How the ultrasound protocol may improve the timely diagnosis of cerebrovascular complications in giant cell arteritis

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Summary

Giant cell arteritis (GCA) is a granulomatous inflammatory vasculitis of medium and large vessels, with a predilection for the external carotid and ophthalmic arteries and, to a lesser extent, for the vertebral arteries. In early phases of the disease, symptoms may be nonspecific, such as malaise, fever, and weight loss. Overt typical GCA symptoms are temporal headache, scalp tenderness, jaw claudication, and sudden vision loss. Inflammatory vessel involvement in GCA results in partial or complete occlusion of the arterial lumen, leading to complications such as acute ischemic optic neuropathy, transient ischemic attack, and ischemic stroke. The latter is a rare but severe complication of GCA, and it has been reported in 2.8-7% of patients diagnosed with GCA. The majority of ischemic strokes are related to inflammation of vertebral and, less frequently, basilar and internal carotid arteries. Stroke in GCA patients affects vertebrobasilar circulation in 50 to 100% of cases, compared to only 20% observed in cerebrovascular accidents in the general population. Prompt diagnosis of GCA cranial involvement is pivotal, since early start of high-dose corticosteroid treatment and/or immunosuppressive drugs (*e.g.*, tocilizumab and methotrexate) is highly effective in preventing further evolution and recurrence of such complications. In this viewpoint, we have briefly pinpointed the current possible value of vertebral ultrasound from both the rheumatologist's and neurologist's points of view.

Introduction

Giant cell arteritis (GCA) is a granulomatous inflammatory vasculitis of medium and large vessels, with a predilection for the external carotid and ophthalmic arteries, and, to a lesser extent, for the vertebral arteries (1, 2). In early phases of the disease, symptoms may be nonspecific, such as malaise, fever, and weight loss. Overt typical GCA symptoms are temporal headache, scalp tenderness, jaw claudication, and sudden vision loss (3).

Inflammatory vessel involvement in GCA results in partial or complete occlusion of the arterial lumen, leading to complications such as acute ischemic optic neuropathy, transient ischemic attack, and ischemic stroke (1). The latter is a rare but severe complication of GCA, and it has been reported in 2.8-7% of patients diagnosed with GCA (1, 4, 5). Most ischemic strokes are related to inflammation of vertebral and, less frequently, basilar and internal carotid arteries. Stroke in GCA patients affects vertebrobasilar circulation in 50% up to 100% of cases, compared to only 20% observed in cerebrovascular accidents in the general population (6, 7).

Therefore, GCA has to be considered in the differential diagnosis of posterior circulation ischemic stroke. Even if only 0.15% of patients with first-ever stroke are related to GCA, consequences can be devastating, and prevention, whenever possible, should be attempted (1, 8).

Prompt diagnosis of GCA cranial involvement is pivotal, since early start of high-dose corticosteroid treatment and/or immunosuppressive drugs (*e.g.*, tocilizumab and methotrexate) is highly effective in preventing further evolution and recurrence of such complications (1, 2).

Vertebral artery ultrasound

The importance of applying an early sonographic assessment in the diagnostic pathway of GCA has become mainstream (9-12). Color duplex ultrasound (CDUS) shows a sensitivity for GCA diagnosis of 69.6%, compared to 52.2% for fluoro-18-deoxyglucose positron emission tomography computed tomography, and 56.5% for magnetic resonance imaging (MRI) in patients with suspected GCA (13). Specificity reaches 100% for all the above-mentioned imaging techniques (13). Current ultrasound (US) protocol recommends examination of temporal and axillary arteries at least (10), with carotid, vertebral, subclavian, and occipital arteries that should be complemented (14). In fact, a halo sign (observed as non-compressible hypo/anechoic vascular wall thickening) at carotid and vertebral territory is rare, but highly specific for an inflammatory vessel involvement, along with stenosis and occlusions in patients with recent GCA diagnosis (15, 16). On occasion, the vertebral artery may be the unique inflammatory vessel involvement in GCA (17). Interestingly, an association has been found between GCA-related cerebrovascular events and vertebral artery thrombosis on Doppler ultrasonography, revealing that vertebral thrombosis is significantly more commonly detected on Doppler US in GCA patients compared to other vascular territo-

