IL9, IL21, gamma IFN as well as cytokines related to th17 development – il6, il1 and il23. The presence of HLA DR4-01 suggests that antigen selection and presentation play a role in the pathogenesis.[15,16,17]

Diagnosis

The diagnosis of GCA is usually suspected in patients with new onset of severe headache. Workup includes ESR and CRP measurements which are typically elevated with ESR above 50. Anemia and mildly elevated liver enzymes may also occur. Temporal artery biopsy is the gold standard for diagnosis but can be negative in 30% of patients with GCA. [18,19] Data has been shown that the temporal artery biopsy needs to be done within two weeks of starting steroids or other treatment. Skip areas are not uncommon which is why a large sample size is recommended when obtaining a temporal artery biopsy. Classic pathology finding is giant cell granuloma formation often near to a disrupted internal elastic lamina. However multinucleated cells are not required for diagnosis. Evidence of arteritis involves all three layers of the artery – adventitia, media and lamina.

Imaging studies also may be used to determine the presence of GCA. These include MRI, ultrasound, CT and pet scan.[19] These techniques have both positive and negative concerns. MRI/MR angiography is very helpful for identifying edema of the vessel wall with wide vascular areas able to be screened. This is minimally invasive but is expensive and has some contraindications (implanted medical devices, contrast allergy). Ultrasonography can assess involvement of temporal arteries and large vessels but is operator dependent and difficult to assess involvement of the thoracic aorta. CT angiography is very good at looking for large vessel involvement and is rapid and not as expensive as MRI but has limited resolution of small vessels and requires radiation. PET with flurodeoxyglucose is also good at looking at large vessels and evaluating the extent of disease in aorta and its branches it is sensitive and reproducible but is expensive and is limited in evaluating cranial vessels.

Treatment

Treatment has been classically with steroids – these were first used in 1955 and still what is recommended initially due to the quick onset of response as well as the risk of irreversible visual loss often within weeks of the onset of symptoms. Generally, 40-60 mg daily for the first month is recommended with taper not faster than 10% per week or per month. Pulse solumedrol has been used in those with impending visual loss with trials showing equivocal results. Other agents have been looked at either in small case reports or in small clinical trials but so far only tocilizumab which

has been shown to be quite effective to decrease relapses and decrease steroid use has been FDA approved for use in GCA.

Methotrexate was used in three randomized trials [20,21,22]– the first randomized controlled trial used low dose methotrexate (10mg weekly) with 21 patients with newly diagnosed disease. This failed to show a decrease in disease flare or prednisone cumulative dose. The second trial included 42 patients and did show fewer relapses (46.6% vs 83.3%) and steroid sparing effects (1302 mg less steroids in methotrexate treated group.) The third study also done with only newly diagnosed GCA was the largest (92 patients) and with higher dose of methotrexate - 15mg weekly maximum dose but no difference in relapse or median dose of steroids was seen in this trial. A meta- analysis was done suggesting methotrexate decrease relapse by 35% and second relapse by 51%. Hydroxychroloquine and azathioprine have been used by rheumatologists as steroid sparing agents Both have been studied in small group of patients with GCA and did not show any benefit.

Biologic agents including TNF blockers, abatacept, rituximab, ustekinimab, rituximab and anakinra as well as tocilizumab have been looked at in GCA. The TNF blocker trials have been unsuccessful in demonstrating efficacy in GCA.[23,24,25] A randomized controlled trial with abatacept was done with a small number of patients which included new and relapsing patients. The results showed definite improvement in relapse rate with 48% participants relapse free versus only 31% on placebo.[26] Ustekinumab was used in a very small open design study in only 14 patients – this did show marked decrease in steroid use – from 20mg to 5mg daily in patients treated with ustekinimab.[27]There was one report with IL 1 receptor inhibitor (anakinra) used in 3 patients with refractory GCA – all three treated with anakinra showed rapid improvement with a decrease in steroids as well as resolution of imaging abnormalities.[28] Rituxamab was used in 2 refractory GCA patients with some improvement in vasculitic manifestations but with limited followup.[29] Tocilizumab was studied in a fairly large randomized placebo-controlled trial.[30] This included both newly diagnosed patients as well as those with relapsing disease. There was a fixed prednisone taper either 26 or 52 weeks depending on the trial arm in the placebo group. The results in the 52-week period showed 60% of patients on weekly tocilizumab and 58% of patients on every other week dosing were relapse free while on 22% of patients on prednisone alone (either the 26 or 52-week taper) were relapse free at 52 weeks. In patients with relapsing disease at the beginning of the trial 52% on weekly TCZ and 48% on every other week TCZ were relapse free while only 7% and 14% in prednisone 26 and 52-week taper arms respectively. The cumulative dose of prednisone in the placebo arms were over 3800 mg in one year but were decreased significantly in those treated with TCZ - 1887 in weekly and 2207 in every other week.

Summary

Giant cell arteritis is the most common large vessel vasculitis - it is classically seen in patients over the age of 50 presenting with headaches, scalp tenderness and jaw claudication. When suspected patients should be treated urgently with high dose steroids until diagnosis is clearly established or ruled out. Temporal artery biopsy is still recommended in making the diagnosis although imaging studies may also be helpful where available. Steroid- sparing agents including methotrexate may be helpful to decrease cumulative doses of steroids and steroid resistant including methotrexate. Tocilizumab is the first agent to demonstrate increased remission rate in both new and relapsing patients as well as significantly total lower doses of glucocorticoids over one year in a large randomized controlled trial.

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Disclosure

AW is on the speaker's bureau for Celegene, Abbvie, Pfizer, Genentech, Regeneron, Sanofi, Bristol Meyers, Squib, and Janssen, and is involved in clinical trials for Abbvie, Amgen, Novartis, Pfizer, Biohaven, Allergan, Theranica, Electrocore, Teva, ATI, Avanir, Ionis, Lilly, Scion, TX-360, and Zosano. DT is on the speaker's bureau for Celgene, and is involved in clinical trials for Abbvie, Amgen, Novartis, Pfizer, Biohaven, Allergan, Theranica, Electrocore, Teva, ATI, Avanir, Ionis, Lilly, Scion, TX-360, and Zosano. **MM**