The diagnostic utility of intima-media thickness measurement compared with the halo sign in temporal artery ultrasonography: a single-centre retrospective study

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Abstract

Objective

We aimed to examine the diagnostic utility of temporal artery ultrasonography (TAUS) based on measurement of intima-media thickness (IMT) compared with the halo sign in diagnosing cranial giant cell arteritis (GCA).

Methods

We retrospectively analysed consecutive patients with clinically suspected GCA who had undergone TAUS between January 2011 and December 2021 in Tenri hospital, Japan. A cut-off value of 0.5 mm was used for the IMT of the temporal arteries. We examined the diagnostic value of TAUS based on each of the halo sign and increased IMT in diagnosing cranial GCA.

Results

In total, 203 patients were included. Temporal artery biopsy (TAB) was performed in 59 patients, with 32 being biopsy-positive. Fifty-three patients were diagnosed with cranial GCA. The sensitivity and specificity of TAUS based on the increased IMT and halo sign were as follows: sensitivity, 62.3% and 32.1%; specificity, 90.0% and 100% compared with the clinical diagnosis; and sensitivity, 81.2% and 46.9%; specificity, 76.9% and 96.2% compared with the TAB. When the relationship between the IMT and halo sign was evaluated, patients with cranial GCA who presented with the halo sign had the highest IMT compared with those without the halo sign or those without cranial GCA.

Conclusion

A TAUS diagnosis relying only on the halo sign is specific but can underestimate cranial GCA. Therefore, evaluation of the IMT in addition to the halo sign can improve the diagnostic accuracy of TAUS when diagnosing cranial GCA.

Key words

giant cell arteritis, sensitivity and specificity, ultrasonography

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Introduction

Giant cell arteritis (GCA) is a form of large-vessel vasculitis that usually affects the aorta and/or its major branches, with a predilection for the branches of the carotid and vertebral arteries (1). The pooled incidence of GCA is estimated to be approximately 10/100,000 in people aged >50 years (2). Due to the risk of permanent visual loss, early diagnosis and initiation of treatment are essential (3).

Temporal artery biopsy (TAB) is the gold standard for diagnosing GCA (4). Despite the high specificity of TAB for diagnosing GCA, its sensitivity is relatively low (77.3%) (5). Moreover, false-negative results due to the presence of skip lesions in GCA (6), invasiveness, and the risk of complications (7) are associated with the use of TAB. Temporal artery ultrasonography (TAUS) has been reported to be effective and reliable for the diagnosis of GCA (8), with some studies indicating that TAUS can replace TAB in appropriate clinical settings (4). The European Alliance of Associations for Rheumatology (EULAR) and the British Society for Rheumatology guidelines now recommend TAUS as the first-line imaging test for patients with suspected cranial GCA (9, 10).

In a TAUS assessment, the halo sign has been used as the most suggestive ultrasonographic finding of GCA. The Outcome Measures in Rheumatology (OMERACT) Large Vessel Vasculitis Ultrasound Working Group defined the halo sign as a homogeneous hypoechoic wall thickening that is well delineated towards the luminal side, visible in the longitudinal and transverse planes. The intima-media thickness (IMT) cut-off values are not included in the definition of the halo sign due to the lack of data (11). With the availability of high-resolution transducers, the IMT of the cranial arteries can be accurately and easily measured (12). Previous studies have reported optimal IMT cut-off values of 0.4–0.44 mm for the common superficial temporal arteries, and 0.29–0.4 mm for the branches to diagnose GCA (13–15). However, data on the measurement of IMT compared with a conventional assessment based on the presence of the halo sign are limited.

Therefore, we aimed to evaluate the diagnostic performance of TAUS based on IMT measurements compared with an evaluation based on the halo sign in diagnosing cranial GCA.

Materials and methods

Study design and population

In this single-centre retrospective cohort study, we included patients who had undergone TAUS for suspected new-onset cranial GCA at Tenri Hospital, a 715-bed hospital in Nara, Japan, between January 1, 2011 and December 31, 2021. In addition, patients who received glucocorticoids (GCs) or disease-modifying anti-rheumatic drugs (DMARDs) for the treatment of other pre-existing diseases were included. We excluded patients who had undergone ultrasonography for follow-up or who were in suspected relapse. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for reporting observational studies (16). The Institutional Review Board of Tenri Hospital approved the study protocol (no.: 1936) and determined that written informed consent was not mandatory.

