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**Review**
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# Giant Cell Arteritis

***E. V. Shevchenko*** ✉ ***, A.M. Izmailova, E.A. Kovaleva, G.R. Ramazanov***

**Scientific Department of Emergency Neurology and Rehabilitation Treatment**
**N.V. Sklifosovsky Research Institute for Emergency Medicine**
**Bolshaya Sukharevskaya Sq. 3, Moscow, Russian Federation 129090**

✉ **Contacts:** Evgeny V. Shevchenko, Candidate of Medical Sciences, Head of the Neurological Department for Patients with Acute Cerebrovascular Accidents, Senior Researcher, Scientific Department of Emergency Neurology and Rehabilitation Treatment, NV Sklifosovsky Research Institute for Emergency Medicine. Email: shevchenkoev@sklif.mos.ru

**ABSTRACT** Giant cell arteritis is a disease characterized by granulomatous inflammation of large and medium-sized arteries. The aorta and its large branches are most susceptible to pathological changes in this arteritis. The course of giant cell arteritis is often complicated by ischemia in the blood supply basin of the artery involved in the pathological process. Variants of such complications may be ischemic optic neuropathy and retinopathy, limb ischemia, and acute cerebrovascular accident. This review presents current data on the etiology and pathogenesis of giant cell arteritis, prevalence, sensitivity, and specificity of clinical and instrumental signs of this disease, as well as practical recommendations for various treatment methods during exacerbation and remission.

**Keywords:** giant cell arteritis, Horton's disease, temporal arteritis, non-atherosclerotic vasculopathy, vasculitis
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**Affiliations**

| | |
|---|---|
| Evgeny V. Shevchenko | Candidate of Medical Sciences, Head of the Neurological Department for Patients with Acute Cerebrovascular Accidents, Senior Researcher of the Scientific Department of Emergency Neurology and Rehabilitation Treatment, NV Sklifosovsky Research Institute for Emergency Medicine;<br>https://orcid.org/0000-0001-9750-3509, shevchenkoev@sklif.mos.ru;<br>27%, search and analysis of literature data, formation of text material, editing of manuscript |
| Aza M. Izmailova | Junior Researcher, Department of Emergency Neurology and Rehabilitation, NV Sklifosovsky Research Institute for Emergency Medicine;<br>https://orcid.org/0000-0002-5979-5667, izmailovaam@sklif.mos.ru;<br>26%, search and analysis of literature data, formation of text material |
| Ella A. Kovaleva | Candidate of Medical Sciences, Senior Lecturer, Educational Department, Senior Researcher, Scientific Department of Emergency Neurology and Rehabilitation Treatment, NV Sklifosovsky Research Institute for Emergency Medicine;<br>https://orcid.org/0000-0002-8490-1417, kovalevaea@sklif.mos.ru;<br>24%, search and analysis of literature data, formation of text material |
| Ganipa R. Ramazanov | Candidate of Medical Sciences, Deputy Director, Head of the Regional Vascular Center, NV Sklifosovsky Research Institute for Emergency Medicine, Head of the Scientific Department of Emergency Neurology and Rehabilitation Treatment;<br>https://orcid.org/0000-0001-6824-4114, ramasanovgr@sklif.mos.ru;<br>23%, concept, manuscript revision, critical content review, final manuscript approval |

ACR - American College of Rheumatology
CT - computed tomography
DS - duplex scanning
ESR - erythrocyte sedimentation rate
FDG - fluorodeoxyglucose
GCA - giant cell arteritis
GCS - glucocorticosteroids
IL - interleukin
PET - positron emission tomography
TLR - Toll-like receptors

## INTRODUCTION

Giant cell arteritis (GCA) is a disease characterized by granulomatous inflammation of large and medium-sized arteries [1]. The aorta and its large branches are most susceptible to pathological changes in GCA [2]. However, the characteristic and frequently encountered clinical manifestations of GCA, headache and visual impairment, are caused by inflammation of the branches of the external carotid

and internal carotid arteries [3]. The course of GCA is often complicated by ischemia in the blood supply basin of the artery involved in the pathological process. Variants of such complications may include ischemic optic neuropathy and retinopathy, limb ischemia, as well as acute cerebrovascular accident [4, 5].

The disease was first described by *B. Horton* in 1932 using two patients with previously unknown arteritis of the temporal arteries as an example. He also wrote the first histopathological description of GCA. One of the modern names of this arteritis contains the name of its discoverer – Horton's disease [6].

