Diagnostic performance of colour duplex ultrasonography along with temporal artery biopsy in suspicion of giant cell arteritis

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Received on November 21, 2016; accepted in revised form on January 30, 2017.

Clin Exp Rheumatol 2017; 35 (Suppl. 103): S119-S122.

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Key words: giant cell arteritis, diagnostic test, observational study, ultrasonography, colour Doppler, temporal arteries, biopsy

Competing interests: B. Gombert has been an invited speaker for Pfizer and BMS. All the other authors have declared no competing interests.

ABSTRACT

Objective. *Giant cell arteritis (GCA) is a vasculitis that occurs in older adults, affecting vessels of medium and large caliber. GCA diagnosis is a challenge for general practitioners and specialists. The aim of this study was to retrospectively analyse performances of temporal artery biopsy (TAB) and colour duplex ultrasonography (CDU) for GCA diagnosis.*

Methods. *All patients with suspicion of GCA and who underwent both TAB and CDU between April 2009 and March 2014 were included in the study. A positive CDU examination was defined by halos on both superficial temporal arteries. Patients were classified based on the physician final diagnosis.*

Results. *Among the 42 eligible patients, 12 had an alternative diagnosis and 30 were diagnosed with GCA. Sensitivities were 77% and 80% for TAB and CDU examinations, respectively. Specificities were 100% for both tests. Twenty-nine (96.7%) patients with GCA had their diagnosis confirmed either by CDU and/or by TAB. Time lengths between the first medical examination and results of TAB and CDU were 15 and 4.2 days (p<0.001), respectively.*

Conclusion. *Our study suggests that in suspected GCA, CDU may be used as first line examination followed by TAB in case of CDU negative results. Such algorithm needs to be further assessed in a multicentre prospective study.*

Introduction

Giant-cell arteritis (GCA) diagnosis is still a challenge for physicians, and the initiation of an effective therapy may subsequently be delayed (1). According to guidelines, when GCA is suspected, oral corticosteroid treatment must promptly be started and patient should undergo a unilateral temporal artery biopsy (TAB) within two weeks (2, 3). However, 10 to 30% of histological examinations are false negative, and TAB has many downsides, such as patient acceptance, inter-pathologist concordance, biopsy failure and related morbidity (4). Alternative diagnostic tools have emerged in vessel imaging area. First described by Schmidt *et al.* (5), inflammatory wall oedema that surrounds vascular lumen can be visualised with colour duplex ultrasonography (CDU) of temporal arteries. It is depicted as a dark hypoechoïc halo or halo sign. Retrospective studies and meta-analyses have shown that CDU is a non-invasive tool, highly specific, and as sensitive as TAB when performed by expert operators for the diagnosis of GCA (6). The aim of our study is to assess the contribution of CDU along with TAB in GCA diagnosis.

Materials and methods

Study design

The present study is a retrospective diagnostic accuracy study. Among patients with GCA suspicion, results of TAB and CDU were compared with physician final diagnosis.

Participants

All files of patients with suspicion of GCA and who underwent both TAB and CDU between April 2009 and March 2014 at our secondary care hospital were retrieved. Patients were considered eligible if GCA suspicion was in agreement with the American College of Rheumatology criteria for the classification of GCA (age at disease onset ≥50 years, new headache, temporal artery abnormality, elevated erythrocyte sedimentation rate), corticosteroid therapy was not yet initiated or was initiated at most 7 days before TAB and CDU examinations, time between TAB and CDU was less than 2 weeks, and level of C-reactive protein was above normal value.

