Paper

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Cranial ultrasound for the diagnosis of giant cell arteritis. A retrospective cohort study

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ABSTRACT

Background: Establishing a diagnosis of giant cell arteritis, or indeed ruling it out, may be difficult. We describe an evaluation of temporal artery colour duplex ultrasound as first line investigation in patients with suspected giant cell arteritis.
Methods: A retrospective cohort study of all patients undergoing colour duplex ultrasound for suspected giant cell arteritis between January 2005 and January 2014 was undertaken at a teaching hospital. A minimum clinical follow-up of three months was required. Patients were classified on the basis of ultrasound reports, using described features such as a halo sign or arterial wall thickening and clinical diagnosis of giant cell arteritis after at least 3 months follow-up, determined by the treating physician. The relationship of colour duplex ultrasound to a final clinical diagnosis of giant cell arteritis was analysed.
Results: A total of 87 patients underwent colour duplex ultrasound: 36 (41%) had clinically confirmed giant cell arteritis at 3-month follow-up. The positive predictive value of colour duplex ultrasound for a clinical diagnosis at 3 months was 97% (95% confidence interval (CI) 93 to 99%) and negative predictive value 88% (95% CI 76 to 95%). Sensitivity was 81% (95% CI 64 to 92%) and specificity 98% (95% CI 90 to 100%).
Conclusions: A high positive and negative predictive value of arteritis on colour duplex ultrasound indicates that temporal artery biopsy may be unnecessary in suspected giant cell arteritis, particularly where clinical suspicion of giant cell arteritis is high or low.

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INTRODUCTION

Establishing a diagnosis of giant cell arteritis (GCA), or indeed ruling it out, may be difficult. This may be for a variety of reasons including: atypical clinical features including disease that does not involve cranial arteries; difficulties in obtaining a timely temporal artery biopsy; an inadequate biopsy or a patient who declines biopsy. Practice guidelines recommend that a temporal artery biopsy is done for diagnostic confirmation. Some regard a positive temporal artery biopsy as the gold standard for diagnosis.[1] However GCA may occur without involvement of the temporal arteries and 15% or more patients with GCA are reported to have negative biopsies despite an adequate tissue sample.[2]

Colour duplex ultrasound (CDUS) combines Doppler flow data and ultrasound images. This permits an evaluation of arterial structure and blood flow. Characteristic changes of GCA on CDUS have been reported. These include vessel wall thickening (> 1mm) and a circumferential hypoechoic region 'halo sign', representing focal perivascular oedema. The precise role of CDUS for GCA is not yet established, especially in the UK where only two centres taking part in a nationally funded research study were using CDUS for the management of patients with suspected GCA at the time of this work.[3] In this report we describe our experience of using CDUS and examine the diagnostic precision, including sensitivity and specificity, of this test compared with a clinical diagnosis of GCA.

PATIENTS AND METHODS

Our study was registered with the clinical governance department of our hospital. This was a retrospective cohort study of all patients undergoing CDUS for a suspected diagnosis of GCA between January 2005 and January 2014. Patients were identified from a database held in the hospital radiology department. The patient record of those identified was reviewed and key data abstracted. Data were sought from primary care

providers and archived paper medical records as necessary. For the purposes of this study, a clinical diagnosis of GCA made by a consultant rheumatologist, alone or in collaboration with other specialists, after a minimum of 3 months of follow-up, served as the reference or 'gold' standard for a diagnosis of GCA. The American College of Rheumatology (ACR) criteria for GCA were also used to classify all cases for comparison.[4]

CDUS was performed on all patients. Examinations were performed by one of two consultant radiologists experienced in vascular ultrasound. Radiologists were not blinded to the suspicion of GCA or clinical data including laboratory test results. Studies were performed using a high-resolution multi-D linear array transducer VFX 13-5 MHz with a Doppler frequency above 6.5 MHz (Hitachi HA700, Hitachi Medical Systems). This probe gives a high frequency range up to 13 MHz and is designed for high resolution imaging of superficial structures. Each patient was examined using standard settings (frequencies of 13.0 MHz for B-mode and 9.0 MHz for colour-mode scanning).

