Colour-duplex ultrasonography of the temporal and ophthalmic arteries in the diagnosis and follow-up of giant cell arteritis

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ABSTRACT

Objectives. *To evaluate the diagnostic value of colour-duplex ultrasonography (CDU) of the temporal and ophthalmic arteries in the diagnosis of giant cell arteritis (GCA) and its usefulness in the follow-up of the disease. Furthermore, to examine the relationship between CDU abnormalities in ophthalmic arteries and blindness.*

Methods. *This is a prospective study of all patients with clinical suspicion of GCA or polymyalgia rheumatica (PMR) seen consecutively at the Internal Medicine Department at Vall d'Hebron University Hospital, Spain, between March 2003 and July 2006. Patients were evaluated with regard to the sensitivity and specificity of the dark halo sign in the temporal artery for the diagnosis of GCA, as well as the sensitivity and specificity of the presence of stenosis in temporal and/or ophthalmic arteries. Additionally, the usefulness of the dark halo sign in the follow-up of GCA was addressed.*

Results. *Forty-seven patients (30 with GCA, 17 with PMR) and 13 controls were included in the study. The sensitivity and specificity for the diagnosis of biopsy-proven GCA were higher for the temporal halo (72% in both cases) than for temporal artery stenosis (41% and 89%, respectively), or for ophthalmic artery stenosis (58% and 89%, respectively). Disappearance of the halo was observed in 50% of patients six months after diagnosis, although all patients were in clinical remission, and laboratory parameters were within normal values.*

Conclusions. *CDU of the temporal arteries may be a valid tool in the diagnosis of GCA. However, its role in the follow up of the disease deserves re-evaluation. CDU of the ophthalmic arteries is less useful for CGA diagnosis and no relationship with blindness is suspected.*

Introduction

GCA is a systemic vasculitis of the large and medium-sized arteries which usually affects individuals 50 years and older (1, 2). The most serious complication of the disease is visual loss, which can be prevented by prompt diagnosis and appropriate treatment with glucocorticoids (3, 4). The American College of Rheumatology (ACR) proposed classification criteria in 1990 with five items for GCA (5) which physicians frequently apply at diagnosis, although their use as a diagnostic tool is debatable (6). Biopsy of the temporal artery (TA) remains the gold standard for the diagnosis of GCA, although in 10 to 42% of patients with GCA the TA biopsy is unable to detect signs of inflammation, probably due to the segmental involvement of the artery because of the disease (7, 8). In addition, TA biopsy can have complications such as damage to the facial nerve resulting in a drooping eyebrow (9, 10), skin necrosis (11), or arterial stroke due to the interruption of collateral circulation (12).

CDU of the temporal arteries has been proposed as a useful, non-invasive, diagnostic test for GCA. Schmidt *et al.* (13) described a specific dark hypoechoic halo round the temporal artery lumen, probably due to arterial wall edema, in patients with GCA. The authors also suggested that the dark halo disappeared on average 16 days after starting glucocorticoid therapy. Stenoses and occlusions of the temporal artery have also been described in patients with clinical suspicion of GCA.

The role of ophthalmic artery sonography for the diagnosis of GCA has yet to be investigated, although some studies have been performed in patients with blindness secondary to GCA (14-16).

In our study, although ophthalmic artery involvement in GCA is not universal, we prospectively studied the value of

CDU of the temporal and ophthalmic arteries in the diagnosis of GCA, as well as the usefulness of CDU in the follow-up of the disease. Furthermore, we evaluated the relationship between CDU abnormalities in ophthalmic arteries and blindness.

