

# Stroke secondary to giant-cell arteritis: A literature review

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**Abstract.** Stroke is a leading cause of death and disability worldwide. In addition to the classical etiologies of stroke as atherosclerosis and cardioembolism there are many unusual, rare causes, which require a high level of clinical suspicion and further investigations for correct and early diagnosis and adequate treatment. Giant-cell arteritis or temporal arteritis, the most frequent vasculitis in the elderly population is one of the uncommon causes of stroke. In the setting of giant-cell arteritis, stroke more likely affects the vertebrobasilar territory and is the main cause of mortality. Duplex ultrasound examination is a routine investigation for stroke patients and may be key to the diagnosis if the classical hypoechoic 'halo sign' is recognized at the level of vertebral arteries. In this situation the ultrasound evaluation of temporal arteries and temporal artery biopsy are mandatory. The Giant-cell arteritis-related stroke is a rare condition; therefore, there are no evidence-based guidelines or standard recommendations for the treatment. In the present review, the main characteristics of giant-cell arteritis-related stroke are discussed.

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## 1. Introduction

Giant-cell arteritis (GCA) or temporal arteritis and Takayasu's arteritis are the main known examples of large-vessel vasculitis (1). GCA is the most common form of systemic vasculitis and affects both medium and large vessels, including mainly the aorta and its major subdivisions, especially the branches of the carotid arteries. GCA appears almost exclusively after the age of 50 years and its incidence increases constantly with advancing age, reaching a peak between 70 and 80 years. The lifetime risk of developing GCA was estimated at 1% in women and 0.5% in men (1,2).

Although permanent vision loss is considered to be the most feared complication of GCA, the main factors responsible for mortality in this pathology are cerebral ischemia and aortic aneurysms and dissections (3-5).

GCA is a rare cause of stroke, but it is difficult to differentiate from other, more common etiologies, such as atherosclerosis because their characteristics and risk factors are similar (6).

There are several publications in the literature, mainly small case series reporting stroke cases secondary to GCA, but there are few population-based studies, using various methodologies, making their results fairly heterogeneous (7).

Temporal artery biopsy is considered the gold-standard for the diagnosis of GCA, revealing necrotizing arteritis with a predominance of mononuclear cell infiltrations or granulomatosis with multinucleated giant cells. The classification of GCA developed by the American College of Rheumatology in 1990 includes five criteria: Age of 50 years or older, new-onset headache, temporal artery tenderness or decreased pulsation, erythrocyte sedimentation rate of at least 50 and abnormal temporal artery biopsy results. If at

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**Abbreviations:** GCA, giant-cell arteritis; HLA, human leukocyte antigen; DCs, dendritic cells; TLRs, toll-like receptors; CD, cluster of differentiation; MHC, major histocompatibility complex; Th, T-helper; IL, interleukin; IFN, interferon; VSMCs, vascular smooth muscle cells; ECs, endothelial cells; MMPs, matrix metalloproteinases; IEL, internal elastic lamina; VB, vertebrobasilar; MRI, magnetic resonance imaging; ICA, internal carotid arteries; VWE, vessel wall enhancement

**Key words:** giant-cell arteritis, temporal arteritis, stroke, ultrasound, halo sign

least three of these five criteria are present in a single case, the diagnosis can be made with a sensitivity of 93.5% and a specificity of 91.2% (8).

In the last few years duplex ultrasound has become an important tool for the diagnosis of temporal arteritis. The presence of a non-compressible, hypoechoic, mostly concentric arterial wall thickening referred to as the 'halo' sign is easily detectable with ultrasonography (9). The 'halo sign' is evidenced, not only at the level of the temporal arteries, but also at the level of the vertebral arteries and, in rare cases, at the level of the carotid arteries too. Sometimes in stroke patients, the accidentally detected halo sign at the level of the vertebral arteries during a routine cervical ultrasound examination may be the first clue for GCA (10).

The aim of the present review was to summarise the relevant literature of temporal arteritis-related stroke. A database search was performed with the following terms: 'Stroke', 'temporal arteritis' and 'giant cell arteritis'. The majority of the relevant articles were found in PubMed. In addition, we also performed screening of Embase, CINAHL (EBSCO) and Cochrane Library databases. Articles with unavailable full text were excluded from the analysis.

Searches were limited to articles written in English.

