Chapter

Giant Cell Arteritis: From Neurologist's Perspective

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Abstract

Giant cell arteritis (GCA) is a granulomatous vasculitis affecting large- and medium-sized arteries in the elderly and potentially causes visual loss. In an elderly patient presenting with acute pain in the distribution of the external carotid artery (e.g., headache, scalp tenderness); polymyalgia rhematica; or acute/transient visual loss or diplopia; a possibility of GCA should be considered in one of the differential diagnosis. Urgent laboratory evaluation (e.g., ESR, CRP, platelet count), followed immediately by empiric high-dose corticosteroid therapy is warranted in patients suspected of having GCA. Although ultrasound techniques are sensitive for the diagnosis of GCA, TAB remains the best confirmatory test. Patients with GCA often require long durations of steroid therapy and steroid-related complications are common. Multidisciplinary care and the use of steroid-sparing regimens are warranted in case of relapse.

Keywords: Giant cell arteritis, Pathogenesis, Advances, Management

1. Introduction

Giant cell arteritis (GCA) is a granulomatous vasculitis affecting medium to large sized arteries, it most commonly involves the aorta, branches of the ophthalmic artery, and extracranial branches of the carotid arteries [1–5]. From a clinical perspective, GCA is a medical emergency because if undiagnosed and treated early, ischemic complications may cause permanent vision loss in up to 15–25% of cases [6]. Early diagnosis and initiation of treatment is essential to improve visual and systemic prognosis in patients with GCA [1, 7, 8]. The complications of GCA result from ischemic injury, systemic inflammation, and aneurysm formation and rupture. Early initiation of corticosteroids in patients with suspected GCA has been found to significantly reduce the risk of permanent visual loss in various studies [6–8]. In this review we provide a brief overview regarding the pathogenesis, clinical features, investigations and management of GCA from a Neurologist's perspective.

2. Pathophysiology

GCA is immune-mediated inflammatory vasculitis affecting the medium and large-size arteries. The immunological cascade is triggered by an unknown antigen that begins with the dendritic cell processing the antigen and presenting it to T cells via the major histocompatibility complex II interaction with the T cell

receptors [1, 2, 6, 9]. In this inflammatory cascade, there is downstream activation and differentiation of T cells to TH1 and TH17 cells, which in turn express interferon γ, a potent macrophage activator. This macrophage activation causes further release of chemokines including but not limited to IL-6 and tumor necrosis factor (TNF) alpha. A large number of inflammatory cells are recruited with production of reactive oxygen species (ROS) and matrix metalloproteinases (MMPs), which then primarily attack the internal elastic lamina of blood vessels. This mechanism damages the vessel wall leading to abnormal vascular remodeling and ultimately occlusion of the vessel lumen [10, 11].

2.1 Risk factors

GCA generally affects elderly population, with the average age of presentation being 74–76 years, and peak incidence at 80 years [3, 5, 9]. While GCA can occur in both men and women, it is more common in women. Women have an increased risk ranging from 2.3 to 2.6 times compared to men [1, 3, 9]. Additionally, It has been found to be affecting Caucasian ethnicity more especially those of Scandinavian, Nordic, or Northern-European ancestry [1, 3, 9]. Other important independent risk factors are smoking, early menopause and low body mass index [9, 12].

2.2 Clinical symptoms and examination findings

The symptoms of GCA include both systemic and ocular. New-onset headache is the most common systemic symptom and the systemic symptoms often precede the ocular manifestations. Fifty percent of patients with GCA have systemic symptoms and these include myalgias, headaches, scalp and temporal artery tenderness, jaw and rarely arm claudication, and constitutional symptoms (e.g., fever, anorexia, and weight loss) [1, 5]. Polymyalgia rheumatica (PMR) is present in approximately 50% of patients with biopsy-proven GCA [5]. The characteristic symptoms of PMR include: persistent pain for at least 1 month with episodes of aching and morning stiffness that lasts at least 30 minutes in the neck, shoulder, or pelvic girdle and an elevated ESR of at least 40 mm/h [5].

The most severe ocular manifestation of GCA is visual loss, with 50% of patients complaining of ocular involvement ranging from eye pain to amaurosis fugax. 19 Ocular involvement is more commonly seen in elderly patients compared to younger individuals, with no gender predilection [9, 13]. The ocular complaints include visual loss of varying severity, amaurosis fugax, diplopia, and eye pain [13]. Amaurosis fugax, precedes permanent vision loss in 44% of GCA patients [5]. Vision loss is usually mono-ocular to begin with and if left untreated, contralateral eye involvement commonly occurrs between 1 and 14 days after initial onset with the longest interval being 9 months [5, 13]. When treated early and adequately with corticosteroids, GCA-mediated blindness is preventable in majority of cases [9, 13].

