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ARTICLE

Comparison of temporal artery ultrasound versus biopsy in the diagnosis of giant cell arteritis

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BACKGROUND/OBJECTIVES: Giant cell arteritis (GCA) is a medical and ophthalmological emergency due to risk of stroke and sudden irreversible loss of vision. Fast and accurate diagnosis is important to prevent complications and long-term high dose glucocorticoids toxicity. Temporal artery biopsy is gold standard for diagnosing GCA. However, temporal artery ultrasound is a fast and non-invasive procedure which may provide a supplement or an alternative to biopsy. This study assesses the diagnostic performance of ultrasound and biopsy in the diagnosis of GCA.
SUBJECTS/METHODS: Examination results of patients suspected of having GCA in the period from August 2018 to June 2019 were reviewed. Patients underwent clinical examination and blood tests. Within a few days of starting glucocorticoid treatment, temporal ultrasound and unilateral biopsy were performed. Experienced physicians established the final clinical diagnosis at 6-months follow-up.
RESULTS: Seventy-eight patients underwent both ultrasound and biopsy. Thirty-five (45%) received the final clinical diagnosis of GCA. Compared with the final clinical diagnosis, biopsy had a sensitivity of 69% (51–83%) and a specificity of 100% (92–100%), and ultrasound a sensitivity of 63% (45–79%) and a specificity of 79% (64–94%). Area under the receiver operating characteristics curves were 0.84 and 0.71 for biopsy and ultrasound respectively ($p = 0.048$). False negative rate of ultrasound was 4 out of 78 (5%).
CONCLUSION: Sensitivity of ultrasound is almost on par with that of biopsy although the overall diagnostic accuracy of ultrasound was slightly lower. We find that ultrasound is a reliable tool for first line diagnosis of GCA.

INTRODUCTION

Giant cell arteritis (GCA) is the most common large vessel vasculitis in patients aged over 50 years. GCA is common in Scandinavia, the annual incidence in Skåne, Sweden, is 14.1 per 100.000 inhabitants aged ≥ 50 years [1]. While the etiology of GCA is unknown, it is likely that both genetic and environmental factors initiate the inflammatory cascade [2]. GCA is a medical and ophthalmological emergency, where rapid and accurate diagnosis is critical to prevent acute irreversible vision loss and stroke. Due to glucocorticoid-related side effects and toxicity, it is also important to promptly identify patients without GCA. Clinically, it may be difficult to diagnose the disease due to insidious symptoms. One approach can be based on the American College of Rheumatology (ACR) 1990 GCA classification criteria, where a patient is said to have GCA if at least 3 of 5 criteria are present. The 5 criteria are age ≥ 50 years, new headache, temporal artery abnormality, elevated erythrocyte sedimentation rate (ESR) ≥ 50 mm/h and abnormal artery biopsy [3]. These criteria are not diagnostic for GCA but can be applied to differentiate GCA from other types of vasculitis. A quarter of patients with a positive biopsy would not have been diagnosed with GCA using these criteria [4]. New ACR/

EULAR criteria for GCA are currently being developed. A temporal artery biopsy is generally used to confirm the diagnosis. However, biopsy as a reference test is not optimal due to low sensitivity. Although a positive biopsy confirms the diagnosis of GCA, a negative biopsy does not rule out the diagnosis. Even though a biopsy is considered a minor invasive procedure, complications can occur and there is a delay from procedure to pathology result. In the field of rheumatology, temporal artery ultrasound has become an increasingly important diagnostic tool in GCA and is now recommended by the European League Against Rheumatism (EULAR) as the first-line diagnostic procedure in patients with predominantly cranial symptoms of GCA [5], if skilled sonographers are available. When using ultrasound in combination with clinical GCA symptoms, the diagnosis could be given or rejected instantly. Pathological characteristics found by ultrasound are increased vessel wall thickening (halo-sign) and non-compressible arteries due to vessel wall thickening (positive compression sign). The inflammation in the vessel wall may also cause stenosis and vessel occlusion [5–8] and can lead to ischemia and necrosis in the end-tissue. Fast-track clinics with ultrasound for patients suspected of having GCA are increasing in numbers, and ultrasound