Materials and methods

Protocol

All patients consecutively seen at the Department of Internal Medicine between March 2003 and July 2006, with clinical suspicion of GCA or PMR, were prospectively enrolled in the study. Diagnosis was obtained after a complete medical history, clinical examination, routine laboratory tests, chest x-ray and temporal artery biopsy. Patients were then classified into 3 groups: GCA group, PMR group and patients without symptoms suggestive of GCA (control group). The GCA group included patients who fulfilled the ACR criteria for GCA, such as headache, jaw claudication, acute vision loss or scalp tenderness, with or without constitutional syndrome, fever, or PMR symptoms. The PMR group included patients who fulfilled well-established classification criteria for PMR, such as persistent aching or morning stiffness of the neck, shoulder or pelvic girdle, for at least one month, with or without constitutional syndrome or fever, and no symptoms suggestive of GCA (17). Finally, a group of patients older than 60 years, with chronic headache, non-arteritic blindness and/or persistent fever, and no symptoms suggestive of GCA or PMR, were included as a control group. Patients with systemic inflammatory diseases were excluded from this group.

Ultrasonographic evaluation

A linear 5-10 MHz pulsed wave probe (Aplio-80, Toshiba) was used for the assessment of both temporal and ophthalmic arteries. Temporal and ophthalmic duplex exams were performed using both longitudinal and coronal planes and by means of both PW and B-mode ultrasound. The presence of a dark halo (hypoechoic halo) or stenosis round on the length (common trunk, frontal and parietal rami) of the superficial temporal arteries was determined, as well as the presence of stenoses or occlusions in both ophthalmic arteries. Halo was defined as a hypoechogenic rim surrounding the colour-coded flow in the temporal artery (Fig. 1). Stenosis was considered to be present if blood-flow velocity was more than twice the rate recorded in the area before the stenosis, perhaps with wave forms demonstrating turbulence and reduced velocity behind the area of stenosis. Ophthalmic artery was identified, based on colour-coded sonography as an arterial signal parallel to the optic nerve. Once identified, the ophthalmic artery was tracked to a depth from 25 to 50 mm.

The settings for CDU were as follows: dynamic range, 50 dB; colour gain, 78 percent; type of colour gain, V; colour wall filter, 100 Hz; velocity scale, 9-13 m/s; focus point position 5-7 mm (adjusted to vessel depth); zoom factor, 1.5; and focus-point position, 7 mm.

CDU of the temporal arteries was performed in all patients at diagnosis, and at six weeks and six months later in all those in whom the dark halo was observed in the initial study.

CDU was carried out by a neurologist specialized in this field who had not been informed of the clinical suspicion of GCA. The same sonographer performed baseline and follow-up exams using the same settings.

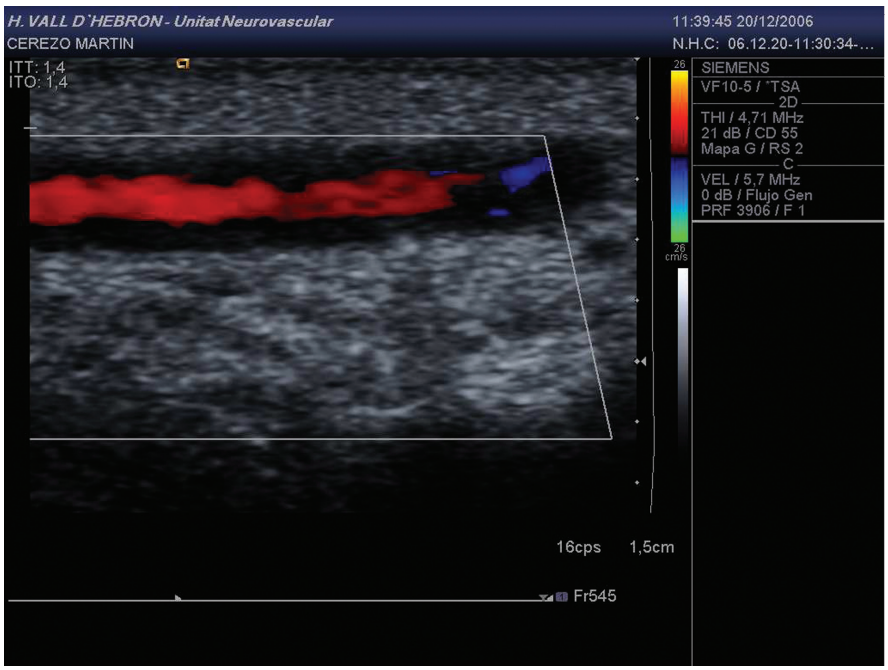

Fig. 1. Halo sign in CDU in a patient with GCA. Hypoechoic area around the temporal artery in longitudinal view.