## 2. Epidemiology

The majority of relevant studies proved that, GCA-related stroke mostly occurs between the onset of arteritis symptoms and one month after the initiation of steroid therapy (11).

Gonzalez-Gay *et al* retrospectively analysed the data of a large series of biopsy-proven GCA patients over a 27-year period of time (12). In total, 287 patients fulfilled the inclusion criteria and 2.8% of these patients experienced stroke between onset of the symptoms and four weeks after the initiation of steroid therapy. The frequency of stroke was significantly higher in male patients, and the best predictors of stroke were permanent vision loss and a history of hypertension prior to the diagnosis of GCA. Furthermore, anaemia at the time of diagnosis was associated with protection against stroke (12).

Samson *et al* conducted a population-based study to evaluate the epidemiology of stroke patients with GCA using two prospective databases (13). They found that 7% of 57 biopsy-proven patients developed stroke. The authors explained this higher incidence relative to that of a previously reported study (12) was the consequence of their population-based search design, which allowed the inclusion both of hospitalised and non-hospitalised patients (13). In addition, they found that the main risk factors for stroke were male sex, history of vision loss, smoking, hypertension and high haemoglobin level.

Authors de Boysson *et al* conducted a retrospective multicentre case-control study using data from four GCA referral centres (14). The incidence of GCA-related stroke ranged from 3 to 7%, which is consistent with the findings of other authors in different geographical regions, such as Salvarani *et al*, with a rate of 2.7% in 180 GCA patients (11); Zenone and Puget, who reported a rate of 6.1% in 98 patients (15); and Nesher *et al*, who reported a rate of 7.4% in 175 patients (16).

The first systematic review and meta-analysis of cohort studies focused on the risk of stroke in GCA was published by Ungprasert *et al* (7). Those authors demonstrated a significant (1.4-fold) increase of risk of stroke in GCA cases compared with non-GCA cases (7).

## 3. Pathogenesis

Numerous studies investigated the genetic susceptibility in GCA, and they found a correlation with certain human leukocyte antigen (HLA) alleles, mainly the HLA-DRB1\*0401 and DRB1\*0404 haplotypes (17). Several non-HLA genetic loci have also been associated with genetic susceptibility to GCA, underscoring the polygenic nature of the genetic background (17).

The first step of autoimmune vascular damage is the activation of indigenous dendritic cells (DCs) in the vessel wall by an unknown trigger (e.g., environmental infectious agent, autoantigen) (18). Then, the activated DCs are enabled to present antigens, leading to the activation of cluster of differentiation (CD)4<sup>+</sup> T-lymphocytes through major histocompatibility complex (MHC) class II expression and costimulatory molecules (CD80 and CD86). DCs can control which vessels are affected as different arteries express variable combinations of Toll-like receptors (TLRs). TLRs are transmembrane proteins that play important roles in the innate immune system. They recognize molecules shared by microorganisms, danger or pathogen-associated molecular patterns released from damaged tissue (19).

After T-cell activation, CD4<sup>+</sup> T cells and macrophages infiltrate the media and secrete proinflammatory cytokines, leading to further T-cell differentiation: T-helper (Th) 1 and Th-17 cells. Interleukin (IL)-12 and IL-18 promote Th1 differentiation and the production of interferon (IFN)- $\gamma$ , which has an important role in macrophage activation and granuloma formation. Additionally, IL-6, IL-1 $\beta$ , IL-21 and IL-23 stimulate Th-17 differentiation, resulting in the expression of IL-17A (19), a proinflammatory cytokine, which has a pleiotropic effect on macrophages, vascular smooth muscle cells (VSMCs), endothelial cells (ECs) and fibroblasts as well (20,21).

Macrophages have an important role in the vasculitic process; thus, multinucleated giant cells and granulomatous infiltration are pathognomonic features in GCA-related vascular lesions. The T cells and macrophages infiltrate the arterial wall through the vasa vasorum. M1-phenotype macrophages secrete proinflammatory cytokines (IL-1, IL-6) and matrix metalloproteinases (MMPs), leading to degradation of the extracellular matrix. The increased proteolytic activity secondary to the expression of MMP-2 and MMP-9 leads to disruption of the internal elastic lamina (IEL), which is the pathological hallmark of GCA. Macrophages also produce reactive oxygen species, leading to VSMCs and EC damage (17). Additionally, M2-phenotype macrophages secrete different growth factors (e.g., vascular endothelial growth factor, platelet-derived growth factor and fibroblast growth factor), leading to myofibroblast proliferation and migration towards the intima and the production of extracellular matrix proteins, provoking intimal thickening and vessel occlusion (17).