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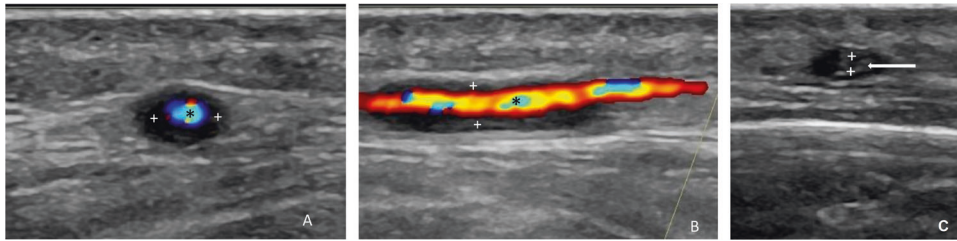
Fig. 1 Temporal artery—common branch. Halo sign: central flow (*) and thickened vessel wall (+). A Transverse view. **B** Longitudinal view. **C** Temporal artery—common branch, transverse view. Compression sign: thickened vessel wall (+), compressed lumen (arrow).

is a non-invasive and cost-efficient [9] procedure. Several studies have shown ultrasound to have a high sensitivity and specificity [5, 6, 9]. The use of diagnostic tests like temporal artery biopsy and ultrasound to confirm GCA should be standard practice. The use of confirmatory tests for GCA is recommended to prevent unnecessary use of glucocorticoids and prescription of second line therapies such as IL-6 inhibitors [10].

A "Real-World" single-centre study was carried out. The purpose of this study was to test the clinical performance of ultrasound as a first line diagnostic of GCA compared with clinical diagnosis and biopsy as the gold standard.

METHODS
Study design and participants
This cross-sectional study was conducted at Rigshospitalet, Glostrup, Denmark, at the Departments of Ophthalmology and Rheumatology (Ethics Committee for the Capital Region of Denmark H-20082624).

The examination results of patients suspected of having GCA in the period from August 2018 to June 2019 were reviewed. All consecutive patients clinically suspected of GCA and referred to a biopsy at the Department of Ophthalmology between August 2018 and June 2019, were included in the study. The cohort included two categories of patients which were grouped: patients seen by the on-call ophthalmologist with ophthalmic symptoms and patients referred from external departments to have a biopsy performed. If GCA was suspected, inflammatory marker blood tests were taken and glucocorticoid treatment initiated. An ophthalmological examination was performed if the patient presented with ophthalmological symptoms. Diagnostic ultrasound was performed immediately prior to biopsy within 14 days of presenting symptoms.

Results from ophthalmological examinations and vascular imaging (ultrasound) were recorded along with C-reactive protein, ESR, blood platelets, and complete blood count. Expert physicians in rheumatology and ultrasonography and expert physicians in neuro-ophthalmology, respectively, established the final clinical diagnosis with a minimum follow-up of 6-months.

The clinical diagnoses "definite GCA" and "definite non-GCA" were given by reviewing a standardized set of data from the first 6 months after initial presentation. Data included symptoms, examination findings, medication, inflammatory markers, vascular imaging, and biopsy results. In case of doubt, agreement was reached by expert consensus.

Test methods
Temporal artery biopsy. Clinically guided unilateral biopsy was performed according to ophthalmology department guidelines as a routine procedure. The biopsy was reviewed by pathologists at the Department of Pathology, Rigshospitalet, Copenhagen, Denmark. Pathologists were masked to the blood tests and vascular imaging.

A positive biopsy was defined as having inflammation (vasculitis) in one or more layers of the main artery wall (intima, media and/or adventitia) characterized by predominance of mononuclear cells or granulomatous inflammation with or without giant cells. Biopsies were performed unilaterally at a length of minimum 1.5 cm, but preferably 2 cm. All surgeries were made by oculoplastic consultants or by residents under the supervision of an oculoplastic consultant. The biopsies were preferably taken on the symptomatic side.

Temporal ultrasound. Ultrasound scans were performed using a GE Logiq® E9 R5 (Milwaukee, Wisconsin, USA) ultrasound machine with 5–16 ML and

L8-18i D linear array transducers. The Doppler frequency was set at 7.5 MHz, color priority at 100%, and Doppler gain just below the noise level. Pulse repetition frequency was adjusted according to the size of the vessel.