Temporal artery biopsy

TA biopsy was performed in all patients (with clinical suspicion of GCA or PMR) between 1 and 7 days after the CDU. A histological fragment was extracted from the temporal artery which showed either morphologic or pulse abnormalities on physical examination and/or greatest CDU abnormalities. GCA was diagnosed when vasculitis with a predominance of mononuclear-cell infiltration or granulomatous inflammation, with or without giant cells, was observed in biopsy specimens (18). In the patients with negative TA biopsy and high GCA suspicion another biopsy was performed in the contralateral temporal artery.

Quantification of the inflammatory infiltrate was assessed according to the number of affected layers in the vessel wall. When all the vessel layers were affected inflammation was considered to be severe, when an isolated infiltrate was observed in the adventitia and/or intima it was considered to be moderate, and no inflammation was when no inflammatory cells were observed.

The pathologist was unaware of either the clinical suspicion of GCA or CDU findings.

Treatment

All patients with clinical suspicion of GCA or PMR received glucocorticoid treatment. Patients in the GCA group received 1 mg/kg/day of oral prednisolone, and those in the PMR group received 0.5 mg/kg/day. When ocular symptoms were present, intravenous glucocorticoid therapy (1g/day of metilprednisolone) was given for 3 days. Patients in the control group received no glucocorticoid therapy.

The interval between glucocorticoid treatment institution, CDU and biopsy performance was recorded for each patient.

Statistical analysis

The SPSS statistical software was used for statistical analysis. The Chi-squared test, the Fisher test, the Mann-Whitney U test, and the Student's *t*-test were used to compare the results among the three groups. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CDU abnormalities were calculated.

Results

Baseline characteristics and final diagnoses (Table I)

Sixty-six patients with clinical suspicion of GCA or PMR were seen at our Department, but only 47 were included in the study. Thirty patients constituted the GCA group, and 17 formed the PMR group. Three patients were excluded from the study due to lack of informed consent to perform arterial biopsy. Another 3 patients were excluded due to the absence of arterial tissue in the biopsy specimen. A group of 13 patients with cephalalgia, amaurosis or fever formed the control group.

The average age of patients in the GCA group was 78 years (range 64 to 93 years), eighteen of whom (60%) were females. The most frequent clinical manifestations were: headache (23 patients, 76%), jaw claudication (16 patients, 53%), unilateral visual loss (10 patients, 33%), scalp hyperesthesia (10 patients, 33%), proximal myalgia (8 patients, 27%), fever (4 patients, 14%) and constitutional syndrome (2 patients, 7%). A thickened temporal artery was present in 14 cases (46%). The mean ESR value was 86.3 mm/h (range 35-170 mm/h); CRP 5.2 mg/l (range 2.2-9.8); haptoglobin 3.7 g/l (range 1.9-7.5); fibrinogen 5.2 g/l (range 2.2-9.8), and α2-globulin 18.4% (range 13-24). All patients in the GCA group received glucocorticoid treatment for an average of 5 days (range 1-10) before undergoing CDU, and 8 days (range 4-15) before TA biopsy was performed.

All patients in the PMR group reported proximal myalgia, mainly involving the shoulder girdle and the proximal aspects of the arms. Constitutional syndrome or fever were present in only 5 patients. All PMR patients received glucocorticoid therapy for an average of 4 days (range 1-8) before undergoing CDU, and 7 days (range 4-12) before undergoing TA biopsy.