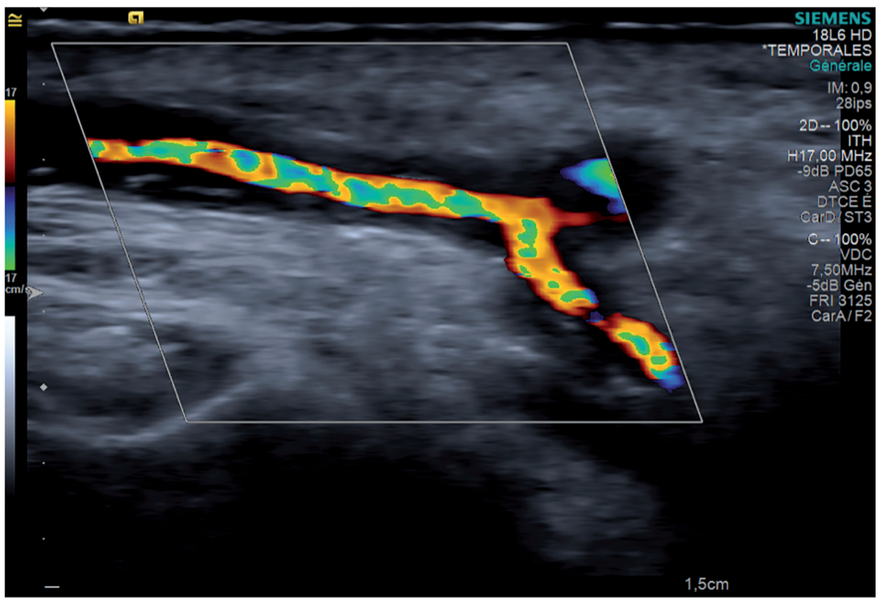

Fig. 1. Halo sign: longitudinal colour Doppler image of the temporal artery in acute temporal arteritis.

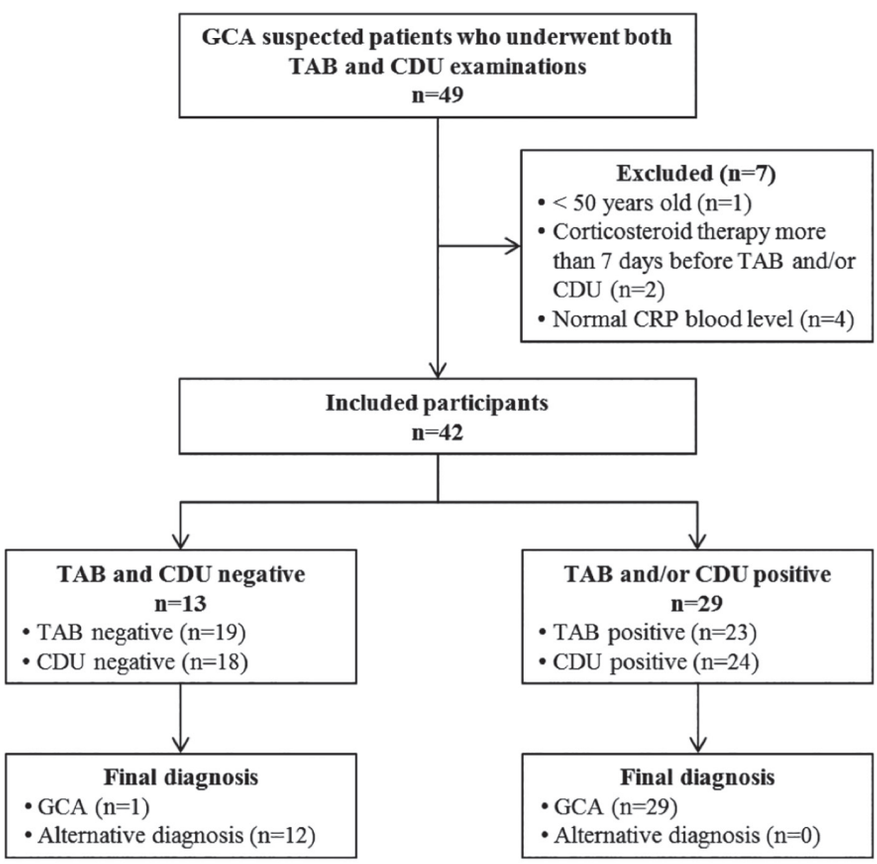

Fig. 2. Patient flow, diagnostic accuracy study.
GCA: giant cell arteritis; TAB: temporal artery biopsy; CDU: colour duplex ultrasonography;CRP: C-reactive protein.

Test method

Unilateral temporal artery biopsy procedure was performed by vascular surgeon. Biopsy side was either guided by physical examination or by CDU result. All biopsies were examined at the same histopathological department. Numerous transversal or longitudinal sections were fixed in paraffin. Specimens were stained with HES and Orceïn.

CDU examinations were performed using the same device (Siemens®, S2000) and by a single experienced vascular physician. Temporal arteries were screened from their common trunk to frontal and parietal branches using a high frequency linear probe (7–18 Mhz). Picture enlargement was used for axial and transversal visualisation. Bilateral analyses of the following arterial segments were performed with a 4–9 MHz frequency probe: vertebral arteries (V1 and V2 portions), extracranial part of internal carotid, common carotid, and subclavian. Clearly defined halo signs on both temporal arteries were considered as CDU positive result (Fig. 1). Negative CDU results comprised unclear or no halo sign.

Final diagnosis of GCA was retained for patients who improved or were cured by corticosteroid therapy according to the follow-up data. Alternative diagnoses were defined by medical review of patient files.