ries, such as temporal arteries, where the halo sign is the predominant US finding (18, 19). The detailed US examination of the vertebral arteries is particularly challenging, and it requires skilled training. To perform an optimal vertebral artery examination, the patient should be in a supine position with the head slightly rotated towards the opposite shoulder to expose the vertebral arteries and avoid obstructions. In some cases, slight neck extension can improve access, especially in patients with a thick neck or challenging anatomy. A 7-10 MHz linear array probe is commonly used for imaging the vertebral arteries. The vertebral arteries are deep-seated and asymmetric, and hypoplasia is frequently observed (20). Otherwise, from temporal and axillary arteries, no recommendation exists regarding the cut-off value for the measurement of the vertebral artery intima-media thickness suggestive of inflammatory involvement (16). Furthermore, two pitfalls may be misinterpreted as a halo sign: vertebral artery dissection and atherosclerosis. In the former, the presence of a vessel wall hematoma might be perceived (21); thus, the hypoechoic area is usually eccentric and not concentric (22, 23). Atherosclerotic plaques are rarer in the vertebral region compared to other vessel districts (24), presenting as irregular and eccentric. Conversely, a concentric and diffuse hypoechoic vessel wall is suggestive of GCA (25). Other possible issues during vertebral US occur with subclavian steal syndrome, which may cause stroke symptoms (26), while GCA may be only a rare cause of subclavian steal syndrome (27). A deceleration of flow during peak systole is common in the halo sign in GCA, but it is different from the bunny waveform sign, which refers to the biphasic pulsed wave morphology occurring in early or partial subclavian steal phenomenon (28) (Figure 1). Also, intracranial segments of the carotid arteries, such as the basilar artery, as a progression of the vertebral artery, should be examined (29). Finally, the US is also emerging in examining ophthalmic arteries, since embolic arterial plaques, previously described as the retrobulbar spot sign, can discriminate non-arteritic central retinal artery occlusion in acute/subacute settings (30).

Which patients to screen?

CDUS is recommended as a first-line investigation in GCA, but a pretest probability score is warranted in stratifying GCA diagnostic probability based on inflammatory markers and clinical appearance (GCA unlikely, GCA uncertain, GCA probable needing further tests, and definite GCA) (31, 32).

While the risk factors for ophthalmic ischemic complications have been widely studied, these are less known in GCA-related ischemic stroke. In fact, only limited data are derived from literature, mainly small case series, and unfortunately, only a few heterogeneous population-based studies exist, making it difficult to draw robust conclusions. For instance, the role of traditional cardiovascular risk factors remains controversial (16).

Elevated inflammatory markers in stroke patients may be considered a “red flag” for ischemic complications, but other studies have reported the opposite (33). Probably, a stronger role is played by the persistence of inflammation (34): delayed treatment, in fact, which may lead to an increased inflammatory burden, has been associated with an increased risk of ischemic events (34).

Regarding clinical features, ophthalmic ischemic complications and jaw claudication have been linked to ischemic stroke (35-37), but this association was not confirmed by other studies (18, 38-40). On a speculative basis, it is the combination of multiple factors, such as high C-reactive protein at GCA onset, together with ophthalmic involvement, which confers a higher risk of stroke (34). On the other side, from a neurological perspective, it is difficult to predict which patient primarily diagnosed with stroke should undergo vertebral artery US. Among clinical symptoms, amaurosis fugax and persistent frontal headache should be suspicious for GCA. (1, 34).

In conclusion, only a few and contrasting evidence exist on risk factors for cerebrovascular accident in GCA, making it difficult to highlight which subset of patients should be screened with vertebral US. Even a recent study performed with MRI showed