None of the patients included in the control group fulfilled the ACR criteria for GCA or PMR. Eight patients were diagnosed with chronic headache (one of them with urinary infection), 3 with having non-arteritic ischaemic optical neuritis, and 2 of atypical pneumonia.

Ultrasonographic and histological findings (Table II)

CDU abnormalities were more frequently observed in the GCA group, particularly in patients who had jaw claudication, and in those with a positive TA biopsy ($p<0.05$). CDU showed abnormal findings in 27 of 30 patients with clinical suspicion of GCA. A dark halo was observed in 22 patients (16 in those bilateral), temporal stenosis in 13

Table I. Characteristics of the 60 patients enrolled in the study. *P*-value calculated for the 3 groups.

	GCA	PMR	Controls	*p*
Number (n)	30	17	13	
Age	78 [64-93]	75 [60-86]	75 [49-88]	0.08
Men	12 (40%)	9 (52.9%)	6 (46.2%)	0.66
Women	18 (60%)	8 (47.1%)	7 (53.8%)	
Hemoglobin (g/dl)	10.1 [9.4-12]	11 [10.1-13]	11.9 [10-12.4]	0.08
ESR (mm/h)	86.3 [35-170]	72.3 [33-120]	45 [5-96]	0.01
CRP (mg/l)	6.7 [0.7-25]	4 [0.1-18]	0.9 [0.3-2]	0.11
Fibrinogen en g/l	5.2 [2.2-9.8]	4.8 [3.3-7.1]	3.4 [2.4-4.3]	0.01
α_2-microglobulin (%)	18.4 [13-24]	16.2 [11-24]	18.8 [11-24]	0.06
Haptoglobin (g/l)	3.7 [1.9-7.5]	2.4 [1.5-3.9]	2 [1-3.6]	0.03
Interval treatment-US (days)	5 (1-10)	4 (1-8)	-	0.21
Interval treatment-biopsy (days)	8 (4-15)	7 (4-12)	-	0.23
Interval US-biopsy (days)	3 (2-7)	4 (2-6)	-	0.31

Table II. Comparation between results obtained by ultrasonography and histologic findings.

	no. of patients	Halo	Temporal stenosis	Ophthalmic stenosis	Histologic findings
GCA (n=30)	8	+	+	+	+
	7	+	–	–	+
	4	+	–	+	+
	3	–	–	+	+
	2	–	+	+	+
	2	+	+	–	+
	1	+	+	–	–
	3	–	–	–	+
PMR (n=17)	13	–	–	–	–
	1	+	–	+	–
	1	+	+	+	–
	2	+	–	–	–
Control group (n=13)	11	–	–	–	ND
	1	+	–	–	–
	1	+	–	+	–

ND: not done.

(2 in those bilateral), and ophthalmic stenosis in 17 (unilateral in all cases). TA biopsy was positive in 29 patients, although 16 patients showed abnormalities on physical temporal artery examination. Characteristics of the inflammatory infiltrates of the 29 patients with a positive TA were as follows: giant cells were observed in 19 cases, panarteritis with a pronounced cell infiltrate involving all vessel wall layers was found in 12 cases, and isolated inflammatory cells in the media and/or inside the adventitial layer were detected in 17 cases. In 11 of the 12 cases with panarteritis and 10 of the 17 cases with isolated inflammatory infiltrates, a dark halo in the temporal arteries was observed. The remaining GCA patient, in whom temporal artery biopsy was negative, was diagnosed using the ACR classification criteria. Stenosis of the ipsilateral ophthalmic artery was observed in 7 of the 10 patients with GCA who experienced acute visual loss.

With regard to those patients with clinical suspicion of PMR, CDU abnormalities were observed in 4 of the 17 patients in this group. Four of them had a dark halo, 1 temporal stenosis, and 2 had ophthalmic artery stenosis. All patients in the PMR group had a normal temporal artery on physical examination. Only one patient who had temporal halo reported fever and constitutional syndrome (asthenia and weight loss). Temporal artery biopsy was negative in all 4 patients with CDU abnormalities and clinical suspicion of PMR. Clinical symptoms disappeared with low doses of glucocorticoids (30 mg of prednisone/day) in all cases, and no patient fulfilled GCA criteria during the follow-up period.

