Diagnostic validity of Doppler ultrasound in giant cell arteritis

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ABSTRACT

Objective. *To assess the validity of Doppler ultrasound in the diagnosis of giant cell arteritis (GCA), using the American College of Rheumatology (ACR) criteria and biopsy and using as gold standard the patient's definitive clinical diagnosis.*

Methods. *An observational, descriptive and analytical study of 451 consecutive patients with suspected GCA was conducted, and the clinical history and ultrasound findings of the patients were reviewed. The validity of ACR criteria, temporal arteritis biopsy (TAB) and Doppler ultrasound in the diagnosis of GCA was calculated using the final diagnosis of the doctor in charge as the gold standard.*

Results. *The validity and security of the diagnostic tests used were as follows: ACR criteria had 65.37% sensitivity and 62.89% specificity; positive predictive value [PPV] 70%; negative predictive value [NPV] 57.82%, likelihood ratio [LR] + 1.7619 and LR - 0.5506. Doppler ultrasonography had 91.60% sensitivity and 95.83% specificity; PPV 96.62%; NPV 89.76%, LR + 21.81 and LR - 0.0876; TA biopsy 42.86% sensitivity and 100% specificity; PPV 100%; NPV 35.71% and LR - 0.5714.*

Conclusion. *The halo sign, especially if bilateral, is a strong predictor of GCA with a level of accuracy sufficient to recommend its introduction into clinical practice and, in our opinion, should be considered in future classification criteria sets.*

Introduction

Giant cell arteritis (GCA) is a large-vessel vasculitis with a predilection for the extra cranial branches of the carotid artery and is the most common vasculitis in the elderly (1-6). The diagnosis of GCA is based on clinical grounds. According to the American College of Rheumatology (ACR) 1990 criteria diagnosis of GCA can be made when 3 of 5 of the following criteria are met: 1) age of onset of 50 years or older; 2) new onset headache; 3) temporal artery tenderness or decreased pulse; 4) erythrocyte sedimentation rate (ESR) >50 mm/hour; 5) positive histology of a temporal artery biopsy (TAB) (7).

The presence of 3 or more of these criteria has a sensibility of 93.5% and a specificity of 91.2% for a diagnosis of GCA compared with other vasculitis (7), therefore the experts tend to be satisfied with these criteria, but there are some authors who indicate possible weaknesses (8-9). The problem lies in the fact that the sensitivity and specificity of any test depends on the sensitivity prior to the test. The results of the ACR criteria come from a vasculitis clinic and the sensitivity and specificity calculations had a high pre-test probability. In that tenor, according to Rao *et al.* (8), who applied these criteria in a general rheumatology clinic, sensitivity reached 75%, with a specificity maintained at 92%, but with a positive predictive value (PPV) of only 29%. PPV points to the probability of having the disease if the results of the criteria employed are positive. In summary, we would treat our patients with a large dose of steroids with a 29% chance of being right, something that is obviously uncomfortable for any clinician. Fortunately, this low probability is due to the fact that the first 4 criteria of the ACR are very sensitive but hardly specific; the need for a fifth criteria, hence biopsy in order to reinforce the specificity of the diagnosis. Reaching this point it seems that the biopsy would offer us the diagnostic solution for this disease. But the biopsy also has weaknesses, it is effective when the result is positive, so it is accepted that its specificity and its PPV are 100%. The problem is its frequently low sensibility (7), as we know; the sensibility indicates the probability of correctly classifying an individual as a patient. The number of false negatives recognised in the biopsy of the temporary artery when we

limit ourselves to patients with GCA ranges between 9–44% (10-13) but, according to the literature, the biopsy can be negative in up to 68% of the cases. The sources of the variability of the biopsy in the negative cases are fundamentally three (14): a) patched and asymmetric affectation of the injuries; b) surgical technique; and c) interpretation of the pathologist. This low sensibility of the biopsy plus the fact that the second biopsy only contributes 3-10% of positive results (15), justifies the search for additional diagnostic methods.