Analysis

Means and standard deviations, numbers, percentages and confidence intervals were used to describe quantitative and qualitative variables, respectively. Sensitivities, specificities and likelihood ratios were calculated. Normal distributions were verified and *t*-test or Mann-Whitney tests were used to compare quantitative data of independent samples where appropriate. Chi-square or Fisher tests were used for qualitative variables. An alpha level of 0.05 was used for all statistical tests.

Ethics

This study has been approved by the local ethical review board (Comité d'éthique du Groupe Hospitalier de la Rochelle). The database has been declared to the French Commission for Data Protection and Civil Liberties.

Results

Study population and clinical and laboratory characteristics

Over the study period, 49 patients with suspicion of GCA underwent both TAB and CDU examinations (Fig. 2). One patient under 50 years old, 2 patients who started corticosteroid therapy 14

and 41 days before TAB and CDU examinations, respectively, and 4 patients with normal CRP blood level were excluded from further analysis. Among the 42 remaining patients, mean age was 75.8 years old, and 69% were women. Thirty patients (71%) were eventually diagnosed with GCA. Alternative diagnosis consisted in polymyalgia rheumatica (n=3), cerebrovascular accident and pulmonary embolism (n=1), tension-type headache (n=1), cirrhosis, pernicious anaemia and suspected Wegener (n=1), S1 lumbar sciatica (n=1), cardio embolic occlusion of the central artery of the retina (n=1), pelvic tumour (n=1), inflammatory rheumatism (n=1), unknown inflammatory syndrome (n=2). Demographic data and clinical symptoms did not differ between patients diagnosed with GCA or with an alternative diagnosis (Table I). Mean follow-up time was 25.4 months.

Table I. Patients' characteristics, examination data and time lengths.

Variable	Total (n=42)	Giant cell arteritis (n=30)	Alternative diagnosis (n=12)	*p*
Demographic data				
Age, years, mean (± SD)	75.8 (± 7.9)	75.5 (± 8.5)	76.7 (± 6.3)	0.623
Female sex, n (%)	29 (69%)	22 (58%)	7 (73%)	0.463
Clinical symptoms				
Headache, n (%)	21 (50%)	18 (60%)	3 (25%)	0.085
Visual loss, n (%)	8 (19%)	7 (23%)	1 (8%)	0.402
CRP, mg/ml, mean (± SD)	77.0 (± 71.1)	83.0 (± 73.1)	60.7 (± 66.2)	0.364
Histological examination				
Right side, n (%)	20 (48%)	14 (47%)	6 (50%)	0.883
Size, mm, mean ± SD	15.7 (± 6.4)	15.0 (± 6.2)	17.5 (± 7.1)	0.255
Granuloma, n (%)	6 (14%)	6 (20%)	0 (0%)	0.159
Disruption of internal elastic lamina, n (%)	28 (67%)	24 (80%)	4 (33%)	0.009
Single mononuclear cell infiltrate, n (%)	20 (48%)	19 (63%)	1 (8%)	0.002
Thrombus, n (%)	1 (2%)	1 (3%)	0 (0%)	1
Imaging examination				
Stenosis, n (%)	3 (7%)	3 (10%)	0 (0%)	0.545
Thrombus, n (%)	2 (5%)	2 (7%)	0 (0%)	1
Other large-vessel involvement				
Vertebral artery, n (%)	10 (24%)	10 (33%)	0 (0%)	0.039
Internal carotid artery, n (%)	1 (2%)	1 (3%)	0 (0%)	1
Time length [days, mean (± SD)] between				
Medical examination and histological result	15.0 (± 8.5)	15.0 (± 7.1)	14.8 (± 11.5)	0.490
Medical examination and CDU result	4.2 (± 4.7)	4.4 (± 4.9)	3.6 (± 4.2)	0.854
Medical examination and corticosteroid therapy	9.1 (± 8.2)	9.1 (± 8.2)	NA	
Length of stay, days, mean (± SD)	11.8 (± 7.5)	11.7 (± 7.6)	11.9 (± 7.6)	0.881
Follow-up, months, mean (± SD)	25.4 (± 20.5)	26.3 (± 18.6)	23.4 (± 25.6)	0.494

GCA: giant cell arteritis; SD: standard deviation; CRP: C-reactive protein; CDU: colour duplex ultrasonography; NA: not applicable.

TAB and CDU examination

Twenty-three biopsies were positive for GCA and 19 were negative. All 23 biopsy positive patients had a definite GCA diagnosis (Fig. 2). Only one case of temporal artery thrombosis was detected but without pathological meaning (recent surgical sampling) (Table I). Granuloma, disruption of internal elastic lamina and single mononuclear cells infiltrate were observed in 6, 28 and 20 patients' specimens, respectively.

