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Clinical science

Does the halo count on temporal and axillary ultrasound predict time to relapse in giant cell arteritis?

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Abstract

Objectives: To determine whether the halo count (HC) on temporal and axillary artery US (TAUS) predicts time to relapse in giant cell arteritis (GCA).

Methods: We conducted a single-centre retrospective study of GCA patients. HC, the number of vessels with non-compressible halo on the TAUS at diagnosis, was determined by retrospective review of the US report and images. Relapse was defined as increase in GCA disease activity requiring treatment escalation. Cox proportional hazard regression was used to identify predictors of time to relapse.

Results: A total of 72 patients with confirmed GCA were followed up for a median of 20.9 months. Thirty-seven of 72 (51.4%) relapsed during follow-up, at a median prednisolone dose of 9 mg (range 0–40 mg). Large-vessel (axillary artery) involvement did not predict relapse. On univariable analysis, a higher HC was associated with shorter time to relapse (per-halo hazard ratio 1.15, 95% CI 1.02, 1.30; $P = 0.028$). However, statistical significance was lost when the 10 GCA patients with an HC of zero were excluded from analysis.

Conclusion: In this real-world setting, relapse occurred at a wide range of glucocorticoid doses and was not predicted by axillary artery involvement. GCA patients with a higher HC at diagnosis were significantly more likely to relapse, but significance was lost on excluding those with HC of zero. HC is feasible in routine care and may be worth incorporating into future prognostic scores. Further research is required to determine whether confirmed GCA patients with negative TAUS represent a qualitatively different subphenotype within the GCA disease spectrum.

Rheumatology key messages

- In this real-world dataset, GCA patients with more US halos were more likely to relapse sooner.
- Further research is needed as to whether this patient group needs more intensive treatment.

Keywords: GCA, halo count, relapse

Introduction

GCA is the most common vasculitis in the over-50s [1, 2]. Untreated, GCA may cause permanent visual loss or stroke. Diagnosis may be confirmed via temporal artery biopsy (TAB) or by temporal and axillary artery US (TAUS). GCA is treated with high-dose glucocorticoid ('steroid'); the dose is tapered gradually, aiming to stop within 1–2 years unless relapse occurs. Guidelines now recommend consideration of tocilizumab or methotrexate (MTX) for GCA; in England and Wales, funding of tocilizumab is restricted to relapsing or refractory GCA [3, 4].

Although not all patients with GCA relapse, it remains challenging to identify at diagnosis which patients are at higher risk of relapse. Reported predictors of relapse include fever, intensity of the systemic inflammatory response, visual symptoms or large vessel involvement [5–7], and perhaps hypertension and diabetes [8].

TAUS is now used to support the diagnosis of GCA in 'fast-track' diagnostic pathways [1, 9, 10]. The cardinal US feature of GCA is the non-compressible halo, indicating vessel wall inflammation. Current guidelines classify the TAUS result as 'positive' or 'negative' [3] but there remains subjectivity in how much vascular thickening (size and number of halos) is required for the TAUS to be 'positive'. False-negative TAUS can occur in glucocorticoid-treated patients or in those with vasculitis sparing the temporal and axillary arteries; false-

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positive TAUS can occur in relation to atherosclerosis. Measuring vascular thickness in each of the eight arterial territories evaluated by TAUS is more precise but means the TAUS takes longer to do. Simply counting the number of involved arterial branches ('halo count', HC) [11, 12] is potentially more feasible for clinical practice.

It is uncertain whether TAUS, as well as providing crucial diagnostic information, could also be prognostic, i.e. predict relapse [13, 14]. Since not all patients with GCA relapse, there is still a need to identify which patients may stand to benefit most from additional immunomodulatory therapies.

The aim of this study was to determine whether information contained within the TAUS report and images can identify GCA patients at greater risk of relapse in a real-world cohort of GCA patients. The objective of the study was to test HC as a predictor of time to relapse in patients who were diagnosed with GCA by a multidisciplinary clinical team (MDT) and followed for at least 6 months to verify the diagnosis.