In a case of suspected giant cell arteritis, the following clinical approach is recommended [4]:

- Palpation of the Temporal artery: Temporal artery may be tender, thickened and beaded. The pulse may be difficult to feel and patient may complain of scalp tenderness.

- The systemic examination should be directed at looking for evidence of large vessel vasculitis, that is looking for delayed or absent pulses in upper limbs, subclavian or carotid bruits, and blood pressure asymmetry in the limbs.

- Detailed ophthalmological exam is warranted – look for transient or permanent visual loss, visual field defect, relative afferent pupillary defect, anterior ischemic optic neuritis, central retinal artery occlusion.

2.3 Investigations

The following investigations are recommended in evaluation of suspected giant cell arteritis complete blood count, renal function tests, liver function tests, C-reactive Protein (CRP) and erythrocyte sedimentation rate (ESR) [1–5]. There is often evidence of an acute-phase response on blood tests. Other investigations recommended are Chest X-ray and urinalysis. Baseline (pre-treatment) markers of inflammation are also useful to assess response to treatment.

There are a number of investigations that can also be carried out to help confirm diagnosis, as outlined below.

- **Temporal artery biopsy**
  The gold standard for diagnosis of giant cell arteritis is Temporal artery biopsy (TAB). 10–20% of GCA can be biopsy negative, however a negative result does not rule out the condition [1–5]. The findings on temporal artery biopsy in GCA is characterized by inflammatory infiltration of the arterial wall by lymphocytes, macrophages and giant cells in about 50% of cases [1–5].

- **Temporal artery ultrasound (color-coded duplex sonography)**
  Color-coded duplex sonography can be utilized to examine the temporal, extracranial, occipital and subclavian arteries. An ultrasound study has a sensitivity of 85% and a specificity of more than 90% [1–4, 14]. The 'halo sign' where Inflammatory oedema of the vascular wall will be shown as hypoechoic wall thickening is characteristic.

- **Positron emission tomography**
  PET uses radioactive metabolites to visualize metabolic processes. Spatial resolution is limited with PET, so visualization can only be determined in the aorta and larger vessels. The ability to visualize the temporal arteries is limited with PET. The European League Against Rheumatism (EULAR) do not advise PET to screen the cranial vessels, however by using newer PET scanners with improved spatial resolution the temporal arteries may be better visualized in the future [15, 16].

- **High-resolution magnetic resonance imaging**
  For imaging of temporal arteries MRI is the imaging modality of choice recommended by the EULAR [16]. Detailed imaging of the walls and lumen of the temporal artery is possible by doing a High-resolution MRI (fat suppression, T1 weighted) allows. A concurrent MR angiography allows imaging of large vessels such as aorta and sub-clavian artery.

3. Diagnosis of GCA

Diagnosis of GCA is based on clinical and laboratory tests and application of the revised ACR criteria (**Table 1**) [17]. It has been suggested that in the presence of 3 points or more out of 11, with at least 1 point belonging to Domain 1, the diagnosis of GCA can be established.

SCORE	
N/A	Age at onset ≥50 years old Absence of exclusion criteria[b]
DOMAIN I	
1	New onset localized headache[c]
1	Sudden onset of visual disturbances[c]
2	Polymyalgia Rheumatica
1	Jaw Claudication[c]
2	Abnormal temporal artery[d] up to 2 points
DOMAIN II	
1	Unexplained fever and/or anemia 1 point
1	ESR ≥50 mm/hour[e] 1p
2	Compatible pathology[f] up to 2 points

[a]In the presence of 3 points or more out of 11 with at least one point belonging to domain I along with all entry criteria, the diagnosis of Giant cell arteritis can be established.
[b]Exclusion criteria are including: ENT and eye inflammation, kidney, skin and peripheral nervous system involvement, lung infiltration, lymphadenopathies, stiff neck and digital gangrene or ulceration.
[c]No other aetiologies can better explain any one of the criteria.
[d]-Enlarged and/or pulseless temporal artery: 1 point/tender temporal artery: 1 point.
[e]It must be ignored in the presence of PMR.
[f]Vascular and/or perivascular fibrinoid necrosis along with leucocyte infiltration: 1 point and granuloma: 1 point.