The incidence of GCA is highest among patients over 50 years of age and peaks in the eighth decade of life [7–9]. The geographic distribution of GCA incidence is characterized by a gradient from the highest in northern European countries and the northern territories of the United States of America to the lowest in Arab and African countries, as well as in Asia. The number of women among those affected exceeds the number of men 2-fold [7, 8].

## PATHOGENESIS

Giant cell arteritis is a non-infectious vasculitis of medium and large diameter arteries (more than 2000 μm). A distinctive feature of this type of arteries, in contrast to small diameter arteries, is the presence of dendritic cells between the middle and outer layers of the vessel [10, 11]. This population of histiocytes plays a key role in the pathogenesis of GCA. On the surface of dendritic cells are located Toll-like receptors (TLR), which bind microbial antigens and proteins formed during damage to the patient's cells. The latter can both initiate and maintain a non-infectious inflammatory response, releasing new TLR ligand proteins and reactivating dendritic cells [12]. It is assumed that proteins serving as ligands for TLR (both microbial antigens and products of the patient's cell decay) can originate from any tissue in the body and enter the dendritic cells of the arteries through *the vasa vasorum* [13]. The composition of the TLR (of which there are more than 10 types) and their distribution in different arteries are not the same, which served as the basis for a hypothesis explaining the regular involvement of certain arteries in the process in GCA [14].

Dendritic cells activated through the TLR migrate to the media of the artery and produce chemokines, which in turn leads to the migration of macrophages and *T*-lymphocytes from the bloodstream into the vascular wall and their activation. The subsequent inflammatory cascade promotes the formation of a granulomatous infiltrate pathognomonic of GCA [10]. Activated macrophages produce interleukins (IL) 1 and 6, maintaining the inflammatory response, and also secrete molecules that lead to damage of the arterial wall and angiogenic growth factors that promote its thickening and narrowing of the arterial lumen [13, 15]. Typical granulomas in GCA consist of *T* -lymphocytes and histiocytes, represented by macrophages and, in 75% of cases, multinucleated giant cells, a fusion product of activated macrophages [10, 16, 17]. Narrowing of the arterial lumen is the cause of ischemic complications in GCA [4].

*T*-lymphocytes play an important role in the development of local and systemic inflammatory response. The action of IL 1, 6 and 23 leads to the differentiation of naive T-lymphocytes into two subpopulations: *T*-helpers 1 and 17. The latter produce IL 17, 21, and 22 and chemokine ligand 20, directly or indirectly contributing to systemic manifestations of the disease [10, 18]. After treatment with glucocorticosteroids (GCS), the number of *T*-helpers 17 and their cytokines decreases [19]. *T*-helpers 1 also synthesize a proinflammatory agent, interferon gamma [11].

Reports on the influence of infection on the development of GCA are contradictory. There is evidence of an increase in the level of interferon gamma years before the onset of GCA, which suggests the role of infection as the last link in the development of the disease in a patient with an altered status of the protective (specific and nonspecific) systems [11, 20].

## CLINICAL MANIFESTATIONS AND COMPLICATIONS

The most common group of GCA symptoms are those related to cranial artery involvement. Newly occurring temporal headache is the most common

symptom in this category, and intermittent jaw claudication is the most specific symptom [21].

The occurrence of a new headache or a change in the nature of a previously existing headache in a patient over 50 years of age is a reason for examination with suspicion of temporal arteritis. However, despite the fact that headache is experienced by 68–76% of patients with GCA, only 33% of patients have this symptom at the onset of the disease [21, 22]. The probability of the presence of GCA in a patient with headache in general and temporal headache in particular, according to a meta-analysis involving more than 14 thousand patients, was low (1.33, 95% CI [1.19–1.48] and 0.97, 95% CI [0.82–1.14], respectively) [22]. In this regard, this symptom should be considered in combination with other manifestations of GCA.

Headache in patients with GCA occurs acutely or subacutely and may be associated with skin tenderness in the area of blood supply of the temporal and/or occipital arteries [21]. The headache pattern is nonspecific: moderate or intense, constant or intermittent, it may imitate tension-type headache, migraine or even cluster headache. An additional diagnostic sign may be a significant regression of pain after the start of GCS therapy [23]. Palpation of the temporal artery may reveal its, often uneven, compaction, tenderness and lack of pulsation [21, 24, 25].

Inflammation of the maxillary and facial arteries leads to intermittent "claudication" of the lower jaw, pain and fatigue in the facial and masticatory muscles during prolonged work, decreasing after rest. This symptom occurs in 34-41% of patients with GCA and has a high specificity (up to 94%). Unlike pain in arthropathy of the temporomandibular joint, pain in GCA occurs after a latent period of intense chewing movements and is localized in the masticatory muscles, and not in the area of the corresponding joint. With arteritis of another branch of the external carotid artery, the lingual artery, pain and transient weakness of the muscles of the tongue occur [22, 26].