Ultrasonographic evaluation of the temporal arteries

Ultrasonography scans were performed using GE LOGIQ 7 machines between 2010 and 2017. GE LOGIQ 7 machines were gradually phased out and replaced with GE LOGIQ S8 machines in 2013, GE LOGIQ E9 machines in 2016, and Canon Aplio i800 machines in 2017. The equipment settings were as follows: GE LOGIQ 7 machines with a 7.5–12 MHz multi-frequency linear probe; GE LOGIQ S8 machines and GE LOGIQ E9 machines with an 815 MHz multi-frequency linear probe; and Canon Aplio i800 machines with a 7–14 MHz multi-frequency linear probe. The highest possible frequency of the probes was generally used for B-mode ultrasound scanning. The sonographers were not blinded to the patients' clinical information and laboratory test results.

The scans were performed by quali-

fied sonographers. We measured the maximum IMT on the arterial wall. A positive TAUS result was defined as the presence of a circumferential IMT of ≥0.5 mm or the halo sign. To determine the cut-off value for the IMT of the temporal arteries, we performed receiver operating characteristic (ROC) analysis and calculated the Youden's index in increments of 0.1 mm (Supplementary Fig. S1). Ultrasound images were reviewed by two sonographers. The halo sign was defined based on the definition proposed by the OMERACT Large Vessel Vasculitis Ultrasound Working Group (11).

Previous studies have shown that previous GC use can affect TAUS findings (17, 18). Therefore, we examined the difference in TAUS findings between patients treated and those untreated with GCs or DMARDs prior to TAUS.

Clinical information

We extracted patient information regarding clinical presentations, laboratory test results, TAUS findings, TAB results, and clinical courses from patients' medical records. The upper detection limit for the erythrocyte sedimentation rate (ESR) was 100 mm/h. The TAB results were defined as positive, based on pathology reports. Patients diagnosed with cranial GCA by treating physicians and who received continuous treatment during the follow-up period were defined as those with cranial GCA. Patients with extracranial lesions without cranial lesions were included in the clinical diagnosis-negative group.

Statistical analysis

Continuous variables were reported as medians and interquartile range (IQR), and categorical variables were reported as absolute values and frequencies. To test for differences between the groups, we used a Fisher's exact test for categorical variables and a Mann-Whitney U-test for continuous variables. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for TAUS based on increased IMT or the halo sign were calculated using the clinical diagnosisor TAB result as a reference standard. We compared the maximum IMT values of the temporal arteries between patients with cranial GCA with and without the halo sign and those without cranial GCA. A Kruskal-Wallis test was used for comparisons of the maximum IMT values between the groups, followed by the Mann-Whitney U-test with Bonferroni correction. A *p*-value <0.05 was considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics (19).

Table I. Baseline characteristics of patients with and without clinical diagnosis of cranial GCA.

	Patients with cranial GCA (n=53)	Patients with other diagnoses (n=150)	*p*-value
Age (years), median [IQR]	76 [69-79]	73 [67-78]	0.09
Female, n (%)	31 (58.5)	88 (58.7)	1
BMI (kg/m^2)	21.6 [19.8-23.4]	21.3 [19.0-23.6]	0.45
Clinical presentation, n (%)			
Headache	48 (90.6)	63 (42.0)	<0.001
Visual symptoms	3 (5.7)	6 (4.0)	0.70
Jaw claudication	20 (37.7)	16 (10.7)	<0.001
Pain in hip or shoulder girdle	26 (49.1)	40 (26.7)	0.004
TA abnormality	43 (81.1)	25 (16.7)	<0.001
Fever	26 (49.1)	66 (44.0)	0.63
Malaise	33 (62.3)	89 (59.3)	0.75
Laboratory values, median [IQR]			
CRP (mg/dl)	10.7 [6.2-15.7]	7.3 [1.0-13.4]	0.003
ESR (mm/h)	82.5 [62.8-100]	67 [42-100]	0.006
Plt (×10^3 /μμl)	337 [282-383]	309 [237-380]	0.05
ACR 1990 criteria, n (%)	51 (96.2)	41 (27.3)	<0.001
Cardiovascular risk factors, n (%)			
Acute coronary syndrome	5 (9.4)	7 (4.7)	0.31
Peripheral artery disease	1 (1.9)	3 (2.0)	1
TIA or acute ischemic stroke	2 (3.8)	5 (3.3)	1
TAA or AAA	0 (0)	3 (2.0)	0.57
Diabetes mellitus	7 (13.2)	31 (20.7)	0.31
Moderate CKD	2 (3.8)	12 (8.0)	0.37
Severe CKD	2 (3.8)	7 (4.7)	1
Pre-existing rheumatic disease, n (%)			
Polymyalgia rheumatica	9 (17.0)	8 (5.3)	0.02
Rheumatoid arthritis	1 (1.9)	8 (5.3)	0.45
Drug use at baseline, n (%)			
GCs	13 (24.5)	29 (19.3)	0.43
Any DMARDs	3 (5.7)	6 (4.2)	0.70
Biologics (Etanercept)	0 (0)	1 (0.7)	1
TAB performed	49 (92.5)	9 (6.0)	<0.001
TAB positive, n (%)	32 (60.4)	0 (0)	<0.001