Ultrasound was performed by expert rheumatological ultrasonographers (>15 years of musculoskeletal ultrasound experience and >7 years of experience with vascular ultrasound) prior to biopsy and within days of presenting symptoms. The temporal arteries were examined bilaterally from the common trunk to the parietal and frontal branches as far distally as possible.

Wall thickening was registered as halo sign (Fig. 1), defined as homogenous, hypoechoic wall thickening [11], and positive compression sign. A positive compression sign was defined according to the consensus based and validated Outcome Measures in Rheumatology (OMERACT) ultrasound definition [12, 13] as a thickened arterial wall that remains visible upon compression with the ultrasound probe. (Fig. 1). Reduced flow was noted as present if Doppler signal in the vessel could only be demonstrated with difficulty despite adjustment of settings. Standard cut-off values in millimeter for intima-media thickness in temporal arteries were used [6].

A positive ultrasound for GCA was defined as either a positive compression sign or a positive halo sign in one or more of the temporal artery branches, as both signs have been used as a positive ultrasound finding of wall swelling compatible with GCA. No attempt was made to distinguish between the two.

If ultrasound was inconclusive, it was considered not positive for GCA. The ultrasonographers were masked to the clinical symptoms. Each ultrasound exam lasted around 20 min.

Statistical analysis
Statistics were performed using the IBM SPSS Statistics version 25 (IBM, Armonk, NY, USA). We summarized data using descriptive statistics. Continuous data were reported using mean and standard deviation and compared using parametric tests if normal distribution was present, and otherwise reported using median and interquartile range and compared using non-parametric tests. Categorical data were compared using the Pearson's chi-square test. Diagnostic test accuracy for ultrasound (index test) and biopsy (index test) were compared to final clinical diagnosis (reference test). We calculated sensitivity, specificity, positive predictive value, and negative predictive value. Confidence intervals for positive and negative predictive values were calculated using the method described by Mercado et al. (2007). Diagnostic test accuracy statistics were calculated using MedCalc (MedCalc Software Ltd, Ostend, Belgium). We calculated the area under the curve (AUC) of the receiver operating characteristic (ROC) curve for each of the index tests investigated. The difference between AUCs was compared by the Z-test. We then evaluated the consequences of an ultrasound-based system rather than a biopsy-based system by comparing the ultrasound test with the biopsy test in a 2×2 contingency table and reviewing individual cases that were ultrasound negative but biopsy positive. P values below 0.05 were considered statistically significant.

RESULTS
Study sample
During the study period, 106 consecutive patients with suspected GCA were evaluated. Twenty-eight patients were excluded either due to invalid biopsy (biopsy of a nerve or a vein) or because the patient did not turn up for ultrasound examination. Thus, 78 individuals were included in the analyses, of which 35 (45%) were diagnosed with GCA. The mean age was 71.9 (SD 9.3) years and 57 (73%) were females.

Patients with GCA did not differ significantly in age ($p = 0.449$, *independent samples t-test*) or gender distribution ($p = 0.214$, *Chi-squared test*) from those without GCA (Table 1).

Clinical description of cases with giant cell arteritis

Of the 106 cases, 38 (36%) presented with ocular symptoms. Fifteen (14%) reported visual loss, 9 (8%) blurry vision, 5 (5%) amaurosis fugax, 4 (4%) ocular pain, 3 (3%) diplopia, and 2 (2%) transient diplopia.

Of the 106 cases, 31 received an ocular diagnosis. Thirteen (12%) had anterior ischaemic optic neuropathy, 4 (4%) sixth nerve palsy, 3 (3%) central retinal artery occlusion, 2 (2%) third nerve palsy, 1 (1%) retinal vasculitis, 1 (1%) branch retinal artery occlusion, 1 (1%) (unspecified) optic neuropathy, 1 (1%) epiretinal fibrosis, 1 (1%) posterior ischaemic optic neuropathy, 1 (1%) cataract, 1 (1%) non-arteritic anterior ischaemic optic neuropathy, 1 (1%) vasospasm, and 1 (1%) visual loss of unknown etiology. Seventy-five (71%) received no ocular diagnosis.