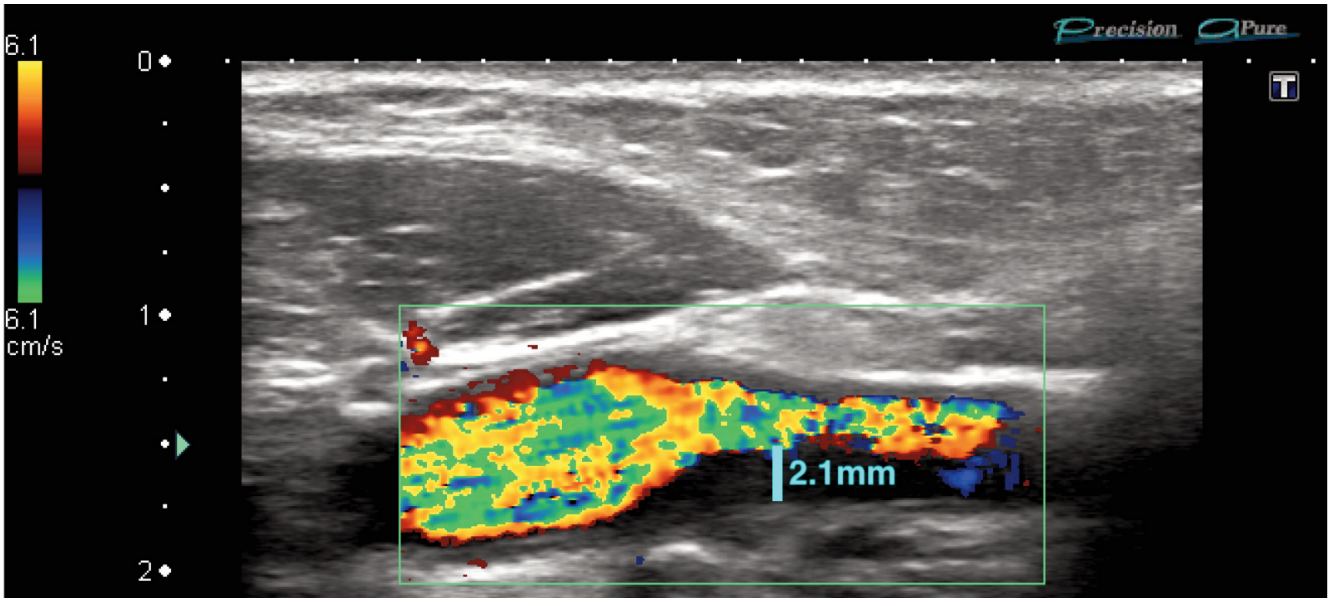

Figure 1. Left subclavian-vertebral artery passage (longitudinal scan) in a 79-year-old female showing false halo sign as appearing hypoechoic 2.1 mm wall thickening, not confirmed at transversal scan. Retrograde flow in the left vertebral and subclavian arteries was then noticed during examination.

that there is no significant correlation between inflammation of the intracranial arteries and clinical symptoms of GCA, in terms of headache and neurological defects (41). However, in the same cohort of 55 GCA patients, 8 (14.5%) presented inflammation of at least 1 intracranial artery, compared to none of the 50 healthy controls. Internal carotid artery (10.9%) and the vertebral artery (7.3%) were the most commonly involved territories (41). Thus, taking into account all these uncertainties, vertebral CDUS could be considered for integration in US GCA protocols in future years and studies, to explore the advantage of its evaluation in GCA patients. Hence, an algorithm for vertebral artery screening should be desirable, but there is currently limited and sometimes contrasting evidence regarding the risk factors for cerebrovascular events in GCA, making it challenging to define a clear subset of patients who would benefit most from vertebral artery US screening.

Conclusions

Stroke is a rare complication of GCA, and GCA is a very rare cause of stroke, but the consequences can be harmful.

Since vertebral artery involvement might be under-recognized in GCA patients, early identification of at-risk patients is crucial to improve prognosis, considering that no defined clinical or laboratory predictive markers of ischemic events in GCA exist. Moreover, not all GCA patients routinely undergo brain MRI, which remains the gold standard for intracranial assessment in GCA (41). However, data are emerging on the speculative role of early vertebral US, as integrated into the current US protocol in GCA, to examine the inflammatory involvement of this vessel. There is not much evidence that vertebral US is particularly reliable (due to technical challenges, difficulty in interpretation, need for high US expertise, *etc.*), but in this paper, we propose to integrate vertebral US findings into routine US protocols, as previously done for axillary and subclavian arteries. This may lead to identifying if this approach has higher US sensitivity in GCA diagnosis (as occurred when axillary and subclavian arteries have been added to the temporal arteries US protocol), especially in patients where vertebral artery involvement is suspected and other imaging techniques are not readily available or affordable. Further, only if vertebral US assessment is routinely performed and compared with clinical and laboratory data, will we be able to collect data on vertebral US usefulness in GCA.

In Figure 2, we have briefly designed a flowchart upon the current possible value of vertebral US from both the rheumatologist's and neurologist's point of view.

Further studies will be needed to grow evidence on such a challenging topic.