The growth factors secreted by macrophages promote angiogenesis, induce neovascularisation and amplify vascular inflammation. According to the literature, neoangiogenesis may also have a compensatory effect and it may prevent ischemia and reduce neuro-ophthalmological complications (22).

VSMCs are not only direct targets of the inflammatory attack, but they may also participate in the generation and maintenance of the pathological process. Specifically, VSMCs have the ability to secrete MMPs, leading to IEL disruption (18).

ECs, especially the micro-ECs in the vasa vasorum, also play an important role in vascular remodelling and they are major targets of inflammatory cytokines. IL-6 has important effects on EC proliferation, tubular formation and the induction of angiogenesis. ECs are themselves able to produce proinflammatory cytokines and adhesion molecules in response to paracrine signals, thus mediating leukocyte trafficking and migration (17,18).

All this complex amplification cascades and the pathological processes result in the remodelling of the vessel wall, which leads to stenosis, occlusion or aneurysm formation in the affected arteries.

#### 4. Stroke characteristics

The majority of stroke cases secondary to GCA are ischemic stroke in nature. There are only a few isolated cases, when development of subarachnoid haemorrhage secondary to GCA was reported (23-25).

In the general population, the carotid-territory strokes are more frequent than the vertebrobasilar (VB) territory strokes; in population-based epidemiologic stroke studies their ratio was 5:1, respectively (26). However, in the active phase of the disease (between the onset of GCA symptoms and one month after the initiation of steroid therapy) the stroke cases secondary to GCA primarily developed in the VB territory. For example, Gonzalez-Gay *et al* reported in a population-based study including a total of 287 GCA patients that seven out of the eight stroke cases occurred in VB territory. Moreover, in six of the seven cases the patients were male (12). In a population-based cohort study published by Salvarani *et al*, all of the five stroke cases among a series of 180 patients with biopsy-proven GCA showed VB localisation (11). Similar results were reported by Samson *et al* (75% of GCA-related strokes) (13), by Pariente *et al* (11/18 stroke cases) (27) and by de Boysson *et al* (73% of cases) (14). Notably, studies, which includes all cases of stroke in GCA patients, regardless of whether it occurs in the active stage of the disease or not, tend to report higher frequency of stroke in the carotid localisation, similar to the data of the general population (28).

Elhfnawy *et al* prospectively screened consecutive patients with VB ischemic stroke for GCA, looking for the halo sign in the temporal and vertebral arteries (29). Among 65 consecutive VB stroke patients, two cases were identified as positive for the halo sign in both temporal arteries and at least one vertebral artery. Those authors concluded that older age, anaemia, elevated inflammatory markers and the presence of multiple VB steno-occlusive lesions could be considered red flags for GCA in patients with VB stroke (29).

García-García *et al* in a prospective study used ultrasound in 1,237 consecutive stroke cases to detect the halo sign (30). Five out of the 1,237 patients had fulfilled the diagnostic ultrasound criteria of GCA and the diagnosis was also confirmed with biopsy. All 5 cases presented as a VB-territory stroke. The outcome was favourable in 4 cases, while one patient died due to aspiration pneumonia. Authors of that study concluded that the recognition of the halo sign in the vertebral arteries is essential to establish a proper and early diagnosis.

GCA could lead to bilateral damage of the vertebral arteries, such as bilateral occlusion, which may result in severe stroke with a high mortality rate. Rüegg *et al* analysed a series of cases with bilateral vertebral artery occlusion-three out of the total number of eight were his own cases (31). The mortality rate was 75%, the mean age of onset was 69 years, with male predominance (n=5 men and n=3 women). All patients presented with new-onset headache, four patients presented with fever and the erythrocyte sedimentation rate was substantially elevated in all the cases. The extradural part of the vertebral arteries between the V2 and proximal V4 segments were affected in all the cases. In isolated cases, bilateral vertebral artery occlusion could be the initial clinical manifestation of GCA (31,32). The early diagnosis and prompt initiation of corticosteroid and antithrombotic treatment could lead to a favourable prognosis even in older patients (33).