Among the 35 cases with the final clinical diagnosis of GCA, 28 (80%) had three or more ACR 1990 GCA classification criteria (Table 1). Having three or more ACR criteria were significantly more frequent in patients with GCA than among those without GCA 12 (27%) ($p < 0.001$, *Chi-squared test*).

Of the 35 cases with GCA confirmed, 26 (74%) had no ocular diagnosis, 5 (14%) had anterior ischaemic optic neuropathy, 2 (6%) sixth nerve palsy, 1 (3%) third nerve palsy, and 1 (3%) retinal vasculitis.

Diagnostic performance of ultrasound and temporal artery biopsy

Of the 78 patients who underwent biopsy and ultrasound, biopsy was positive in 24 (31%) cases, all of which were clinically diagnosed with GCA. Among the remaining 54 (69%) cases with a negative biopsy, 11 cases were clinically diagnosed with GCA. In comparison, ultrasound was positive in 31 (40%). Of these 22 were clinically diagnosed with GCA, whereas 9 were false positives.

Among the remaining 47 (60%) cases with negative GCA-findings by ultrasound, 13 cases were clinically diagnosed with GCA. Diagnostic test accuracy measures are presented in Table 2. Biopsy and ultrasound had comparable sensitivities (69%, 95% CI: 51–83%; 63%, 95% CI: 45–79%; respectively, for biopsy and ultrasound), whereas specificity was higher in biopsy compared with ultrasound (100%, 95% CI: 92–100%; 79%, 95% CI: 64–94%; respectively for biopsy and ultrasound). The AUC of ROC curves for biopsy and ultrasound differed ($\text{AUC}_{biopsy} - \text{AUC}_{ultrasound} = 0.133$, CI: 0.0015–0.265, *Z-test*; $p = 0.048$). (Fig. 2, Table 2).

We found that most patients with positive biopsy were also test positive on the ultrasound, and most patients who with negative biopsy were also test negative on the ultrasound. Ultrasound led

Table 1. Patient characteristics.

	GCA	Non-GCA	*p* value	Total
Age, mean (SD)	72.8 (7.6)	71.2 (10.5)	0.449	71.9 (9.3)
Gender, n (%)				
Female	28 (80)	29 (67)	0.214	57
Male	7 (20)	14 (33)		21
ACR criteria, n (%)				
≥3	28 (80)	12 (27)	<0.001	40
<3	7 (20)	31 (73)		38
Time from glucocorticoid to (median no. of days (Q1–Q3))				
Biopsy	7 (4–8.5)	6 (4–8.5)	0.984	6.5 (4–8)
Ultrasound	5 (3–7.5)	4 (2–6.5)	0.226	4 (2–7)

The ACR 1990 GCA classification criteria is based on a score system where the presence of three or more of five items is required for a clinical diagnosis of GCA. These are: (1) Age of onset ≥50 years; (2) A new headache; (3) Temporal artery abnormality such as tenderness to palpation or decreased pulsation; (4) Erythrocyte sedimentation rate ≥50 mm/h; (5) Abnormal artery biopsy showing vasculitis with mononuclear cell or granulomatous inflammation, usually with giant cell infiltrates. Median *p* value, Mann–Whitney U Test.
ACR American College of Rheumatology, *GCA* giant cell arteritis.

Table 2. Diagnostic performance of temporal artery biopsy and ultrasound features for detecting giant cell arteritis.

		Clinical diagnosis			Performance [95% Confidence interval]
		GCA (*n* = 35)	Non-GCA (*n* = 43)	Total	
Temporal Artery Biopsy	Positive	24	0	24	Sn: 0.69 [0.51;0.83]
	Negative	11	43	54	Sp: 1.00 [0.92;1.00] PPV: 1.00[a] NPV: 0.80 [0.71;0.86] AUC: 0.84 [0.75;0.94]
Ultrasound Compression sign	Positive	22	9	31	Sn: 0.63 [0.45;0.79]
	Negative	13	34	47	Sp: 0.79 [0.64;0.94] PPV: 0.71 [0.57;0.82] NPV: 0.72 [0.62;0.81] AUC: 0.71 [0.59;0.83][b]
Ultrasound Halo-sign	Positive	16	5	21	Sn: 0.47 [0.30;0.65]
	Negative	18	16	34	Sp: 0.77 [0.53;0.92] PPV: 0.76 [0.58;0.88] NPV: 0.47 [0.37;0.57] AUC: 0.67 [0.55;0.80]
Ultrasound Reduced flow	Positive	2	3	5	Sn: 0.06 [0.01;0.20]
	Negative	31	38	69	Sp: 0.93 [0.80;0.98] PPV: 0.40 [0.11;0.79] NPV: 0.55 [0.52;0.58] AUC: 0.49 [0.36;0.63]