Ultrasound examination of the temporal arteries included longitudinal and transverse views of the common superficial temporal arteries and the frontal and parietal branches on both sides as completely as possible (dynamic range 45–50 dB, wall filter low or general, pulse repetition frequency 2250 Hz). The temporal and common carotid artery wall thicknesses on both sides were also routinely examined. Precise definitions and measurements for the presence or absence of disease were not routinely applied when reporting ultrasound scans, as they are not when clinicians make judgments about the presence or absence of clinical signs. This reflects clinical practice. However, ultrasound studies were regarded as positive if one of the following major features of vessel wall inflammation was present: perivascular wall thickening, arbitrarily defined as a homogenous wall swelling of at least 1 mm, or a halo sign, defined as either an eccentric or concentric hypoechoic ring (perivascular oedema) around the vessel wall. A halo sign was ascertained as present only if it appeared repeatedly in both planes. Presence of a halo sign was not mandatory for defining arteritis. Features such as occlusions and stenoses alone were not sufficient to designate a scan as positive but, if present with another feature such as perivascular thickening or presence of a halo sign, were reported as positive. Occlusions were reported when colour flow was not delineated. Stenoses, in our practice, required an artery lumen of less than 50% of the original lumen with increased systolic and diastolic blood flow velocities.

Two investigators independently reviewed CDUS radiology reports. Reports were classified as either showing, or not showing, evidence of an arteritis or not. Only unequivocally positive CDUS data were regarded as positive. Uncertain results were designated negative.

TABLE 1 Characteristics of patients, comparing those with a clinical diagnosis of GCA and those not diagnosed

	GCA (n=36)	Not GCA (n=51)
Age (years) (SD)	75 (9)	71 (8)
Female (%)	26 (72)	34 (67)
ESR (mm) (SD)	87 (32)	67 (28)
CRP (mg/L) (SD)	62 (18)	47 (14)
Platelets ($x10^9$) (SD)	388 (88)	281 (78)
Temporal headache (%)	33 (92)	47 (92)
Temporal tenderness (%)	26 (72)	4 (8)
Jaw claudication (%)	13 (36)	3 (6)
Visual disturbance (%)	17 (47)	25 (49)
PMR symptoms (%)	22 (61)	27 (53)
Weight loss (%)	6 (17)	9 (18)
Thickened TA (%)	18 (50)	2 (4)

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PMR: polymyalgia rheumatica; TA: temporal artery

The treating physician determined whether a temporal artery biopsy was done; our usual practice is to do a unilateral temporal artery biopsy. In all cases this was done after ultrasound studies and as soon as feasibly possible. There was no protocol requiring that biopsies were done on sections of arteries known to be affected on CDUS. For the purposes of this study a biopsy was considered positive if the reporting pathologist concluded this in their report. Equivocal reports were designated negative.

The relationship between the ACR criteria alone or in combination with CDUS and a final clinical diagnosis of GCA was analysed. The diagnostic accuracy of CDUS and ACR criteria was compared to the gold standard of clinical diagnosis and temporal artery biopsy, where the latter was performed.

RESULTS

CDUS studies of cranial soft tissues were done in 87 patients with suspected GCA. Patient characteristics are shown in Table 1 and the study flow diagram and diagnostic pathway for the cohort, illustrating the role of temporal artery biopsy, is shown in Figure 1. Fifty-seven (66%) patients had a negative CDUS and 30 (34%) a positive CDUS. Of CDUS positive patients 16 (53%) had a positive temporal artery halo sign alone, in 8 (27%) a bilateral halo was seen. Vessel wall thickening was seen in 13 (43%) and 4 (13%) had both a halo and vessel wall thickening. Vessel occlusion (believed to be due to previous GCA) and stenosis (luminal narrowing) was reported in only one case. Six patients had evidence of inflammatory thickening of the common carotid artery on CDUS, in association with other features of GCA and never in isolation. Therefore the presence of carotid thickening alone was insufficient to diagnose GCA and did not contribute to the clinical utility of the test.