It appeared that the intracranial arteries were spared in GCA because they contain no or little IEL, according to previous literature. By contrast, the supra-aortic arteries contain IEL from the aortic arch to the place of entry into the dura mater and it may extend 5 mm distally too (34,35). The newer literature, based on data from contrast-enhanced 3-Tesla magnetic resonance imaging (MRI) demonstrated the frequent involvement of intradural arteries, mainly the internal carotid arteries (ICA). Siemonsen *et al* (36) in a prospective study evaluated 28 patients with suspected GCA, using an MRI protocol focused on the assessment of the intradural arteries. 3-Tesla MRI with fat-saturated pre- and postcontrast T1-weighted sequences were adapted to detect mural thickening and contrast enhancement of the vessel wall, which are considered to be the signs of mural inflammation. Ten out of 25 patients presented with vessel wall enhancement (VWE) of the intradural ICA, and all these cases were positive for GCA. Five patients presented bilateral, and four patients presented unilateral VWE of the vertebral arteries, respectively. The basilar artery did not show VWE in any of the cases. Moreover, involvement of the intradural vessels did not correlate with the intracranial steno-occlusive lesions, nor the cerebral ischemic lesions (36).

Several publications proved that the ischemic cerebrovascular events are mainly related to the stenosis or occlusion of the extradural vessels rather than to the intradural vasculitis (35,37).

There is no clear explanation for the more frequent involvement of the VB territory predominance in GCA-related strokes. The smaller diameter of the vertebral arteries relative to the carotid arteries and the higher vulnerability of these vessels to high-grade stenosis or occlusion could be a plausible explanation (34).

Small case series reported that multiple cerebral ischemic lesions secondary to GCA during the active phase of the disease could lead to multi-infarct dementia (34,38).

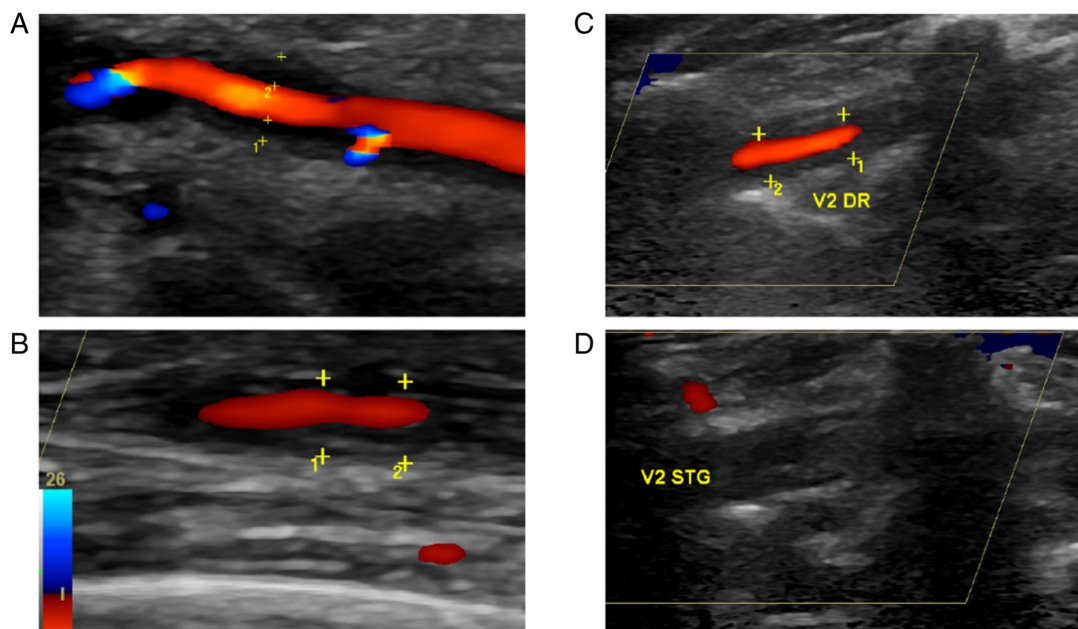


Figure 1. Duplex ultrasound examination showing the hypoechoic halo sign at the level of the (A and B) right and left superficial temporal arteries, respectively, and (C) the V2 segment of the right vertebral artery. (D) The lumen of the V2 segment of the left vertebral artery is filled completely with a hypoechoic material, suggestive for occlusion.

Carotid and vertebral artery dissections with severe cerebral ischemic complications secondary to GCA had been published in isolated case reports. The radiological distinction between the vasculitic vessel wall changes and the mural hematoma secondary to the dissection is challenging (39-43).