AUC area under the curve, *PPV* positive predictive value, *N* number, *NPV* negative predictive value, *Sp* Specificity, *Sn* Sensitivity.
[a]Not possible to calculate due to division by zero.
[b]Significant difference between temporal artery biopsy and ultrasound ($p = 0.048$).
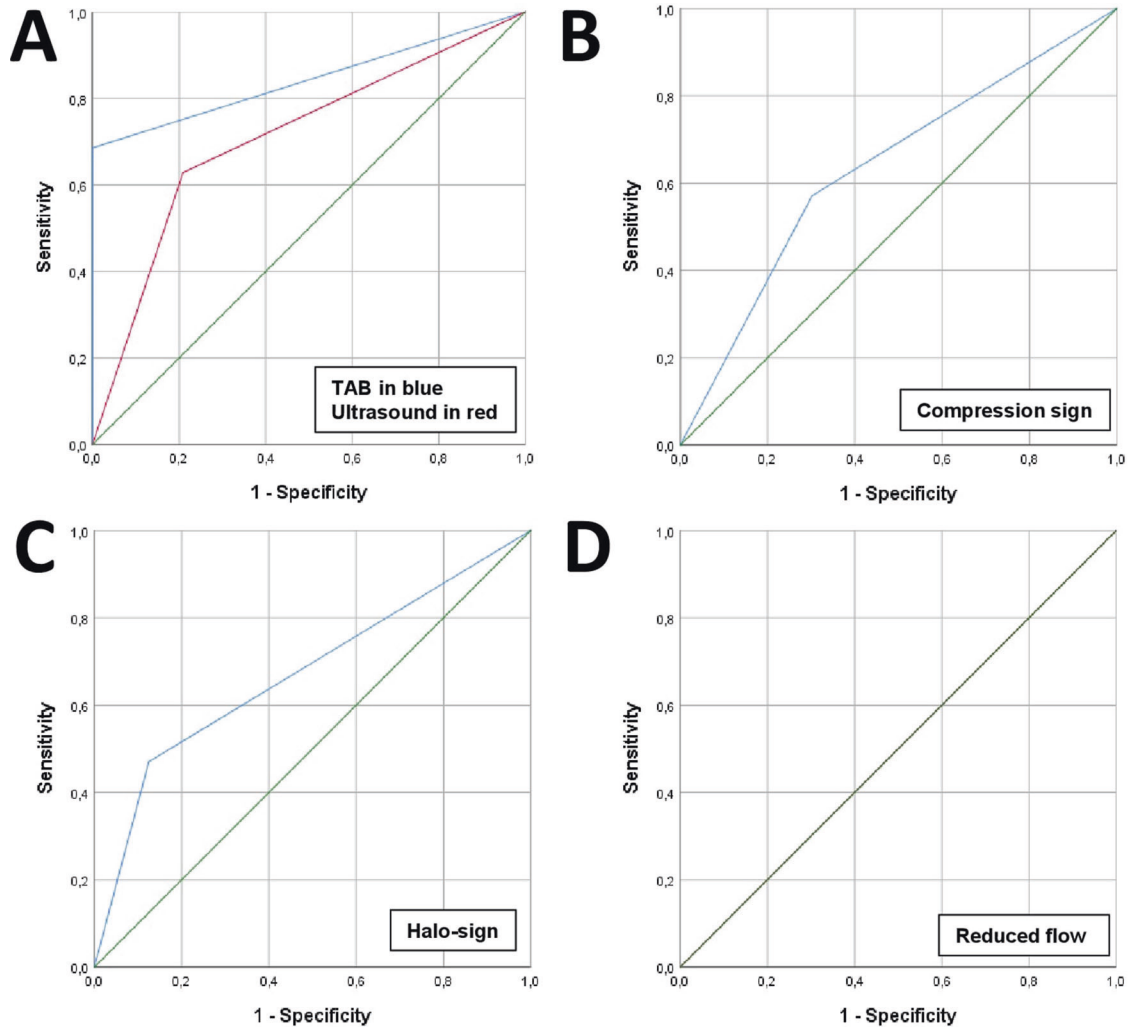
Fig. 2 Receiver operating characteristic (ROC) curves in diagnosis of giant cell arteritis. The reference line is shown in green. **A** ROC curve of temporal artery biopsy (in blue) and ultrasound (in red) (**B**) ROC curve of compression sign. **C** ROC curve of halo-sign. **D** ROC curve of reduced flow (overlapping with reference line).