Table 1.
Revised ACR criteria (rACR) for diagnosis of GCA[a] [17].

4. Treatment

4.1 Corticosteroids

Initiation of prompt corticosteroid treatment is recommended [1–5]. In cases where there is a clinical suspicion of giant cell arteritis, corticosteroid treatment should be initiated immediately and not delayed awaiting results of blood tests or temporal artery biopsy.

In cases of complicated giant cell arteritis, that is when there is evolving visual loss or amaurosis fugax: Intravenous methylprednisolone in a dosage of 500 mg–1 g IV for three days followed by corticosteroid dose is advised.

A corticosteroid tapering regimen is suggested below [18]:

- Start with prednisolone 40–60 mg daily continue for at least three to four weeks until clinical symptoms and laboratory abnormalities begin to resolve
- Subsequently reduce the dose by 10 mg every two weeks to 20 mg daily, followed by further reduction of dose by 2.5 mg every two to four weeks to 10 mg daily
- Subsequently it is recommended to reduce the dose by 1 mg every one to two months, provided the condition does not relapse again.

Corticosteroids can generally be reduced when the clinical features of active disease are absent and when the laboratory markers for acute inflammation such as ESR, C-reactive protein are normalized.

4.2 Aspirin

The usage of Aspirin is controversial; albeit it remains in the recommendations [18], when not contraindicated. Aspirin has been found to be protective against

cerebrovascular and cardiovascular events in previous studies [19]. Apart from its antiplatelet effects and Aspirin also has disease-modifying effects through suppression of interferon (IFN) gamma [18, 19].

4.3 Management of relapse

All patients with suspected relapse should be referred to, or have their treatment discussed with, a specialist [1–5, 18, 19]. In case of relapse, a rise in inflammatory markers (ESR/CRP) is usually seen, however these markers can remain normal in some cases. In case of recurrence of headache, the patient should revert to the previous higher corticosteroid dosage. In case of jaw claudication, a prednisolone dosage of 60 mg daily is recommended. Ocular symptoms need prednisolone 60 mg daily orally or intravenous pulse methylprednisolone 1 g and immediate opthalmology consultation.

4.4 Management of Recurrent relapse

Despite an initial good response to therapy, about 30–50% of patients will suffer a relapse, within the next two years [1–5, 18–20]. The use of secondary agents such as methotrexate (or others such as azathioprine in patients, who are intolerant to methotrexate) should be considered in patients with recurrent relapse or failure. Various clinical trials have shown that Methotrexate (7.5–15 mg once a week) reduces the relapse rate and overall duration of exposure to corticosteroids [20].

4.5 Tocilizumab

Tocilizumab is an interleukin-6 (IL-6)-receptor inhibitor. The Giant Cell Arteritis Actemra (GiACTA) trial demonstrated increased rates of sustained remission using a combination of tocilizumab plus corticosteroids compared with those treated with corticosteroids alone [21]. Furthermore, steroid-induced adverse effects were reduced with the usage of tocilizumab for treatment.

Tocilizumab is recommended by NICE as an option for treating GCA in adults, in case they have relapsing, or refractory disease and they have not already taken tocilizumab; it is stopped after one year of uninterrupted treatment at most [20].

Tocilizumab is a potent suppressor of IL-6, which is important producer of CRP. Therefore, patients on tocilizumab may not produce a biochemical inflammatory response in the setting of infection/inflammation. Caution should be taken while taking Tocilizumab, particularly in patients with a history of diverticulitis, as it carries a risk for gastrointestinal perforation [22].

5. Conclusion

In an elderly patient presenting with acute pain in the distribution of the external carotid artery (e.g., headache, scalp tenderness); PMR; or acute/transient visual loss or diplopia; a possibility of GCA should be considered in one of the differential diagnosis. Urgent laboratory evaluation (e.g., ESR, CRP, platelet count), followed immediately by empiric high-dose corticosteroid therapy is warranted in patients suspected of having GCA. Although ultrasound techniques are sensitive for the diagnosis of GCA, TAB remains the best confirmatory test. Patients with GCA often require long durations of steroid therapy and steroid-related complications are common. Multidisciplinary care and the use of steroid-sparing regimens is warranted in case of relapse.

Disclosure

The authors report no conflicts of interest in this work.

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