Methods

This was a single-centre retrospective analysis of routinely collected data from a service evaluation of the efficiency of the fast-track GCA pathway at Leeds Teaching Hospitals National Health Service (NHS) Trust. The Caldicott Guardian of Leeds Teaching Hospital NHS Trust approved the analysis and reporting of the data. We identified consecutive patients evaluated with TAUS for possible GCA between January 2019 and May 2021. These patients were also sent for TAB where necessary, except during the first wave of the COVID-19 pandemic (spring 2020).

For inclusion, patients had to have confirmed GCA and have had a complete TAUS (axillary artery, common superficial temporal artery, and its parietal and frontal branches on both sides) at the time of diagnosis. Our US protocol did not include the facial, subclavian or carotid arteries. 'Confirmed GCA' was defined as GCA confirmed by our MDT (expert consensus based on clinical, laboratory, imaging and pathological features) and ongoing treatment for GCA, including at least 6 months of glucocorticoid therapy, without emergence of a better explanation for the original symptoms. For inclusion patients needed to have had at least one clinical evaluation after initial treatment-induced remission of GCA. The 1990 ACR classification criteria for GCA [15] were not required for diagnosis. In our MDT meetings, we had observed that some cases had a negative TAUS but GCA was confirmed instead by TAB or another vascular imaging technique. Therefore, we did not require a positive TAUS for confirmation of GCA diagnosis.

TAUS was performed by four experienced operators. Halo sign was defined as a non-compressible 'homogeneous, hypoechoic wall thickening, well delineated towards the luminal side, visible both in longitudinal and transverse planes, most commonly concentric in transverse scans' as per the OMERACT definition [16]. The HC per patient was defined as the number of vascular territories showing a clear halo sign. Relapse was defined as new/worsening GCA symptoms occurring after successful induction of remission and resulting in treatment escalation. Major and minor relapses were defined as per EULAR [4]. Glucocorticoid treatment of GCA patients followed British Society for Rheumatology guidelines. Routinely collected data included sex, age, comorbidities, presenting symptoms, baseline inflammatory markers, outcome of TAB (if performed), initial treatment and taper rate for steroids.

Our objective was to determine whether HC at GCA diagnosis predicted time to relapse. Cox proportional hazards regression was used to model the time to first relapse. Based on the literature, the following variables were selected as potential predictors: sex, cardiovascular morbidity, ischaemic or constitutional symptoms of GCA at presentation (definitions in Supplementary Table S1, available at *Rheumatology* online), pre-treatment inflammatory markers (CRP and platelet count) and HC at diagnosis. Pre-treatment C-reactive protein (CRP) was treated as missing in patients already taking long-term glucocorticoid treatment for PMR at the time of GCA presentation. Due to the small number of relapse events in our dataset, we primarily report the result of the univariable analysis. As an exploratory analysis we also investigated whether multivariable modelling could add further predictive value, dropping variables if they did not appear to contribute substantially to prediction. Analyses were performed using SPSS version 22.0 (SPSS, Chicago, IL, USA).

We initially planned to include all patients regardless of TAUS HC value, as we wanted to develop a score that could be used in a real-world clinical setting. To ensure the results would be generalizable to the whole spectrum of GCA patients, we did not exclude patients with an HC of zero. However, as a sensitivity analysis, we repeated our analysis excluding patients with an HC of zero.

Ethics

This study complies with guidance set by the Declaration of Helsinki. The authors received permission and support from the Caldicott Guardian of Leeds Teaching Hospitals NHS Trust for data collection and the reporting of the results. All data have been fully anonymized.

Results

Seventy-eight patient records with newly diagnosed GCA were identified. Six patients were excluded (one incomplete baseline scan; one death before achievement of remission; four GCA diagnoses later revised from 'confirmed' to 'possible'). Seventy-two patients with newly diagnosed GCA, a complete baseline TAUS scan and at least one clinical evaluation after successful induction of remission were included in the final analysis; 64 of these completed at least 12 months of follow-up; 6 patients died before 12 months of follow-up and 2 were lost to follow-up.