Ophthalmic symptoms are one of the most specific manifestations of GCA [22]. These include: blurred vision, transient (*amaurosis fugax*) or permanent blindness, diplopia [21, 27, 28]. The cause of this group of symptoms is ischemia in the territory of the blood supply of the anterior and posterior ciliary arteries, the cilioretinal artery, the central retinal artery and the branches of the ophthalmic artery that supply the muscles of the eye and the soft tissues of the orbit. In addition, visual disturbances can be a consequence of inflammation of the arteries of the posterior basin of the blood supply to the brain [29].

The frequency of visual symptoms varies considerably in different studies: from 10% to 70%. Loss of vision is the most common ophthalmic symptom: *amaurosis fugax* occurs in 31%, while diplopia occurs in only 6% of patients. Irreversible loss of vision develops in every fifth patient with ophthalmic symptoms [30]. In 8% of patients, visual symptoms may be accompanied by pain in the eye area. Simultaneous bilateral visual impairment has been described in clinical observations, however, it should be noted that changes in the examination of the fundus reveal different duration of ischemia and damage to one eye may proceed unnoticed by the patient until acute loss of vision in the other eye [28].

The combination of *amaurosis fugax* and intermittent "claudication" of the lower jaw are the symptoms most often associated with subsequent permanent vision loss, whereas systemic manifestations at the onset of the disease, on the contrary, are associated with a lower risk of irreversible blindness [27, 31, 32].

General symptoms such as malaise, weight loss, subfebrile fever, night sweats, myalgia are observed in 36–84% of patients [22]. Rheumatic polymyalgia, characterized by pain and stiffness mainly in the muscles of the neck, shoulders and hips, accompanies the course of GCA in 40–60% of patients and vice versa: 16–21% of patients with rheumatic polymyalgia develop GCA [33].

Acute cerebral ischemia is an uncommon but most severe complication of GCA [9, 34]. The incidence of stroke in the first 4 weeks after the onset of the disease or exacerbation is 2.4–7% [35–37]. The vertebrobasilar system is the most common

localization of ischemia in GCA — 88% of cases [35, 36]. Factors associated with the development of stroke in patients with GCA include vision loss, smoking, arterial hypertension, and high hemoglobin levels [36].

Symptoms of vasculitis of the arteries of the upper and lower extremities, pulse deficit, Raynaud's syndrome, intermittent claudication, trophic disorders are detected in 3-16% of patients with GCA. Proximal arteries of the extremities are more often involved in the pathological process than distal ones, while inflammatory changes in the aorta are detected in 69% of patients with GCA [38]. In 6-16% of patients with vasculitis of the arteries of the extremities, gangrene occurs, requiring amputation at one level or another [39].

Rare complications of GCA include ischemic lesions of the tongue, lips, and scalp. The latter is an unfavorable prognostic sign associated with a high mortality rate of up to 38%. Cutaneous manifestations of GCA include paniculitis, nodules, and elements resembling erythema nodosum [40].

Aortic aneurysm may be a complication of GCA, occurring in the late stages of the disease, sometimes after a long clinical remission. The risk of aneurysm formation increases with the duration of the disease and may be 17 times higher than that in the population [41, 42]. Hyperlipidemia and coronary atherosclerosis are risk factors for both aortic aneurysm formation and its dissection in GCA [43].

## DIAGNOSIS OF THE DISEASE

The diagnosis of GCA is a combination of clinical and laboratory data, supported by radiological diagnostic methods and histological examination.

In 1990, the American College of Rheumatology (ACR) published diagnostic criteria for GCA, which included the following five items: 1. Age at onset of at least 50 years; 2. New onset of headache or new location of headache; 3. Tenderness or decreased pulse in the temporal artery; 4. Erythrocyte sedimentation rate (ESR) of at least 50 mm/h (Westergren method); and 5. Histologic evidence of vasculitis characterized by infiltration predominantly by mononuclear cells or granulomatous inflammation involving multinucleated giant cells. The diagnosis of GCA was established if the clinical picture met at least three of these five listed criteria [44].

The sensitivity and specificity of the 1990 GCA diagnostic criteria can reach 93.5 and 91.2% [45]. However, there are also alternative data with a diagnostic accuracy of only 51% if the diagnosis was established without biopsy and 73% if histological examination was performed [46].