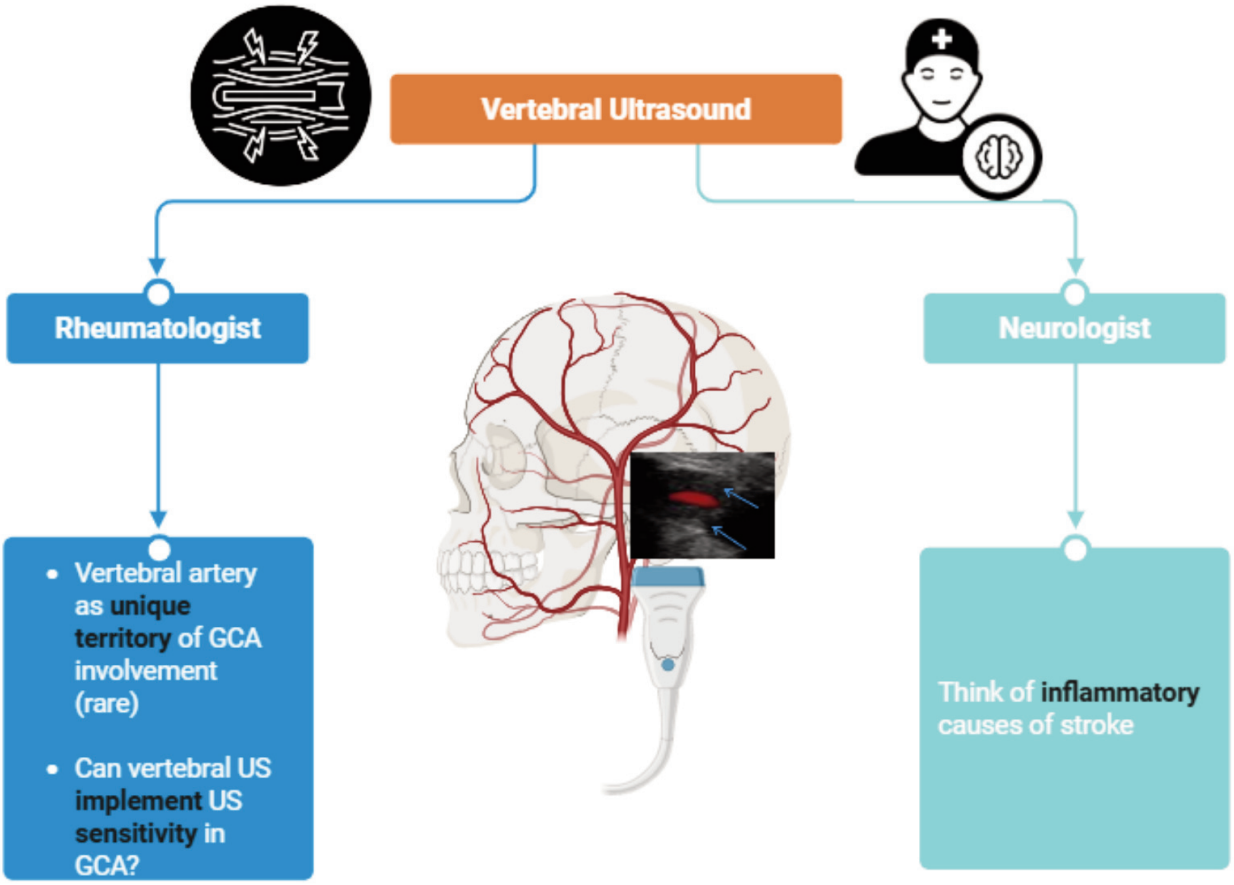

Figure 2. Flowchart of the current possible value of vertebral ultrasound from both the rheumatologist's and the neurologist's points of view. GCA, giant cell arteritis; US, ultrasound.