Table 3. 2 × 2 contingency table of the performance of temporal artery biopsy and ultrasound.

		Temporal artery biopsy		
		Positive	**Negative**	**Total**
Ultrasound[a]	Positive	20	11	31
	Negative	4	43	47
	Total	24	54	78

[a]A Positive ultrasound for GCA was defined as positive compression sign of one or more of the temporal artery branches.
A positive biopsy was defined as having inflammation through one or more layers of the main artery wall and the presence of giant cells.

to more positive tests and fewer negative tests than did biopsy (Table 3).

Eleven patients had a negative test on biopsy and a positive test on ultrasound. These consisted of two cases (18%) with GCA and nine without (82%).

Four patients had a positive test on biopsy and a negative test on ultrasound. All these cases had clinical GCA.

Diagnostic performance of individual ultrasound features of giant cell arteritis
Compression sign had the best diagnostic performance of the individual ultrasound features (Table 2). ROC curves demonstrating the relationship between individual ultrasound lesions and the final clinical diagnosis of GCA are shown in Fig. 2. The highest AUC were seen using compression sign (AUC = 0.71) followed by halo sign (AUC 0.67) and, reduced flow (AUC = 0.49).

DISCUSSION
In this clinical study based on review of 106 consecutive patients suspected of having GCA of whom 78 underwent ultrasound and biopsy, we found a comparable sensitivity of the two methods for first line diagnosis of GCA. The lower specificity of ultrasound resulted in a slightly lower overall diagnostic accuracy. The patients with GCA with negative biopsy or ultrasound all presented with marked clinical symptoms, markedly abnormal inflammatory markers and/or fulfilled 3 or more of the ACR criteria.

Biopsy has remained the gold standard for diagnosing GCA for decades, a positive biopsy confirming the diagnosis. Still, the procedure is not without limitations and it lacks sensitivity. The true sensitivity is unknown but is estimated to be 87.1% [14]. Our

study found a biopsy specificity of 100% and a slightly lower sensitivity of 69%.

In an era of emerging non-invasive imaging techniques for diagnosis of GCA, the clinical set-up for managing suspected GCA patients is changing. Different clinical tools have different strength and limitations when diagnosing GCA.

Although a positive biopsy confirms the defining pathological feature of GCA, limitations of biopsy include a high rate of false negatives, which may be due to skip lesions in the relatively short vessel segment examined [15, 16]. Another factor is the pathologist´s assessment of the biopsy. Pathologist interobserver variation ranging between 4.3 and 13.5% has been reported [17]. Performing biopsy demands a surgical set-up with pathology service. Also, the procedure puts the often elderly, fragile patient at perioperative discomfort and risk of surgical complications such as damage to the facial nerve, infection, and hematoma. Finally, awaiting the result of the biopsy may delay the diagnosis for up to 2 weeks or more.

The use of ultrasound has emerged as an accessible, fast, and non-invasive tool for the diagnosis of GCA. Ultrasound for diagnosing GCA was proposed in 1997 by Schmidt et al. [7], and its use has since been supported by increasing evidence. Using ultrasound for GCA, information from the entire length of the artery becomes available, thus potentially overcoming challenges with skip lesions and insufficient length of the biopsy specimen.

The performance of ultrasound has been evaluated in several studies. In a meta-analysis on which the EULAR recommendations were based, Duftner et al. found a sensitivity of 77% (95% CI 62–87%) and a specificity of 96% (95% CI 85–99%) using ultrasound (halo sign) as an index test and clinical diagnosis as reference standard [18]. Using TAB as a reference standard the sensitivity was 70% (95% CI 56–81%) and specificity was 84% (95% CI 73–91%) [18].