During the last decade, ultrasonography has attracted considerable interest as a non-invasive diagnostic tool for patients suspected of having GCA. Four meta-analyses (16-19) have reported the high value and validity of CDUS in diagnosing GCA. The results of these meta-analyses show a sensibility of 88% and a specificity of 96%; these results are obtained by means of the detection of three ultrasonography signs: a) oedema, referred to as the halo sign, indicated by a dark hypoechoic circumferential wall thickening around the artery lumen; b) stenoses, expressed by segmental increases of blood flow velocity; and c) occlusions, expressed by the absence of flow in the temporal artery (in colour or power Doppler ultrasonography). The halo is the most specific sign and demonstrates the characteristic oedema of the vascular wall of the vasculitis and this specificity is particularly high if the halo is bilateral (1-2). Other advantages of CDUS include limited cost (9), a relatively short time required for the examination and the absence of radiation. CDUS, which combines imaging with flow velocity determination, can assess both vessel anatomy and luminal status, and it may detect early vessel wall alterations. US transducers have an upper resolution limit of 0.1 mm, which is at least ten-fold higher than a MRI (20). This high resolution power allows ultrasound not only to visualise the halo sign for diagnostic purposes but it can also be used to monitor disease activity (21).

The aim of our study was to assess the validity of Doppler ultrasonography for the diagnosis of GCA, compared with ACR criteria and biopsy, using the definitive clinical diagnosis of the patient as gold standard.

Material and methods

This was an observational, descriptive and analytical study that comprised 451 consecutive patients with GCA suspicion. The clinical history of the patients who received an ultrasound scan of the temporal artery (CDUS) in our hospital on suspicion of GCA was checked. GCA diagnosis was based on the American College of Rheumatology (ACR) criteria and confirmed by the clinician. Biopsies were conducted in 166 patients. Medical history data, a clinical examination, routine laboratory examinations and the ESR were collected at the time of inclusion to the study. The study protocol was approved by an ethics board of our hospital, and all subjects provided informed consent.

Ultrasonography

A baseline CDUS of the temporal superficial artery was performed. The standard exploration consists of the bilateral examination of the temporary superficial artery, with its common trunks and the frontal and parietal branches including the longitudinal and transversal views, as completely as possible. In the case of diagnostic doubt, the exploration is extended to the occipital and/or axilar arteries. An ultrasound diagnosis of arteritis was made if a dark concentric halo surrounding a residual colour flow signal appeared in at least 1 vessel segment of the superficial temporal artery or its branches. We defined a halo as a homogeneous dark wall surrounding a colour Doppler signal of at least 0.3 mm in the longitudinal view at the time of peak systolic blood flow. To improve results we checked in grey scale that the halo sign corresponded with a true increased in the wall thickness.

For reliability purposes and to avoid bias the ultrasound scans were realised and informed by the same expert sonographer, with more than ten years of experience in GCA CDUS examinations. The sonographer had no access to the clinical data and laboratory results. Baseline and follow-up examinations were conducted with the same protocol, using Mylab Twice Esaote equipment with a 10–22 MHz probe for grey scale and 5–12.4 MHz probe for Doppler imaging. For colour Doppler imaging, a frequency of 12.5 MHz, a colour gain of 60 and PRF of 2 KHz were used.

Statistical analysis

For statistical comparisons, we made a descriptive study, calculated the mean value, range and standard deviation, maximum and minimum for quantitative variables and the absolute and the relative frequency of each of the qualitative variables. Sensitivity, specificity, predictive positive value, negative predictive value, positive and negative likelihood ratio were calculated for validity. SPSS v. 17.0 was used for all statistical analyses.

Results

Demographic data

We studied 451 patients with GCA suspicion (399 were women and 52 men, 88.5% *vs.* 11.5%; mean age 76.47 (9.42) years). Two hundred and fifty six patients (58.8%) had a final clinical diagnosis of GCA while 195 (43.2%) presented other diagnoses. Two hundred and forty patients (55.79%) fulfilled the ACR criteria and 211 did not (46.78%). Of the 166 biopsies, 54 (32.53%) were positive.