A dark halo round the temporal artery was found in 2 control patients, and ophthalmic stenosis in one of them. TA biopsy was performed in both these patients and no abnormalities were found. No patient developed arteritic symptoms during the follow-up period.

Sensitivity and specificity of CDU findings (Table III)

The sensitivity and specificity of the dark halo sign for GCA diagnosis were 73% and 80%, respectively, according to the ACR criteria, and 72% and 72%, respectively, according to the TA biopsy results. Sensitivity and specificity for temporal stenosis were 43% and 97%, respectively, according to the ACR criteria, and 41% and 89%, respectively, according to the TA biopsy results. Finally, the presence of ophthalmic stenosis had a sensitivity and specificity of 56% and 90 % for GCA diagnosis, respectively, according to the ACR criteria, and of 58% and 89%, respectively, according to the TA biopsy results.

Table III. Sensitivity and specificity of CDU of the temporal and ophthalmic arteries compared with the clinical diagnosis of GCA (based on ACR criteria) and with temporal artery biopsy findings.

Finding	GCA clinical diagnosis		Biopsy-proven GCA	
	Sensitivity	Specificity	Sensitivity	Specificity
H	22/30 (73%)	24/30 (80%)	21/29 (72%)	13/18 (72%)
TS	13/30 (43%)	29/30 (97%)	12/29 (41%)	16/18 (89%)
OS	17/30 (56%)	27/30 (90%)	17/29 (58%)	16/18 (89%)
H or TS	24/30 (80%)	24/30 (80%)	23/29 (79%)	13/18 (72%)
H or TS or OS	27/30 (90%)	24/30 (80%)	26/29 (89%)	13/18 (72%)

H: halo; TS: temporal stenosis; O: ophthalmic stenosis.

Follow-up findings

Twenty-two patients with clinical suspicion of GCA and 4 with PMR showed a dark halo round the temporal artery at diagnosis. A new CDU study was done 6 weeks after starting treatment in all patients in order to evaluate whether the halo had disappeared. The persistence of the halo sign in 50% of patients at this time, prompted us to carry out a new CDU study 6 months later, at which time CDU was only performed in 18 of the 22 patients with GCA who showed a dark halo at the beginning of the study. In 4 patients, a second CDU was not feasible due to patient death in 2 cases, and to lack of consent in a further 2. In the PMR group, CDU was also performed in all patients who showed abnormalities at the start of study. The halo persisted in 10 of the 18 patients with GCA, and in all patients with PMR. All patients in both groups were symptom-free and showed normal laboratory parameters when the second CDU was performed.

Discussion

In our study, the sensitivity and specificity of the halo sign and temporal stenosis for the diagnosis of GCA were similar to those reported by other authors (13, 19-25).

The variability of sensitivity and specificity of CDU findings reported in the literature may be due to multiple factors. The stage of the disease at diagnosis has shown that patients with severe arteritic symptoms have a greater probability of showing a temporal artery halo sign on CDU (24). The duration of corticosteroid treatment may also influence CDU results and disappearance of the aforementioned halo sign after some weeks of such treatment has been described (13, 21). However, in our study the mean interval between starting corticoid therapy and CDU performance was only of 4.5 days (range 1-10 days), and no significant differences were observed between the two groups of patients studied. The presence of a dark halo sign (or stenosis) on the temporal artery in patients with arteriosclerosis may lead to false positive values. In fact, in the present study, temporal biopsy showed severe arteriosclerosis in the 4 patients with PMR and the 2 patients of the control group. Finally, it is well known that the accuracy of results obtained from CDU often depend on the investigator's skill and experience.