## 5. Diagnosis

The diagnosis of GCA in stroke patients may be challenging, especially if stroke is the first clinical manifestation. Anorexia, malaise, weight loss, fever, headache or arthralgia in the prior medical history of the patient may turn attention to the diagnosis of GCA, but these nonspecific symptoms could easily be overlooked in case of acute stroke. Both C-reactive protein level and the erythrocyte sedimentation rate are significantly higher in the majority of the GCA cases, but these findings are also nonspecific (13). However, duplex ultrasonography, which is a standard diagnostic tool in acute stroke, could help to establish the diagnosis of CGA.

The presence of the halo sign at the level of the cervical vessels, mainly in the vertebral arteries and less often in the carotid arteries may be the first proof of GCA. In these cases, the Doppler ultrasound examination of the superficial temporal arteries is mandatory, because the classic sonography signs, e.g., hypoechoic halo sign, compression sign, of GCA are usually present at this level in the majority of cases.

The halo sign was first described by Schmidt *et al* in 1995 (44). The swollen vessel wall of the temporal arteries is characterised by ultrasound as a hypoechoic circumferential mural thickening localised around the lumen, with a diameter ranging from 0.3 to 0.5 mm (Fig. 1). The halo sign can be present, not only at the level of the superficial temporal arteries, but at the level of the vertebral, occipital, subclavian or axillary arteries too, and in rare cases, at the level of the carotid arteries (45). Vessel stenosis or occlusion can also be evidenced

at the level of temporal arteries, but the diagnostic value of such is lower. The ultrasound examination can also help to navigate or to plan the precise localization of biopsy (44).

The other temporal arteritis related ultrasound sign is the so-called 'compression sign'. This term refers to the continuous feature of a hypoechoic halo during the compression of the vessel lumen by the ultrasound transducer (Fig. 2). This sign has high specificity for the diagnosis (46).

The main advantages of the ultrasound examination are its non-invasive nature, fast availability, lack of radiation exposure and the possibility of simultaneous image acquisition and interpretation. Conversely, the disadvantage of this method is its operator-dependent nature, the need for high-quality equipment, the adequate probe setting and the standardisation requirement.

The so-called 'fast-track clinics' in Europe and in the United States with well-trained ultrasound specialists may help to initiate treatment before the appearance of severe complications (47,48).

Temporal artery biopsy remains the gold standard of the diagnosis; however, it is more time-consuming compared to ultrasonography. Moreover, false-negative results are not uncommon, due to the segmental involvement of the vessel walls. The mural edema and vessel wall enhancement were demonstrated with high-resolution contrast-enhanced MRI and MR angiography (49).

Finally, positron-emission tomography can also be useful in diagnosis in selected cases (50).

## 6. Treatment options

The GCA-related stroke is a rare condition; therefore, there are no evidence-based guidelines or standard recommendations for the treatment. The role of antiplatelet therapy in the prevention of severe ischemic complications of GCA is