Ultrasound data

Of the total number of patients we found 206 negative ultrasound explorations and 245 positive ultrasound explorations. Of these, 30 patients had one affected branch in ultrasound examination, 50 patients had two affected branches, 52 patients had three affected branches and 113 patients had more than four affected branches (Table I).

Validity data

The validity (sensitivity and specificity) and security (positive predictive value [PPV], negative predictive value [NPV], likelihood ratio [LR] + and LR -) of diagnostic tests used were as follows in Table II.

Of all the patients with positive ultrasound explorations, 236 had a definite diagnosis of GCA and 20 had other di-

Table I.

Number of affected branches	Definite diagnosis of ACG (n=256)	Other diagnoses (n=195)
0	20	186
1	26	4
2	47	3
3	51	1
>4	112	1

n: sample size.

Table II.

	Sensitivity	Specificity	VPP	VPN	LR+	LR-
ACR criteria	65.37%	62.89%	70%	57.82%	1.7619	0.5506
Biopsy	42.86%	100%	100%	35.71%		0.5714
Doppler ultrasonography	91.60%	95.83%	96.62%	89.76%	21.81	0.0876

PPV: positive predictive value; NPV: negative predictive value; LR: likelihood ratio.

agnoses. On the other hand, among the patients with negative ultrasound explorations, 20 had a definite diagnosis of ACG and 186 had other diagnoses. We analysed the ultrasound results in the group of patients with false positives and we saw that 44.44% of patients had one affected branch in ultrasound examination and 33.33% had two affected branches.

Discussion

In this paper, we were fundamentally interested in the ultrasonography validity and accuracy for diagnosing temporal arteritis and its applicability in clinical practice. Today, four meta-analyses support the validity of ultrasound in the diagnosis of GCA, but ultrasound is not yet included in the classification criteria and its use in clinical practice remains scant.

The aim of our analysis was to assess the validity of ultrasound in the diagnosis of GCA using these three possible ways: a) 1990 GCA ACR classification criteria; b) TA biopsy; and c) the final clinical diagnosis revised months after the initial visit.

The possible limitations of the ACR criteria have been discussed in the literature (8), but revision(s) are not available to date. In 1998, Rao *et al.* (8) examined the diagnostic operating characteristics of the 1990 ACR criteria for a prospective cohort of patients evaluated by university-based rheuma-

tologists for a possible vasculitis. In their analyses, the positive predictive value of the ACR criteria improved as the prevalence of specific types of vasculitis increased. However, if these four ACR criteria were applied in a setting in which the prevalence of vasculitis is very low, such as a primary care or a population-based setting, the likelihood of identifying persons who meet the ACR vasculitis criteria but who do not have vasculitis would be even higher than seen in their cohort. These results offer a different perspective on the ACR classification criteria: that is, their performance as diagnostic criteria for rare conditions in usual clinical practice. Although the ACR vasculitis classification criteria were never intended for diagnostic purposes, as pointed out by Hunder *et al.* (7), clinicians often use these criteria, as they use other ACR criteria, to diagnose vasculitis (35). For this reason we did not use the ACR criteria in our analysis of validity and, as Table II shows, the accuracy of the ACR criteria is lower than that commented in the original criteria data, as corresponds to a pre-test probability of 56.7% that our population presents. A LR+ of 1.762 improves the probability of diagnosis to a small degree; consequently this is the reason why we need a positive biopsy when we use the ACR criteria, because the application of these clinical criteria only has little value.