In our study, we used the compression sign as an indicator for positive GCA ultrasound. Studies have found it to be reliable, simple and on par with the halo sign [11, 19]. The use of ultrasound in a fast-track set-up for early diagnosis of GCA has been found to significantly reduce the number of patients with visual impairment [20, 21]. We found that the compression sign was more specific than the halo sign for the GCA diagnosis. Compression sign is recommended to be used to confirm a halo sign [22]. Other signs like stenosis, occlusion or, as in our study, reduced flow have not been found to be as specific or sensitive for GCA. The use of ultrasound in assessment of suspected GCA patients is in accordance with newly published EULAR recommendations for managing GCA and enables rapid diagnosis of large vessel vasculitis with low burden to patients. Ultrasound is therefore recommended as the first diagnostic test provided it is readily available and performed with high quality [5].

Finally, the cost of biopsy is higher than ultrasound. The TABUL study found a cost-effectiveness of £485 per patient in favor of ultrasound [9]. We estimate a cost saving of 3.782 DKK (£457) per patient in favor of ultrasound.

Ocular complications to GCA include cranial nerve palsy and anterior ischaemic optic neuropathy, of which the latter is a feared complication that can lead to blindness. Ocular involvement was diagnosed in nine of 35 (26%) patients with GCA. This is consistent with other studies that found an ocular involvement of 33.9% [23].

The study has its limitations. Randomization to different examination modalities was not possible due to the acute nature of the disease. The axillary artery was not scanned as part of the ultrasound procedure. There is evidence to support improved diagnostic yield when performing axillary artery ultrasound [24]. Also, most study participants were referred to our department due to cranial symptoms, which may give rise to selection bias. This may, however, work in favor of biopsy. Only 22 (21%) patients were lost to follow-up. Ideally biopsy and ultrasound were performed on the same day and ideally only a few days after

prescribing glucocorticoid treatment. The vast majority of patients had it done within one week. This is a potential source of bias. Another limitation is the use of "GCA" and "no GCA" as the only categories for the clinical diagnosis. Adding "possible GCA" could potentially have increased the diagnostic certainty. Lastly patients were excluded when ultrasound could not be performed. This is another potential source of bias. The strengths of the study were the use of highly trained ultrasonographers, the use of validated, consensus-based ultrasound definitions, and biopsy evaluation by a small group of pathologists. The final ophthalmological diagnosis was given by a highly experienced neuro-ophthalmologist.

In conclusion, this clinical study supports the EULAR recommendations advocating the use of ultrasound as first line imaging modality for diagnosing GCA. The procedure is well tolerated, fast, non-invasive, and cost-effective. More prospective studies are needed to evaluate procedures like ultrasound, biopsy, and 18F-fluorodeoxyglucose positron emission tomography/computed tomography and their individual place and role in the diagnostic set-up of GCA patients.

SUMMARY

What was known before

- Biopsy was the "gold Standard" for confirmation and diagnosis of GCA.
- GCA remains a medical emergency and can be difficult to diagnose.
- Scandinavia has a high GCA incidence, and easy access to confirmatory tests is important.

What this study adds

- Confirmatory tests for GCA should be standard practice.
- This clinical study supports the use of temporal ultrasound as first line imaging modality for diagnosing GCA.
- Ultrasound is well tolerated, fast, non-invasive, and cost-effective.

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AUTHOR CONTRIBUTIONS

MSH: literature review, drafting of the paper, and data collection. LT: rheumatology expert in GCA and ultrasound; drafting and critical review of the paper. MRJ: expert in GCA and PET; drafting and critical review of the paper. JMB: expert in GCA and PET; drafting and critical review of the paper. UMD: rheumatology Expert in GCA and ultrasound; drafting and critical review of the paper. CF: data collection and review of the paper. SHe: histopathologist; critical review of the paper. ONK: critical review of the paper and statistics. EBK: critical review of the paper. YS: critical review of the paper and statistics. AKW: critical review of the paper. SHa: neuro-ophthalmologist expert in GCA; drafting and critical review of the paper. All authors have read and approved the paper.

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ADDITIONAL INFORMATION

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