TABLE 2 Diagnostic accuracy of colour Doppler ultrasound for giant cell arteritis

	Sensitivity	Specificity	PLR	NLR	PPV	NPV	DOR
Clinical diagnosis as gold standard (n=87)*							
CDUS	81% (64–92)	98% (90–100)	41 (6–288)	0.2 (0.1–0.4)	97% (83–99)	87% (76–95)	207 (24–1769)
ACR	58% (41–74)	71% (56–83)	2.0 (1.2–3.3)	0.6 (0.4–0.9)	58% (41–74)	71% (56–83)	3.4 (1–8.2)
CDUS+ACR	50% (33–67)	98% (90–100)	26 (4–182)	0.5 (0.4–0.7)	94% (74–99)	74% (61–83)	50 (6–402)
Clinical diagnosis as gold standard in patients having a biopsy (n=24)							
TAB	53% (27–79)	100% (66–100)	-	0.5 (0.3–0.8)	100% (63–100)	56% (30–80)	26 (1–522)
TAB confirmed GCA as gold standard							
CDUS	88% (47–98)	63% (35–85)	2.3 (1.2–4.6)	0.2 (0–1.3)	54% (25–81)	91% (59–98)	12 (1–119)

ACR: American College for Rheumatology criteria for GCA; CDUS: colour Doppler ultrasound; DOR: diagnostic odds ratio; NLR: negative likelihood ratio; NPV: negative predictive value; PLR: positive likelihood ratio; PPV: positive predictive value; TAB: temporal artery biopsy. *Data in brackets shows 95% confidence intervals

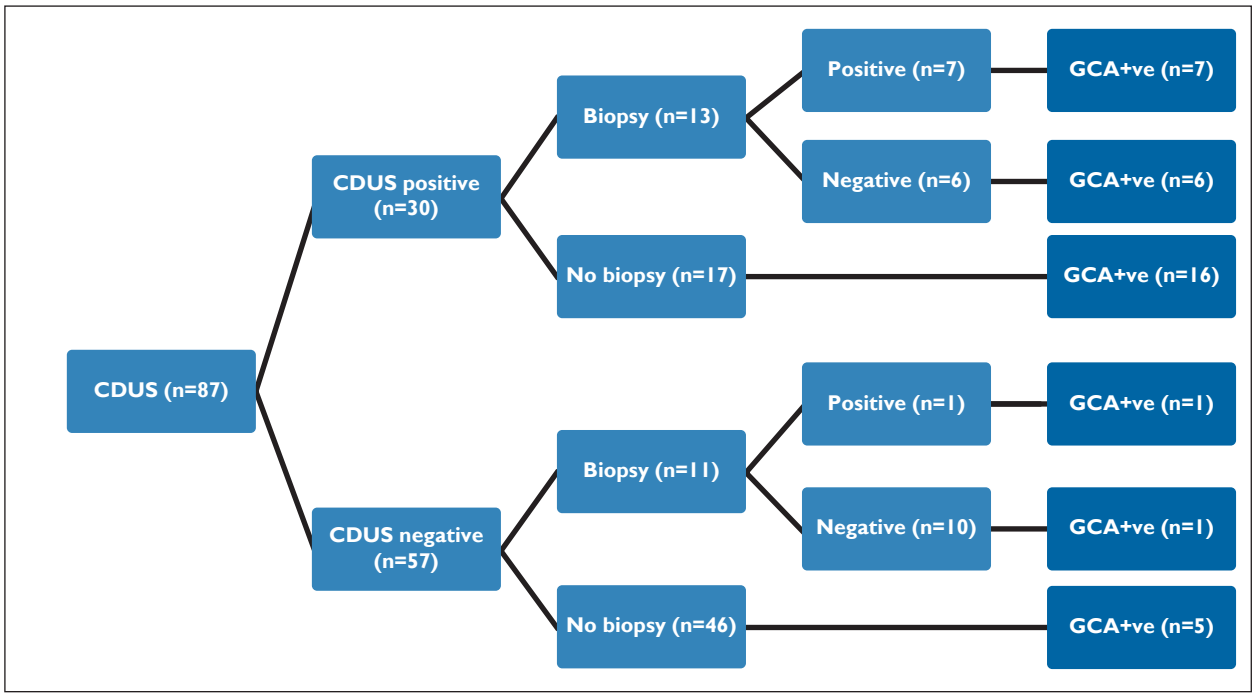

FIGURE 1 Study flow diagram illustrating use of temporal artery biopsy in patients undergoing CDUS for suspected GCA