References

1. Soriano A, Muratore F, Pipitone N, Boiardi L, Cimino L, Salvarani C. Visual loss and other cranial ischaemic complications in giant cell arteritis. Nat Rev Rheumatol 2017; 13: 476-84.
2. Fein AS, Ko MW. Neuro-ophthalmologic complications of giant cell arteritis: diagnosis and treatment. Semin Neurol 2019; 39: 673-81.
3. Bilton EJ, Mollan SP. Giant cell arteritis: reviewing the advancing diagnostics and management. Eye 2023; 37: 2365-73.
4. Coronel L, Rodríguez-Pardo J, Monjo I, de Miguel E. Prevalence and significance of ischemic cerebrovascular events in giant cell arteritis. Med Clin 2021; 157: 53-7.
5. Pariente A, Guédon A, Alamowitch S, Thietart S, Carrat F, Delorme S, et al. Ischemic stroke in giant-cell arteritis: French retrospective study. J Autoimmun 2019; 99: 48-51.
6. Marte Furment M, Antigua Jimenez S, Pabolu S. Acute stroke due to vertebral artery dissection in giant cell arteritis. Case Rep Rheumatol 2021; 2021: 5518541.
7. Bajko Z, Balasa R, Maier S, Motataianu A, Barcutean L, Andone S, et al. Stroke secondary to giant-cell arteritis: a literature review. Exp Ther Med 2021; 22: 876.
8. Wiszniewska M, Devuyst G, Bogousslavsky J. Giant cell arteritis as a cause of first-ever stroke. Cerebrovasc Dis 2007; 24: 226-30.
9. Monti S, Floris A, Ponte CB, Schmidt WA, Diamantopoulos AP, Pereira C, et al. The proposed role of ultrasound in the management of giant cell arteritis in routine clinical practice. Rheumatology 2018; 57: 112-9.
10. Dejaco C, Ramiro S, Bond M, Bosch P, Ponte C, Mackie SL, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice: 2023 update. Ann Rheum Dis 2024; 83: 741-51.
11. Mukhtyar CB, Beadsmoore C, Ducker G, Fordham S, Sisson K, Jones C. Ultrasonography led multimodal diagnostic pathway for giant cell arteritis. Rheumatology 2025; 64: 2077-82.
12. Bosch P, Bond M, Dejaco C, Ponte C, Mackie SL, Falzon L, et al. Imaging in diagnosis, monitoring and outcome prediction of large vessel vasculitis: a systematic literature review and meta-analysis informing the 2023 update of the EULAR recommendations. RMD Open 2023; 9: e003379.
13. van Nieuwland M, Colin EM, Vermeer M, Wagenaar NRL, Vijlbrief OD, van Zandwijk JK, et al. A direct comparison in diagnostic performance of CDUS, FDG-PET/CT and MRI in patients suspected of giant cell arteritis. Rheumatology 2025; 64: 1392-9.
14. Skoog J, Svensson C, Eriksson P, Sjöwall C, Zachrisson H. The diagnostic performance of an extended ultrasound protocol in patients with clinically suspected giant cell arteritis. Front Med 2021; 8: 807996.
15. Soares C, Costa A, Santos R, Abreu P, Castro P, Azevedo E. Clinical, laboratory and ultrasonographic interrelations in giant cell arteritis. J Stroke Cerebrovasc Dis 2021; 30: 105601.
16. Kargiotis O, Psychogios K, Safouris A, Bakola E, Andreadou E, Karapanayiotides T, et al. Cervical duplex ultrasound for the diagnosis of giant cell arteritis with vertebral artery involvement. J Neuroimaging 2021; 31: 656-64.
17. Lambrechts RA, Uyttenboogaart M, Drost G. A vertebral artery halo sign indicates giant cell arteritis affecting the posterior circulation of the brain. Lancet 2021; 397: e6.
18. Penet T, Lambert M, Baillet C, Outteryck O, Hénon H, Morell-Dubois S, et al. Giant cell arteritis-related cerebrovascular ischemic events: a French retrospective study of 271 patients, systematic review of the literature and meta-analysis. Arthritis Res Ther 2023; 25: 116.
19. García-García J, Ayo-Martín Ó, Argandoña-Palacios L, Segura T. Vertebral artery halo sign in patients with stroke: a key clue for the prompt diagnosis of giant cell arteritis. Stroke 2011; 42: 3287-90.
20. Psychogios K, Magoufis G, Kargiotis O, Safouris A, Bakola E, Chondrogianni M, et al. Ultrasound assessment of extracranial carotids and vertebral arteries in acute cerebral ischemia. Medicina 2020; 56: 711.
21. Reinhard M, Schmidt D, Schumacher M, Hetzel A. Involvement of the vertebral arteries in giant cell arteritis mimicking vertebral dissection. J Neurol 2003; 250: 1006-9.
22. de Bray JM, Penisson-Besnier I, Dubas F, Emile J. Extracranial and intracranial vertebrobasilar dissections: diagnosis and prognosis. J Neurol Neurosurg Psychiatry 1997; 63: 46-51.
23. Ben Hassen W, Machet A, Edjlali-Goujon M, Legrand L, Ladoux A, Mellerio C, et al. Imaging of cervical artery dissection. Diagn Interv Imaging 2014; 95: 1151-61.
24. Zwicker J, Atkins EJ, Lum C, Sharma M. An atypical presentation of giant cell arteritis. CMAJ 2011; 183: E301-5.
25. Rüegg S, Engelter S, Jeanneret C, Hetzel A, Probst A, Steck AJ, et al. Bilateral vertebral artery occlusion resulting from giant cell arteritis: report of 3 cases and review of the literature. Medicine 2003; 82: 1-12.
26. Bajko Z, Motataianu A, Stoian A, Barcutean L, Andone S, Maier S, et al. Prevalence and clinical characteristics of subclavian steal phenomenon/syndrome in patients with acute ischemic stroke. J Clin Med 2021; 10: 5237.
27. Zalaquett Z, Zgheib G, Karam L, Zaatar M, Nehme K, Tabet G. A rare association of subclavian steal syndrome with bilateral carotid artery stenosis: a case report. J Vasc Surg Cases Innov Tech 2023; 9: 101243.
28. De Brucker Y, Peeters E, Goethals LR, Van Looveren K, François O, Van Hedent E. The vertebral bunny waveform: an early manifestation of the subclavian steal syndrome. JBR-BTR 2012; 95: 340.
29. Mahjoub Y, McKenzie ED, Raouf S, Almekhlafi M. Progressive vertebrobasilar vasculopathy and stroke secondary to giant cell arteritis. Stroke 2022; 53: e435-8.
30. Smith AT, Wilbert CD, Ferre RM. Using the retrobulbar spot sign to assist in diagnosis and management of central retinal artery occlusions. J Ultrasound Med 2020; 39: 197-202.
31. Sebastian A, Tomelleri A, Kayani A, Prieto-Pena D, Ranasinghe C, Dasgupta B. Probability-based algorithm using ultrasound and additional tests for suspected GCA in a fast-track clinic. RMD Open 2020; 6: e001297.
32. Sebastian A, van der Geest KSM, Tomelleri A, Macchioni P, Klinowski G, Salvarani C, et al. Development of a diagnostic prediction model for giant cell arteritis by sequential application of Southend giant cell arteritis probability score and ultrasonography: a prospective multicentre study. Lancet Rheumatol 2024; 6: e291-9.
33. Prünte MKR, Naumann A, Christ M, Naumann M, Bayas A. Giant cell arteritis with vertebral artery involvement-baseline characteristics and follow-up of a monocentric patient cohort. Front Neurol 2023; 14: 1188073.
34. Bonnan M, Debeugny S. Giant-cell arteritis related strokes: scoping review of mechanisms and rethinking treatment strat-