Clearly defined halo sign on both temporal arteries were observed among 24 patients. They were all diagnosed with GCA (Fig. 2). A halo was also observed in vertebral and internal carotid arteries in 10 and 1 of these patients, respectively. Stenosis and thrombosis were observed in 3 and 2 of the patients, respectively (Table I).

Diagnostic performance of histological and imaging examination

TAB and CDU alone yielded sensitivities of 76.7 and 80% for GCA diagnosis, respectively (Table II). Both had specificities of 100%. Six patients had halo signs on temporal arteries while their histological result was negative. Conversely, five patients had a positive biopsy but a negative CDU result. Overall, the combined results of TAB and CDU examinations provided a sensitivity of 96.7%.

Time length analysis

Time between medical examination, histology and imaging results were recorded (Table I) and did not differ between patients with GCA or with an alternative diagnosis. Time between first medical examination and TAB result (15 days±8.5) was significantly higher than time between first medical examination and CDU result (4.2 days±4.7) (p<0.001).

Discussion

In our study, diagnostic performance of TAB is in accordance with published data where reported TAB sensitivities were between 70 and 80% (7). Negative results are partly due to focal and segmental vascular tropism of the disease, to presence of more «proximal» form exclusively on aorta and its large trunks, and also to diagnosis difficulty and inter-operators variability (skip lesion, specimen size, histological section number, physician experience, consideration of vasa vasorum and peri-adventitial vessel vasculitis).

As described in meta-analyses (6), CDU was relatively accurate for GCA diagnosis, and TAB and CDU have similar sensitivities and specificities. A recent study even showed a higher CDU sensitivity than TAB sensitivity, 96% *versus* 67%, with same 100% specificity (8). CDU diagnostic performance can further be increased by exploring other arterial segments (subclavian, axillary and internal carotid arteries) potentially affected by GCA. The compression sign, as described by Aschwanden *et al*., could also have been investigated but its description was posterior to the start of the study and data were not collected (9). In our

Table II. TAB and CDU diagnostic performances. The clinical diagnosis is the reference standard.

Diagnosis method	Sensitivity % (95% CI)	Specificity % (95% CI)	PLR % (95% CI)	NLR % (95% CI)
TAB	76.7 (58.7-88.4)	100.0 (71.3-100.0)	∞	23.3 (12.2-44.6)
CDU	80.0 (62.2-90.7)	100.0 (71.3-100.0)	∞	20.0 (9.8-40.9)
TAB + CDU	96.7 (81.6-100.0)	100.0 (71.3-100.0)	∞	3.3 (0.5-22.9)

TAB: temporal artery biopsy; CDU: colour duplex ultrasonography; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio.

study, a halo sign was found on vertebral arteries in one-third of the cases. Rare false negative situations reported in the literature concerned other types of vasculitis (peri-arteritis nodosa or ANCA-associated vasculitis, tuberculosis, endocarditis, arteriosclerosis, Angiolymphoid hyperplasia and amyloidosis) (8, 10-12). These false negative results could largely be avoided if probability pretest is high (rigorous patient selection), operator is experienced and CDU positivity criteria are strictly defined. The real limit of CDU is its imperfect sensitivity. This could be due to certain histological phenotypes of GCA. Indeed, a poorer CDU sensitivity (20%) was observed in situations of isolated vasa vasorum and/or periadventitial vessel vasculitis in comparison with conventional GCA disease (82.5%) (6). Acceptable maximal time between treatment onset and CDU examination is still unspecified, as time to halo sign extinction after treatment is not clearly defined. In a prospective cohort study including 22 patients, Schmidt *et al*. found a mean of 16 days (range 7 to 56) before halo sign extinction (13). Conversely, Aschwanden *et al*. reported persistence of vasculitis CDU sign (with an increase of halo echogenicity) at 6 months in 9 patients, raising the question of after-effect or active inflammatory situation (14).

TAB and CDU seem to be complementary diagnosis tools. A high sensitivity of 96.7% and 100% of specificity were achieved using both. Although European and British recommendations position CDU as second-line examination (2, 3), many authors suggest the possibility to avoid TAB in many situations (15). Moreover, as shown in this study, time to CDU results was significantly shorter than time to histology results, which could be a real advantage in a cost-efficacy viewpoint, as it is not invasive and more accessible for outpatients

This retrospective study had several limitations and weaknesses due to small sample size and CDU interpretation by a single operator that did not allow to measure inter-rater reliability.

In conclusion, a diagnosis algorithm consisting in using CDU as first line screening tool and considering TAB according to CDU results and strength of GCA suspicion should be assessed on a prospective multicentre study

Acknowledgements

We would like to thank Karen Renaud, Dr Chanel, Dr Faba, Dr Pottier, Dr Roncato-Saberan and Dr Vandamme.

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