At the time of CDUS, 51/87 (59%) patients were taking oral corticosteroids at doses between 30–60 mg a day for a median duration of 4 days (range 1–11 days). Corticosteroids were discontinued over a maximum of 4 weeks in 50/57 cases with a negative CDUS and who were eventually diagnosed as not having GCA. There were no adverse consequences in these patients.

A temporal artery biopsy was performed in 13/30 (43%) CDUS positive patients and 11/57 (19%) CDUS negative patients (Figure 1). Biopsy was more likely to be done in CDUS positive patients: relative risk (RR 2.2, 95% CI 1.1–4.4, p = 0.04). Of the 24 biopsies done, 8 (33%) showed evidence of arteritis. Of the CDUS positive patients, 7/13 (54%) had a positive biopsy compared with 1/11 (9%) CDUS negative patients. Data for the positive and negative predictive value (PPV and NPV) and other data for diagnostic precision are shown in Table 2. The temporal artery biopsy had a false negative rate of 44% (95% CI 19–68%) in our study.

The PPV of CDUS, the number of patients who test positive who actually have disease, was 97% (95%CI, 93–99%) compared to our gold or reference standard of clinical diagnosis after a minimum follow-up of 3 months.

The NPV of CDUS, those with a negative result who truly do not have disease, was 88% (95%CI 76–95%). Comparable values for ACR criteria, a combination of ACR criteria and CDUS and temporal artery biopsy are shown in Table 2. Combining ACR criteria and CDUS results yielded worse PPV and NPV values than if CDUS result alone was used.

Sensitivity and specificity of CDUS for a clinical diagnosis of GCA were 81% (95%CI 64–92%) and 98% (95%CI 90–100%), respectively (Table 2). The diagnostic odds ratio for CDUS was 207 (95%CI 24–1769), by contrast the ratio for ACR criteria was 3.4 (95%CI 1.0–8.2).

DISCUSSION

The pathways for investigating and managing a patient with suspected GCA show considerable variation, in part due to variable clinical presentations but also to variable local interest and expertise, including access to investigations such as CDUS and temporal artery biopsy. This problem is compounded by a doubling of hospital admissions with suspected GCA in the past decade.[5]

CDUS is currently not widely used for the diagnosis of GCA. Our data indicate that a positive CDUS (usually indicating the presence of a halo sign and/or perivascular wall thickening), as judged by an experienced radiologist, had a high PPV (97%) and a good NPV (88%) for GCA diagnosed by a senior clinician after follow-up of at least 3 months. A meta-analysis[6] of the diagnostic value of CDUS focusing on the halo sign alone, concluded that the pooled diagnostic odds ratio of the halo sign for GCA was 34 (95%CI 8–138) compared with our value of 207 (95%CI 24–1769). Our study used clinician diagnosis after 3 months follow-up as the reference or gold standard for GCA diagnosis, whereas Arida et al. relied on ACR criteria as the reference standard.[6] We show that ACR criteria alone had a poor predictive value (PPV 58%) for clinician diagnosed GCA. The limitations of ACR classification criteria for clinical diagnosis of vasculitis have been highlighted elsewhere.[7]