egy? Front Neurol 2023; 14: 1305093.
35. de Boysson H, Liozon E, Larivière D, Samson M, Parienti JJ, Boutemy J, et al. Giant cell arteritis-related stroke: a retrospective multicenter case-control study. J Rheumatol 2017; 44: 297-303.
36. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Gomez-Acebo I, Pego-Reigosa R, Lopez-Diaz MJ, Vazquez-Triñanes MC, et al. Strokes at time of disease diagnosis in a series of 287 patients with biopsy-proven giant cell arteritis. Medicine 2009; 88: 227-35.
37. González-Gay MA, Blanco R, Rodríguez-Valverde V, Martínez-Taboada VM, Delgado-Rodriguez M, Figueroa M, et al. Permanent visual loss and cerebrovascular accidents in giant cell arteritis: predictors and response to treatment. Arthritis Rheum 1998; 41: 1497-504.
38. Hočevar A, Ješe R, Tomšič M, Rotar Ž. Risk factors for severe cranial ischaemic complications in giant cell arteritis. Rheumatology 2020; 59: 2953-9.
39. Parreau S, Dumonteil S, Montoro FM, Gondran G, Bezanahary H, Palat S, et al. Giant cell arteritis-related stroke in a large inception cohort: a comparative study. Semin Arthritis Rheum 2022; 55: 152020.
40. Lo Gullo A, Koster MJ, Crowson CS, Makol A, Ytterberg SR, Saitta A, et al. Venous thromboembolism and cerebrovascular events in patients with giant cell arteritis: a population-based retrospective cohort study. PLoS One 2016; 11: e0149579.
41. Guggenberger KV, Vogt ML, Song JW, Fröhlich M, Schmalzing M, Venhoff N, et al. High-resolution magnetic resonance imaging visualizes intracranial large artery involvement in giant cell arteritis. Rheumatology 2025; 64: 842-8.

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