In 2016, the diagnostic criteria for ACR were revised to include an expanded panel of clinical features (Table 1) [47].

*Table 1*

**American College of Rheumatology 2016 Diagnostic Criteria for Giant Cell Arteritis**

| | |
|---|---|
| MANDATORY CRITERIA | |
| Age of onset of the disease is not less than 50 years | |
| No exclusion criteria 1 | |
| CRITERIA GROUP I | |
| New onset localized headache | 1 point |
| Sudden onset of visual disturbances | 1 point |
| Polymyalgia rheumatica | 2 points |
| "Limping" of the jaw | 1 point |
| Objective changes in the temporal artery 2 | 2 points |
| CRITERIA GROUP II | |
| Unexplained fever and/or anemia | 1 point |
| Erythrocyte sedimentation rate is not less than 50 mm/hour | 1 point |
| Corresponding histological changes 3 | 2 points |

Notes: [1] - inflammation of the ENT organs and organs of vision, damage to the kidneys, skin and peripheral nervous system, infiltrative changes in the lungs, lymphadenopathy, stiff neck, gangrene or ulceration of the fingers; [2] — thickening of the temporal artery or absence of pulsation (1 point), pain on palpation of the temporal artery (1 point); [3] — vascular and/or perivascular fibrinoid necrosis with leukocyte infiltration (1 point) and granulomas (1 point). The diagnosis of giant cell arteritis requires a score of at least 3 and the presence of at least one criterion of the two mandatory ones

In 2022, the ACR and the European League Against Rheumatism developed classification criteria for GCA taking into account ultrasound diagnostic methods and positron emission tomography (PET) (Table 2) [25].

*Table 2*

**American College of Rheumatology / European Antirheumatic League classification criteria for giant cell arteritis, 2022**

| | |
|---|---|
| MANDATORY CRITERION | |
| Age of onset of the disease is not less than 50 years | |
| ADDITIONAL CLINICAL CRITERIA | |
| Morning stiffness of shoulders and neck | +2 |
| Sudden loss of vision | +3 |
| "Limping" of the jaw or tongue | +2 |
| New onset headache | +2 |
| Scalp soreness | +2 |
| Objective changes in the temporal artery | +2 |
| VISUALIZATION, LABORATORY AND HISTOLOGICAL CRITERIA | |
| The highest ESR is not less than 50 mm/hour or the content of C- reactive protein in the blood is not less than 10 mg/l | +3 |
| Positive temporal artery biopsy or temporal artery halo sign on duplex scanning | +5 |
| Bilateral changes in axillary arteries | +2 |
| Aortic accumulation of fluorodeoxyglucose (18F) on PET/CT | +2 |

Notes: Notes: GCA classification criteria are applicable when vasculitis of medium and large arteries is established and alternative causes of symptoms are excluded. The total score should be at least 6. CT - computed tomography; ESR - erythrocyte sedimentation rate; PET - positron emission tomography

Histological examination of temporal artery biopsy has been called the "gold standard" in many studies (as opposed to studies in which the consensus opinion of experts in clinical assessment was the gold standard). The sensitivity of biopsy for GCA varies across studies. In a meta-analysis by *Rubenstein E. et al*. (2020) involving more than 3,000 patients, the sensitivity of the method was 77%. However, it was found that the sensitivity was significantly lower in studies performed after 2012. The authors interpret this result as an increasing consensus among experts in establishing GCA without histological confirmation [48]. It should be borne in mind that the sensitivity of histological examination after the start of GCS therapy decreases to 20% [49].

Duplex scanning (DS) is an accessible and noninvasive method for diagnosing GCA [25]. A non-compressible “halo” surrounding the artery and thickening of the intima-media complex are sonographic signs of GCA.

The halo symptom is a hypo- or anechoic area surrounding the lumen of the vessel, a sign of arterial wall edema. The sensitivity and specificity of this symptom are 55–69% and 82–94%, respectively [50]. Expanding the scope of diagnostics by adding a large artery (e.g., carotid, subclavian, or axillary) to the temporal artery had higher sensitivity and specificity — 86% and 96%, respectively [51]. It should be noted that despite clinical and laboratory remission, the halo symptom may persist for more than 6 months [52].

Another method of radiological diagnostics regulated by the criteria of GCA is PET computed tomography (CT) with fluorodeoxyglucose (*18F*) (FDG). The examination includes the aorta and extracranial parts of the brachiocephalic arteries. In GCA, homogeneous segmental FDG uptake is detected, exceeding the uptake by the liver. Persistent FDG uptake is observed in many patients with GCA, despite clinical remission. In this regard, FDG-PET/CT is not suitable for monitoring disease activity [53].