Although the overall PPV for temporal halo was 78% and the NPV was 62%, in the GCA group 21 of the 22 patients who showed temporal halo in CDU had histologic findings consistent with GCA (PPV 95%). Similarly, all 13 patients in the PMR group with no temporal halo had negative biopsy (NPV 100%). So, the presence of temporal halo in the high risk GCA group, and the absence of it in the low risk GCA, could avoid the need for carrying out

a temporal biopsy. On the other hand, since PMR may be the presenting manifestation of GCA and a temporal biopsy may yield positive histological features of GCA in approximately 9% of patients with isolated PMR presenting with constitutional syndrome (asthenia, anorexia and weight loss) and/or an ESR greater than 80 mm/h (23), the presence of halo sign in this subgroup of PMR patients may be considered as an alert sign to perform a temporal artery biopsy and exclude the presence of a "silent" GCA.

In our study the role of the ophthalmic artery sonography in GCA diagnosis was also addressed and its probable relationship with the development of GCA-related amaurosis. The presence of stenosis in the ophthalmic artery had a sensitivity and a specificity of 58% and 89%, respectively, for the diagnosis of GCA, and is less useful than the presence of dark halo sign. In addition, although the majority of patients who presented visual disturbances had stenosis of the ipsilateral ophthalmic artery, no statistical relationship was found between these findings. The presence of ophthalmic stenosis only showed a PPV of 41% and a NPV of 76% for predicting amaurosis, although our results may be influenced by the small study sample.

Taking into account that the presence of dark halo has been related to the presence of edema and inflammatory infiltrate in the TA wall, we investigated a possible relationship between the presence of dark halo and inflammatory findings in TA biopsy. We found a clear relationship between the presence of halo and the presence of a severe inflammatory infiltrate in the artery wall. In fact, 11 out of 12 patients with panarteritis in the temporal biopsy had dark halo. This relationship was less marked in patients with isolated inflammatory cells or diffuse infiltrates in the temporal artery. Our results agree with those previously reported in the literature (27).

However, in contrast to other published studies, we found that the halo sign did not disappear after several weeks of glucocorticoid therapy. Conversely, in 50% of patients the halo remained detectable 6 weeks and 6 months after starting glucocorticoid therapy, in fact all patients were symptom-free and laboratory parameters were within normal limits. No histologic differences in edema, inflammatory infiltrate, or giant cell presence were found between those with persistent halo and those without. It would therefore be interesting to investigate whether major inflammatory activity might be initially present in patients in whom the halo persists. To assess more accurately the inflammatory activity in TA biopsies, quantitative rather than qualitative methods should be used. Several studies in patients with GCA have linked IFN-γ expression with the presence of arteritic symptoms and moreover, IL-1β, IL-6, and TNF-α have been associated with the presence of systemic symptoms (28-32). Measurement of these cytokines in TA biopsies might be a way of quantifying inflammatory activity in the artery.

In conclusion, CDU of the temporal arteries is a very useful and widely available method in the diagnosis of GCA. It has a better diagnostic accuracy than other imaging methods as a 1T magnetic resonance imaging (33), but it has limitations especially at the large thoracic vessels (34).

Conclusions

Abnormalities in CDU, especially the presence of a dark halo round the temporal artery lumen, are useful for GCA diagnosis. The presence of the temporal halo sign could strongly support the diagnosis of the disease especially in patients with a high pre-test probability of GCA, thereby avoiding the need for a temporal biopsy. Similarly, in patients with a low pre-test probability of GCA, the absence of temporal halo sign could rule out the presence of this disease. Detecting stenosis in the ophthalmic artery is less useful than the presence of temporal halo in the diagnosis of GCA, and, in our limited study, shows a low value for predicting amaurosis. In clear contrast to published data, our study suggests that the temporal halo disappears in only 50% of patients after glucocorticoid therapy. Whether patients with temporal halo persistence experience more relapses or complications of the disease at a later date deserves further study.

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