The value of TA biopsy is corroborated in our study with a specificity of 100%. The problem of the biopsy occurs when the results are negative. In our study TA biopsy had only a sensitivity of 42.86%, a result that is also commented in the literature (10-13). This low sensitivity was the reason for using the final clinical diagnosis instead of the TA biopsy as gold standard. The use of the final clinical diagnosis as gold standard has the advantage of seeing the evolution of the patient after months to be sure that other diseases are not confounding factors. We used this gold standard in our ultrasound study which revealed a sensitivity of 91.60% and a specificity of 95.83%, with a LR+ value of 21.81. The levels of LR above 10 or below 0.1 are considered to be strong evidence, respectively, to rule in or rule out a diagnosis in most circumstances. As limitations, the biopsy was performed when the doctor considered it necessary; some doctors did this routinely, while others only when they had doubts. In addition, the acceptance of the biopsy by the patient was taken into account, but it is possible that it would be a selection of patients with a low pre-test probability.

The use of better machines and improvement of the technique has allowed us to obtain better results than previous papers. In recent studies the halo sign improves the result of specificity in contrast to the classical data of the halo, stenosis or occlusion. In the meta-analysis of Karassa *et al.* (17), assessing the test-performance of ultrasonography for GCA in studies published up to April 2004, the sensitivity and specificity of the halo sign *versus* the ACR criteria were reported to be 55% and 94%, respectively (17), but the variability of the results was high, with a range of sensitivity between 35% and 86% and a range of specificity between 78% and 100%. In the last meta-analysis by Arida *et al.* (19), they observed a sensitivity and specificity for unilateral halo sign, versus the ACR criteria, of 68% and 91%, respectively and the data improved if the bilateral halo was considered.

In our opinion, the segmental nature of the disease conditions the sensitivity

and specificity in ultrasonography and increases the probability of false negative results in TA biopsy but that cannot exclude the diagnosis of vasculitis when negative (26-28). For example, in a recent study, 19% of patients with suspected GCA and a negative temporal artery biopsy were eventually diagnosed as GCA (29). A similar percentage of 19% of patients with GCA had negative biopsy results in a cohort of 271 patients from another centre (30). Moreover, as a recent study suggests, up to 13% of patients with GCA could have been misdiagnosed as biopsy-negative had a biopsy been done only unilaterally (31), which is the case in the vast majority of patients included in all relevant studies. Finally, in 8 of 9 studies analysed herein, the presence of the halo sign in ultrasonography was used to direct temporal artery biopsy, clearly leading to an underestimation of the true diagnostic performance of the halo sign.

The reason we observed better sensitivity in our study could be that we used top quality ultrasound machines, we performed ultrasound of 4–8 arteries if necessary (four temporal, two axilar and two occipital arteries), we chose a low measure threshold (>0.3 mm of halo sign and tested that this halo corresponded with wall thickness by grey scale) and we also used the compression halo sign to reduce variability.

At the moment, the discrepancy concerns wall thickness for a positive halo sign. Only Schmidt reported a 0.3mm measure in the longitudinal view compared to the criteria used in the majority of other studies (>0.7 mm) (1, 21). In our study, we assessed the reliability of the halo measurement, and our results support 0.3mm as a reliable lower measure to define the halo sign.

Our results confirm the usefulness of colour Doppler ultrasound in the diagnosis of GCA in agreement with a previously proposed algorithm by Karassa that suggests that, after a careful clinical examination and assessment of relevant laboratory data, temporal artery ultrasonography examination should precede the biopsy in patients with suspected GCA, whereas among the various abnormalities which can

be found in ultrasonography, only the halo sign should be considered. In case of bilateral halo signs, treatment could be initiated without proceeding with biopsy. If unilateral halos are present, a decision of directional biopsy is justified (17). The results of Arida's meta-analysis further substantiate this algorithm (19). At this point, we might emphasise that our findings of affectation of one or two branches also agree with this algorithm.

In summary, our findings support the conclusion that the ACR classification criteria do not achieve sufficient accuracy for diagnosis of GCA. The halo sign, especially if bilateral, is a strong predictor of GCA with a level of accuracy sufficient to recommend its introduction into clinical practice and, in our opinion, should be considered in future classification criteria sets.

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