Table 1 describes these 72 patients. The median follow-up time was 20.9 months. Mean HC at GCA diagnosis was 3.6 (range 0–8). Of the 10 patients with an HC of zero, TAB was performed in 6 patients and was positive in 4. In 3 of the 10 cases, the TAUS scan was reported as equivocal (vascular noncompressibility without a halo being clearly visualized). One patient had extracranial GCA diagnosis confirmed by PET-CT. After achieving remission, 60/72 patients were treated using the fastest steroid taper recommended by British Society for Rheumatology guidelines.

Thirty-seven (51.4%) patients relapsed. Of these first relapses, 13 were classified as major and 24 as minor relapses. Similar proportions of males and females relapsed. Major relapse occurred in 8 (53%) of the 15 males, and in 5 (23%) of

Table 1. Demographic and clinical characteristics of study sample

Variable	Sample ($N = 72$)	Relapsers ($N = 37$)	Non-relapsers ($N = 35$)
Age at diagnosis, mean (range), years	74.8 (52–90)	74.3 (60–90)	75.3 (52–89)
Female sex, *n* (%)	43 (59.7)	22/37 (59.5)	21/35 (60.0)
ACR 1990 criteria fulfilment, *n* (%)	56 (77.8)	33/37 (89.2)	23/35 (65.7)
TAB, *n* (%)	Positive 25 (34.7) Negative 6 (8.3) Not done 41 (56.9)	Positive 17 (45.9) Negative 1 (2.7) Not done 19 (51.4)	Positive 8 (22.9) Negative 5 (14.3) Not done 22 (62.9)
US halo count, mean (range)	3.6 (0–8)	4.1 (0–8)	3.0 (0–8)
Constitutional symptoms, *n* (%)	44 (61.1)	23 (62.2)	21 (60.0)
Ischaemic symptoms, *n* (%)	51 (70.9)	29 (78.4)	22 (62.9)
CV morbidity, *n* (%)	47 (65.3)	24 (64.9)	23 (65.7)

TAB: temporal artery biopsy; CV: cardiovascular.

Table 2. Predictors of time-to-first relapse in univariable and multivariable analysis, considering the full cohort ($n = 72$) and the sensitivity analysis considering only patients with halo count ≥1 ($n = 62$)

	Full cohort ($n = 72$)						Sensitivity analysis including only patients with halo count ≥1 on diagnosis US ($n = 62$)					
	Univariable analysis			Multivariable analysis			Univariable analysis			Multivariable analysis		
Predictor of time to first relapse	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Halo count	**1.15**	**1.02, 1.30**	**0.028***	**1.19**	**1.04, 1.35**	**0.012***	1.12	0.96, 1.29	0.146	1.15	0.98, 1.34	0.083
Male sex (reference)	0.97	0.50, 1.87	0.924	0.64	0.31, 1.30	0.218	1.02	0.52, 2.00	0.964	0.72	0.34, 1.51	0.384
CRP (mg/dL)[a]	1.05	0.99, 1.10	0.058				1.04	0.99, 1.01	0.147			
Platelet count ($\times 10^6$/uL)[b]	1.10	0.87, 1.38	0.451				1.07	0.85, 1.36	0.567			
Presence of ischaemic symptoms (reference)	1.60	0.73, 3.51	0.239	1.79	0.81, 3.97	0.152	1.69	0.73, 3.88	0.218	1.84	0.79, 4.30	0.157
Presence of constitutional symptoms (reference)	1.15	0.59, 2.23	0.689				1.20	0.60, 2.40	0.605			
Presence of CV morbidity (reference)	1.20	0.61, 2.37	0.590				1.45	0.71, 2.98	0.311			

The total number of patients included in the analysis is the full cohort unless otherwise specified.
[a] CRP measurement was available in 60 patients before significant exposure to steroids, when considering the full cohort ($n = 60/72$); 51 patients, when considering the sensitivity analysis, where patients with halo count ≥1 were included ($n = 51/62$).
[b] Platelet count available in 71 patients when considering the full cohort ($n = 71/72$).
* Statistical significance at $P < 0.05$. Bold text highlights significant values. HR: hazard ratio; CV: cardiovascular.