Computed tomography and magnetic resonance imaging are currently not included in the diagnostic criteria for GCA, but these methods, as well as DS and PET/CT, have the ability to detect signs of vasculitis.

CT angiography of the brachiocephalic arteries can reveal “blurred” edges of the walls of the superficial temporal artery, a symptom reminiscent of cigar smoke. The sensitivity and specificity of this sign are comparable to DS — 71% and 88%, respectively [54]. Narrowing of the lumen of the branches of the external carotid artery is a sign that does not have high specificity; however, in the absence of stenotic atherosclerosis of the brachiocephalic arteries, it can be an important addition to the clinical picture of the disease (Figure) [55]. Circular thickening of the aortic wall by more than 3 mm on native CT is detected in more than half of patients with arteritis of the extremities. In addition, CT angiography can detect a complication of GCA — aortic aneurysm [38].

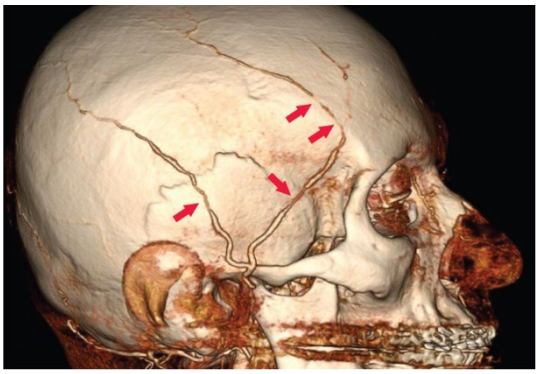

Figure. Computed tomographic angiography of the right superficial temporal artery and its branches in a patient with the onset of giant cell arteritis. Areas of the most pronounced narrowing of the lumen of the branches of the superficial temporal artery (indicated by arrows)

Contrast-enhanced magnetic resonance imaging with T1-weighted images (T1WI) with high spatial resolution reveals accumulation of contrast agent in the vessel wall in GCA [56, 57]. The central bright spot sign - an area of contrast agent accumulation in the center of the anterior optic nerve on T1WI, was detected in 100% of patients with GCA complicated by ischemic optic neuropathy before it, and was not detected in healthy volunteers in a small study *by Remond P. et al*. (2017) [58].

### TREATMENT

Glucocorticosteroids are currently the mainstay of pathogenetic treatment of GCA and should be prescribed as soon as possible. There are two clinical situations requiring the choice of the GCS dosage regimen: GCA with acute visual loss (including *amaurosis fugax* ) and uncomplicated GCA [40, 59]. According to the recommendations of the European League Against Rheumatism, patients with ophthalmic symptoms require intravenous methylprednisolone at a dose of 250-1000 mg per day for 3 days, followed by a transition to oral prednisolone at a daily dose of 40-60 mg for 4 weeks. Then it is recommended to reach a daily dose of 15-20 mg within 2-3 months and maintain it until the end of the year from the onset of the disease or exacerbation. After one year of therapy, continue taking no more than 5 mg of prednisolone per day. Treatment of uncomplicated GCA involves prescribing 40–60 mg of prednisolone for the first month, followed by tapering as described above [60–62].

The use of antiplatelet therapy in routine practice for the treatment of GCA is not recommended unless required by concomitant diseases (secondary prevention of ischemic stroke and myocardial infarction). In some situations, for example, with the development of ischemic complications or a high risk of cardiovascular or cerebral events, the decision to prescribe an antiplatelet agent should be made individually [60, 62].

The use of the IL-6 blocker tocilizumab for the treatment of GCA in clinical practice has been approved in a number of countries, but is currently an *off-label indication* in the Russian Federation. There is evidence of the high efficacy of tocilizumab in terms of both the incidence of persistent remission and the reduction of the cumulative dose of prednisolone [40, 61, 62].

## CONCLUSION

Awareness of the symptoms of giant cell arteritis and understanding of diagnostic approaches are important for physicians of various specialties such as therapists, rheumatologists, ophthalmologists, neurologists, vascular surgeons and radiologists. The use of modern diagnostic criteria for giant cell arteritis in combination with additional research methods available in a multidisciplinary hospital - duplex scanning, computed tomography, magnetic resonance imaging, will increase the detection of this disease. When diagnosing giant cell arteritis, timely pathogenetic therapy, choice of dosage regimen and the ability to adjust the dose of the drug during the course of treatment are required.

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