Values are presented as median [interquartile range] or number (%). *p*-values are calculated using the Mann-Whitney U-test for numerical data and Fisher's exact test for categorical data. Moderate and severe CKD were defined as an estimated glomerular filtration rate of less than 45 ml/min/1.73m^2 and 30 ml/min/1.73m^2, respectively.

GCA: giant cell arteritis; IQR: interquartile range; BMI: body mass index; TA: temporal artery; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Plt: platelets; ACR: American College of Rheumatology; TIA: transient ischaemic attack; TAA: thoracic aortic aneurysm; AAA: abdominal aortic aneurysm; CKD: chronic kidney disease; GCs: glucocorticoids; DMARDs: disease-modifying antirheumatic drugs; TAB: temporal artery biopsy.

Results

During the study period, 203 patients had undergone TAUS, and 53 had been clinically diagnosed with cranial GCA. The baseline characteristics of the pa-

tients with and without a clinical diagnosis of cranial GCA are shown in Table I. The median age was 76 (IQR, 69–79) years, and 31 (58.5%) patients were females in the clinically diagnosed group. The groups did not differ significantly in age or sex distribution. Patients with a clinical diagnosis of cranial GCA were more likely to present with clinical manifestations associated with cranial GCA, such as new-onset headache, and had higher baseline C-reactive protein (CRP) and ESR levels. In total, 51 (96.2%) patients diagnosed with cranial GCA fulfilled the American College of Rheumatology (ACR) 1990 GCA classification criteria (20), and 41 (27.3%) patients without cranial GCA also fulfilled the criteria. There was no significant difference between the two groups regarding the prevalence of cardiovascular risk factors.

The TAUS results, based on increased IMT and the halo sign, were compared with the clinical diagnosis and TAB results (Table II). Notably, 15 of 150 patients without cranial GCA presented with increased IMT; however, the halo sign was not identified in patients without cranial GCA (Table II A). TAB was not performed on these 15 patients. The suspected causes of increased IMT in patients without cranial GCA included other forms of vasculitis (n=3, 20%), atherosclerosis (n=3, 20%), polymyalgia rheumatica (n=3, 20%), and unspecified (n=6, 40%). The halo sign was observed in one patient with a negative TAB finding (Table II B), who had been clinically diagnosed with cranial GCA. The sensitivity, specificity, PPV, and NPV of increased IMT and the halo sign were calculated and are shown in Table III. Furthermore, the TAUS findings classified by the previous use of GCs or DMARDs were evaluated (Supplementary Table S1); the diagnostic performance of TAUS classified by the previous use of GCs or DMARDs was calculated (Supplementary Table S2). Similar diagnostic yields of TAUS were observed between patients with and those without a history of GCs or DMARDs use.

The relationship between the presence of the halo sign and increased IMT in patients with and without a clinical diagnosis of cranial GCA is shown in Table IV. The halo sign was not observed in patients without increased IMT. As shown in Figure 1, the maximum IMT of the temporal arteries was significantly greater in patients with cranial GCA with the halo sign than in those with cranial GCA without the halo sign and in those without cranial GCA.

Table II. A 2×2 contingency table comparing TAUS with clinical diagnosis and TAB.

	(A) Clinical diagnosis			(B) TAB		
	Positive (n=53)	Negative (n=150)	Total (n=203)	Positive (n=32)	Negative (n=26)	Total (n=58)
Increased IMT	33	15	48	26	6	32
No increased IMT	20	135	155	6	20	25
Halo sign positive	17	0	17	15	1	16
Halo sign negative	36	150	186	17	25	42

TAUS findings are evaluated based on increased IMT and the halo sign. (A) Clinical diagnosis and (B) TAB results are used as reference standards.
TAUS: temporal artery ultrasonography; TAB: temporal artery biopsy; IMT: intima-media thickness.

Table III. Diagnostic performance of TAUS for the diagnosis of cranial GCA.