the 22 females, who relapsed. The proportion of relapses in the group with and without axillary artery involvement was 52.5% and 50.5%, respectively. Eight patients relapsed more than once during follow-up (subsequent relapses not counted in this report). Median time to first relapse was 190.5 days, or 6.3 months (range 48–643 days). Median daily dosage of prednisolone at relapse was 9 mg (range 0–40 mg); two patients experienced a first relapse after stopping glucocorticoids and nine first relapsed at >10 mg prednisolone; 26 (70.3%) of the patients who relapsed commenced tocilizumab or MTX due to the relapse.

On univariable analysis (Table 2), patients with higher HC were more likely to relapse [per-halo hazard ratio (HR) 1.15, 95% CI 1.02, 1.30; $P = 0.028$]. Ischaemic features at presentation did not significantly predict relapse (HR 1.60, 95% CI 0.31, 3.51; $P = 0.239$), nor did constitutional symptoms, cardiovascular morbidity, platelet count or pre-treatment CRP (HR 1.05, 95% CI 0.99, 1.10; $P = 0.055$; $n = 60$) although the latter analysis excluded 12 patients already on long-term glucocorticoid treatment for PMR. In exploratory multivariable modelling, HC retained significance. In the *post hoc* sensitivity analysis excluding the 10 patients with an HC of zero, statistical significance of the HC was lost (Table 2).

Discussion

GCA has a spectrum of severity of clinical presentation, both regarding vascular inflammation on TAB and regarding intensity of the systemic inflammatory response. In this study, similar to other studies, about half the patients with confirmed GCA relapsed. GCA patients who relapse have a greater burden of long-term glucocorticoid therapy and may therefore need more intensive efforts to prevent glucocorticoid toxicity, including arguably earlier introduction of immunomodulatory therapy [17]. In our study, when we considered the whole spectrum of GCA patients, patients with a higher HC tended to relapse earlier. However, on restricting the spectrum of severity of GCA patients included in the analysis by excluding patients with an HC of zero, statistical significance of the HC in relapse prediction was lost. This was likely due to the small number of patients included, a major limitation of our study.

Two prior studies had investigated the prognostic significance of TAUS halo [13, 14], both with only 6 months of follow-up. In our study, 19/37 of first relapses occurred >6 months after diagnosis. We suggest that relapse studies in future should follow patients for longer than 6 months. A strength of our study was that it was designed to be representative of the whole spectrum of GCA patients, regardless of TAUS result, and therefore is more likely to be generalizable than studies with more restricted inclusion.

The real-world nature of the data also brings other limitations. Firstly, glucocorticoid taper rate and timing of follow-up were chosen by clinicians in full knowledge of TAUS findings; however, we used standardized taper rates, in line with current guidelines, and patients were instructed to seek immediate medical advice on return of symptoms. HC was not part of the TAUS report, but images were discussed at MDT meetings, and reports were available to the treating physician. For MDT diagnosis, TAUS was usually viewed as 'positive' (definitive halo), 'negative' (normal arteries) or 'equivocal'. Patients with the strongest clinical suspicion of GCA were treated with glucocorticoids immediately, before TAUS was done, potentially reducing the HC. Secondly, the small number of patients limited the statistical power; the multivariable analysis must be considered exploratory and at high risk of overfitting. Thirdly, we could not provide more precise composite 'halo scores' based on intima-media thickness measurements [11, 12] as these measurements were not done. Finally, we did not include pre-treatment CRP in the exploratory multivariable model because some patients were already on glucocorticoid treatment for PMR; for the same reason, we did not classify patients according to intensity of the initial systemic inflammatory response, which prior studies had shown was important [8]. A scatter plot of pre-treatment CRP against HC is presented in Supplementary Fig. S1, available at *Rheumatology* online.