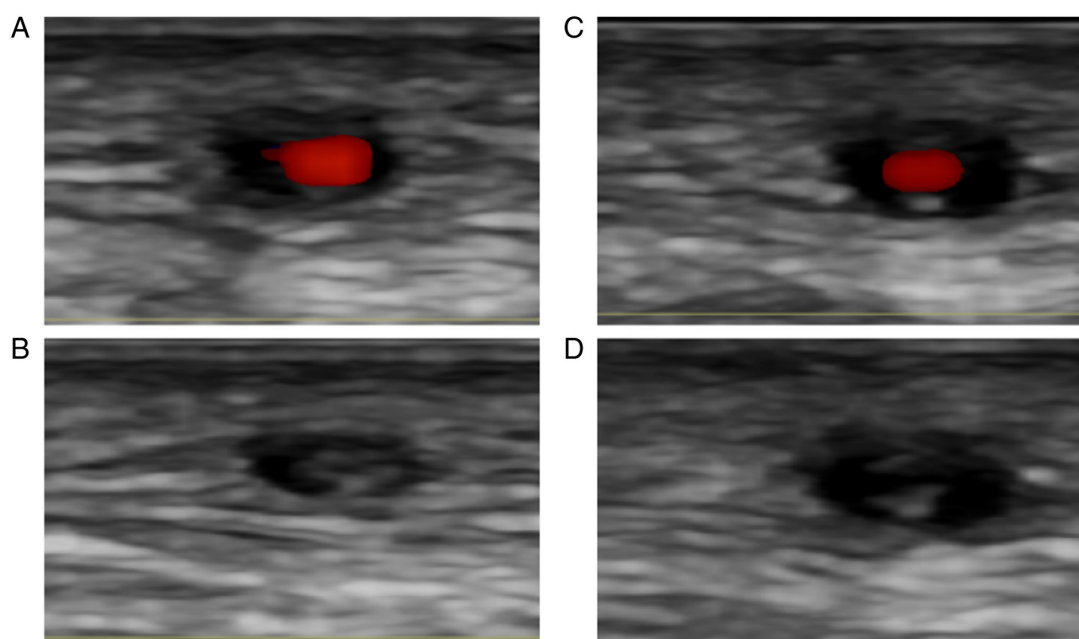


Figure 2. Duplex ultrasound examination showing the presence of compression sign in both superficial temporal arteries (right and left), meaning the persisting visibility of the hypoechoic halo during the compression of the vessel lumen. Ultrasound images (A and C) before and (B and D) after compression.

debated. Nesher *et al* retrospectively analysed 175 consecutive cases of GCA, and 21% of the patients got a low-dose aspirin treatment at the time of the diagnosis of GCA (51). The cranial ischemic complications were less frequent in the aspirin-treated group compared to the non-treated group. As such, authors of that study concluded that low-dose aspirin decreases the rate of visual complications and stroke in patients with GCA. A retrospective study published by Lee *et al* included 143 patients with GCA and the mean follow-up time was up to four years (52). They reported that the antiplatelet or anticoagulant therapy significantly reduced the frequency of the cranial ischemic events compared to the non-treated group, i.e., 16.2 vs. 48%, respectively, while there was no significant difference between the two groups regarding to the haemorrhagic complications. On the other hand, two other studies failed to prove a beneficial effect of the antiplatelet therapy on the occurrence of severe visual complication or stroke in newly diagnosed GCA (11,53).

Martínez-Taboada *et al* published a cumulative meta-analysis based on the data of 914 GCA patients. According to their results the antithrombotic therapy applied prior to the diagnosis of GCA did not provide a protective effect against severe ischemic complications (54). However, the combined antithrombotic and corticosteroid treatment applied after the diagnosis of GCA resulted in a slightly favourable outcome.

High-dose glucocorticoids are the core therapy in patients with GCA-related severe complications and it should be instantly initiated once the diagnosis of GCA is strongly suspected. The superior efficacy of methylprednisolone pulse therapy in comparison with high-dose oral prednisone is not clearly proven, but it is widely used (14,55).

The possible beneficial effects of anticoagulant treatment are not well-documented (52), while the influence of statins on the risk reduction of cardiovascular complications of GCA

was not proven. Moreover, the possible use of statins in terms of the glucocorticoid-sparing effect was not evident (55).

The spectrum of glucocorticoid-sparing agents used in GCA treatment is large, encompassing classical immunosuppressant drugs such as azathioprine, methotrexate, cyclophosphamide, cyclosporine and mycophenolate mofetil together with newer agents including tocilizumab, ustekinumab, abatacept and adalimumab (19). Some authors have recommended using immunosuppressive drugs as first-line therapy because of steroid-induced side effects and the risk of relapse (56).

## 7. Conclusions

Stroke is a rare but outcome-defining complication of GCA, because it is one of the leading factors, which influence the mortality and disability rates. GCA-related stroke typically develops in the VB territory and is more frequent in patients who have ophthalmic ischemic symptoms. In the context of constitutional symptoms and elevated inflammatory markers, clinicians must search for GCA in elderly stroke patients because the prompt institution of corticosteroid treatment and antithrombotic therapy may improve the prognosis. The widely available imaging modality of duplex ultrasound may easily guide the diagnosis if the suggestive halo sign is identified in the extracranial vessels. The diagnosis of this entity requires a high level of suspicion.

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## Authors' contributions

ZB, RB, AS and RCF conceived and designed the study; ZB, SM, RCF, AS performed the literature search and assessed the authenticity of raw data; ZB, SM, AM, LB, AS, and SA analyzed the relevant literature and wrote the manuscript; ZB, RB, RCF, AS and SA contributed to the interpretation of data and the revision of the manuscript, provided critical review for the manuscript. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

None to declare.

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