	(A) Clinical diagnosis		(B) TAB	
	Increased IMT	Halo sign	Increased IMT	Halo sign
Sensitivity	62.3% (47.9-75.2)	32.1% (19.9-46.3)	81.2% (63.6-92.8)	46.9% (29.1-65.3)
Specificity	90.0% (84.0-94.3)	100% (96.4-100)	76.9% (56.4-91.0)	96.2% (80.4-99.9)
PPV	68.8% (53.7-81.3)	100% (72.7-100)	81.2% (63.6-92.8)	93.8% (69.8-99.8)
NPV	87.1% (80.8-91.9)	80.6% (74.2-86.1)	76.9% (56.4-91.0)	59.5% (43.3-74.4)

Diagnostic performance of TAUS based on increased IMT and the halo sign is calculated using (A) clinical diagnosis and (B) TAB results as reference standards. Data are presented as percentage values (95% confidence interval).
TAUS: temporal artery ultrasonography; GCA: giant cell arteritis; IMT: intima-media thickness; PPV: positive predictive value; NPV: negative predictive value.

Table IV. Relationship between the halo sign and increased IMT on TAUS.

	(A) Cranial GCA			(B) Other diagnoses		
	Increased IMT			Increased IMT		
	Positive	Negative	Total	Positive	Negative	Total
Halo sign positive	17	0	17	0	0	0
Halo sign negative	16	20	36	15	135	150
Total	33	20	53	15	135	150

The relationship between the halo sign and increased IMT is evaluated in patients (A) with and (B) without the clinical diagnosis of cranial GCA.
IMT: intima-media thickness; TAUS: temporal artery ultrasonography; GCA: giant cell arteritis.

Discussion

In this study, we aimed to examine the diagnostic utility of TAUS, based on an evaluation of increased IMT compared with the conventional evaluation using the halo sign in the diagnosis of GCA. Our study showed differences in diagnostic characteristics between the two evaluation methods. The halo sign showed high specificity but relatively low sensitivity. This result suggests that TAUS can replace TAB when the typical halo sign is observed. In terms of the sensitivity, the IMT cut-off value of ≥0.5 mm was shown to be superior to the halo sign. This finding confirms that the evaluation of the IMT of the temporal arteries is helpful in improving the sensitivity of TAUS in diagnosing cranial GCA.

The halo sign of the temporal arteries has been recognised as the most relevant TAUS finding in GCA (9). The halo sign on TAUS is included in the 2022 ACR/EULAR GCA classification criteria (21). Previous meta-analyses