Temporal artery biopsy is regarded by some as the reference standard for GCA diagnosis. Yet many published series show that GCA is commonly diagnosed with negative biopsies and it is widely appreciated that GCA may occur without involvement of the temporal arteries. It is possible that this knowledge and local confidence in CDUS results led to a decision to manage patients as though they had GCA, or not, without recourse to biopsy. In our study, it appeared that diagnostic uncertainty led to the next, more invasive, step of biopsy in order to gain diagnostic and managerial confidence. Thus temporal artery biopsy and CDUS appear not to be used as competitor tests but rather as complementary investigations. This seems appropriate bearing in mind that temporal artery biopsy has high specificity but lacks sensitivity, is invasive and has potential complications. For example, the recently completed but unpublished multicentre study of temporal artery ultrasound versus biopsy in the diagnosis of GCA (TABUL) reported that investigators failed to obtain an artery in 6.3% of cases and that inadvertent nerve biopsies were done in 0.5% of cases [Singh S et al, data presented to American College for Rheumatology meeting, November 2014].

High dose steroids may modify sonographic findings. In our study 59% were given steroids prior to CDUS and all patients were scanned within 11 days. There is evidence that halo size on CDUS decreases rapidly within the first 7 days of steroid treatment (Serafim AS, data presented to British Rheumatology Society, April 2015). However, other studies indicate that a halo seldom disappears before 2 months.[8,9,10]

All patients with a positive CDUS in our study received a final diagnosis of GCA with the exception of one patient with low risk clinical features (headache, normal inflammatory markers). This patient did not receive steroids prior to CDUS and no halo sign was found but temporal artery thickening was seen, resulting in a classification consistent with a diagnosis of GCA. On review, symptoms had resolved and inflammatory markers remained normal and thus GCA was not diagnosed at clinical review.

Seven patients were diagnosed with GCA despite a negative CDUS. All seven had convincing clinical features such that clinicians chose to treat as GCA despite a negative CDUS. Such an approach is common where only biopsy, rather than non-invasive tests, are available to investigate GCA and entirely justified where treatment may have modified the test result. One might argue that a diagnostic test is unnecessary in this situation, especially an invasive test. CDUS however is non-invasive and free of complications. As there is potential for prolonged corticosteroid therapy, supportive imaging data may increase clinical confidence and allow a potential avenue for monitoring disease activity by repeating CDUS as steroid therapy is tapered. Of these seven patients with a negative CDUS, two had biopsies and one was positive.

Our study has a number of limitations. First, retrospective observational cohort studies such as ours are prone to a number of biases;[12] in particular, work-up and verification bias. Thus the choice of subsequent tests or actions, including a managerial decision to treat a patient for GCA (our reference standard) and decision to perform temporal artery biopsy, was likely to have been influenced by preceding tests such as the CDUS result. Also our study was confined to a population undergoing CDUS but did not include patients assessed by clinical means alone or with diagnostic tests such as PET-CT or temporal artery biopsy without CDUS.

Our study design does not permit clear conclusions about the diagnostic performance of CDUS since studies such as ours are known to overestimate sensitivity and specificity.[11,12,13] Sensitivity and specificity tend to be regarded as a stable characteristic of a diagnostic test but variations are commonly found in different populations, independent of disease prevalence. This is true in diseases such as GCA where presence or absence of disease is not black and white.[13]

Another aspect of whether our data are generalisable relates to radiological expertise. Reports from radiology, as is true in routine care, described findings of imaging and depended on judgments made, rather than very precise measurements to determine whether disease was present or not. Most of our scans were done by a single radiologist who was not blinded to clinical data. This in turn may have introduced biases in reporting. However we do not believe that radiological interpretation of CDUS requires unique skills. Our view is supported by other studies indicating the value of CDUS for GCA, including meta-analyses.[6,12]

Despite these study limitations we suggest an alternative approach to the diagnostic pathway in evaluating suspected GCA is feasible. This requires a coordinated response to local service organisation including access to radiological skills. We propose that CDUS should precede temporal artery biopsy, not for the purposes of guiding biopsies, as has been suggested elsewhere,[14] but as a first decision aid. Clinicians who judge, on the basis of clinical features, routine laboratory data and CDUS, that there is still uncertainty about diagnosis should proceed to temporal artery biopsy with patient consent and informed discussion.

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