The interpretation of our study depends on whether GCA patients with a TAUS HC of zero (essentially, negative or equivocal TAUS, but clinical, imaging or histological evidence of vasculitis, including in other arterial territories) are considered to be qualitatively different from those with an HC of ≥1. At present, there is little research evidence either way on this point. Importantly, our results should not be used to make any clinical treatment decisions. Larger prospective studies are needed to confirm or refute our hypothesis that HC could convey prognostic as well as diagnostic information, ideally in combination with other clinical predictors of risk such as markers of intensity of the initial systemic inflammatory response. With this study we demonstrate that collecting HC as part of routine care is feasible and may be worth incorporating into new prognostic scores.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Anonymized data are available upon reasonable request by qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA) with Leeds Teaching Hospials NHS Trust.

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References

1. Ponte C, Martins-Martinho J, Luqmani RA. Diagnosis of giant cell arteritis. Rheumatology (Oxford) 2020;59:iii5–16.
2. Dejaco C, Brouwer E, Mason JC *et al.* Giant cell arteritis and polymyalgia rheumatica: current challenges and opportunities. Nat Rev Rheumatol 2017;13:578–92.
3. Mackie SL, Dejaco C, Appenzeller S *et al.* British Society for Rheumatology guideline on diagnosis and treatment of giant cell arteritis. Rheumatology (Oxford) 2020;59:e1–23.
4. Hellmich B, Agueda A, Monti S *et al.* 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2020;79:19–30.
5. Muratore F, Boiardi L, Restuccia G *et al.* Relapses and long-term remission in large vessel giant cell arteritis in northern Italy: characteristics and predictors in a long-term follow-up study. Semin Arthritis Rheum 2020;50:549–58.
6. de Mornac D, Espitia O, Néel A *et al.* Large-vessel involvement is predictive of multiple relapses in giant cell arteritis. Ther Adv Musculoskelet Dis 2021;13:1759720X211009029.
7. Nesher G, Nesher R, Mates M, Sonnenblick M, Breuer GS. Giant cell arteritis: intensity of the initial systemic inflammatory response and the course of the disease. Clin Exp Rheumatol 2008;26(3 Suppl 49):S30–4.
8. Labarca C, Koster MJ, Crowson CS *et al.* Predictors of relapse and treatment outcomes in biopsy-proven giant cell arteritis: a retrospective cohort study. Rheumatology (Oxford) 2016;55:347–56.
9. Luqmani R, Lee E, Singh S *et al.* The Role of Ultrasound Compared to Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis (TABUL): a diagnostic accuracy and cost-effectiveness study. Health Technol Assess 2016;20:1–238.
10. Schmidt WA. Ultrasound in the diagnosis and management of giant cell arteritis. Rheumatology (Oxford) 2018;57:ii22–31.
11. van der Geest KSM, Borg F, Kayani A *et al.* Novel ultrasonographic Halo Score for giant cell arteritis: assessment of diagnostic accuracy and association with ocular ischaemia. Ann Rheum Dis 2020;79:393–9.
12. van der Geest KSM, Wolfe K, Borg F *et al.* Ultrasonographic Halo Score in giant cell arteritis: association with intimal hyperplasia and ischaemic sight loss. Rheumatology (Oxford) 2021;60:4361–6.
13. Monti S, Ponte C, Pereira C *et al.* The impact of disease extent and severity detected by quantitative ultrasound analysis in the

diagnosis and outcome of giant cell arteritis. Rheumatology (Oxford) 2020;59:2299–307.
14. Ponte C, Serafim AS, Monti S *et al.* Early variation of ultrasound halo sign with treatment and relation with clinical features in patients with giant cell arteritis. Rheumatology (Oxford) 2020;59:3717–26.
15. Hunder GG, Bloch DA, Michel BA *et al.* The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122–8.
16. Chrysidis S, Duftner C, Dejaco C *et al.* Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: a study from the OMERACT Large Vessel Vasculitis Ultrasound Working Group. RMD Open 2018;4:e000598.
17. Sebastian A, van der Geest KSM, Coath F *et al.* Halo score (temporal artery, its branches and axillary artery) as a diagnostic, prognostic and disease monitoring tool for Giant Cell Arteritis (GCA). BMC Rheumatol 2020;4:35.