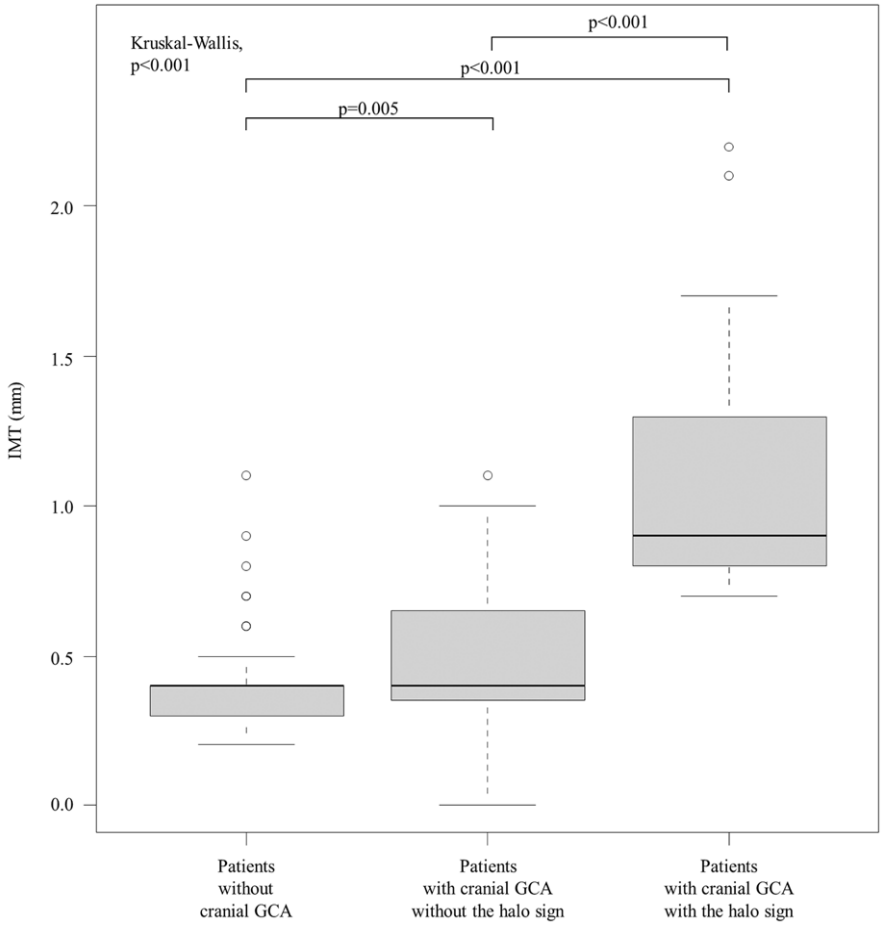

Fig. 1. IMT of temporal arteries in patients with and without cranial GCA.
IMT: intima-media thickness; GCA: giant cell arteritis.

have reported that, based on the halo sign, TAUS sensitivity ranged from 67% to 77% and specificity ranged from 93% to 96% compared with the clinical diagnosis (22-25). Compared with the halo sign, there are limited data available concerning the diagnostic accuracy of increased IMT in diagnosing cranial GCA. However, the IMT cut-off value has been shown to be useful in differentiating between patients with and without GCA, and some optimal cut-off values for the temporal arteries have been proposed (13-15). Furthermore, some quantitative analysis methods, in which the IMT and its extent are included in the scoring items, have been found to be useful in GCA diagnosis and disease monitoring (26-28).

Our study findings are similar to those of previous studies regarding the diagnostic performance of the halo sign (22-25). However, the diagnostic accuracy of the IMT cut-off value of ≥0.5 mm was inferior to that reported in other studies (13-15). We only performed ultrasonographic assessments of the temporal arteries, and some patients with cranial GCA may have had lesions located in other cranial arteries. Drug use at baseline might influence the TAUS results. However, previous use of GCs or DMARDs did not consistently decrease the diagnostic performance of TAUS. Furthermore, some conditions have been reported to cause false-positive results on TAUS (29, 30). Martire *et al*. reported that cardiovascular risk can also influence the IMT and that 10.1% of patients had arteries with IMT higher than the proposed cut-off value (31). Therefore, caution is needed especially when only increased IMT is observed because of the possibility of false-positive results. The observed discrepancy between the increased IMT and halo sign could be attributed to the degree of inflammation in the affected arteries. Wang *et al*. reported that a limited distribution of inflammation in the media or adventitia was observed in 13% of TAB specimens from patients with cranial GCA (32). Another study indicated that there may be sequential steps in the progression of inflammation in GCA, and a striking correlation was observed between the extent of inflammatory infiltrates and the severity of intimal thickening (33). Our findings indicated that the maximum IMT was significantly higher in patients with cranial GCA with a halo sign than in those with cranial GCA without a halo sign or in those without cranial GCA. We hypothesised that the assessment of increased IMT might facilitate the detection of lesions with milder inflammatory infiltrates.

Our study has several strengths. The sample size was relatively large, and the TAUS results were reviewed by two sonographers to maintain reliability. In addition, this is the largest study to investigate the diagnostic performance of TAUS in Japan. This study also has some potential limitations. This was a retrospective single-centre study, and neither the treating physicians nor the sonographers were blinded. We evaluated the presence of the halo sign on morphological changes alone, and ultrasonography was only performed for common temporal arteries and their major branches. Previous studies have described that axillary artery ultrasound, in addition to TAUS, improves the diagnostic yield of GCA (34-36). We compared the diagnostic performance of TAUS classified by the previous use of GCs or DMARDs; however, the results might be affected by the sample size of each group. Ultrasonographic examinations were performed using several different machine types. The recommended B-mode frequency for an ultrasound scan of the temporal arteries is ≥15 MHz (8); however, B-mode probes with a frequency of <15 MHz were used in some cases. We used a common cut-off value for the IMT of the temporal arteries, and the IMT value was evaluated in increments of 0.1 mm. We defined the cut-off value, based on the result of ROC analysis, and we used the common cut-off value for clinical convenience. A common

cut-off value has been reported to be diagnostically accurate (14); however, different cut-off values for common superficial arteries and their branches might further improve the diagnostic performance of TAUS. Further validation of the optimal cut-off values in diagnosing GCA is needed.

Despite these limitations, our findings indicated that the halo sign and increased IMT on TAUS have distinct diagnostic properties. The halo sign exhibited high specificity, whereas increased IMT showed higher sensitivity than the halo sign. Thus, evaluating the presence of increased IMT in addition to the halo sign is likely to be valuable in improving the diagnostic performance of TAUS. Our findings are expected to serve as a foundation for future studies that focus on refining the diagnosis of GCA.

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