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BRIEF COMMUNICATION

Symptomatic intracranial atherosclerotic disease: an ultrasound 2-year follow-up pilot study

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Abstract

Introduction The objective of this single-center pilot study was to assess if symptomatic intracranial atherosclerotic disease (ICAD) ultrasound features change through the 2 years after acute ischemic stroke or TIA, being ICAD a relevant cause of acute ischemic stroke or TIA, linked to high rates of recurrent stroke.

Methods We consecutively enrolled 48 patients with acute ischemic stroke or TIA with symptomatic ICAD detected by transcranial color-coded duplex sonography (TCCS) and confirmed by MR-angiography and/or CT-angiography. We set a neurosonological and clinical follow-up at 3, 6, 12, and 24 months (T0, T1, T2, T3, and T4).

Results We observed that the hemodynamic effect of the stenosis changed during the 2-year follow-up, as revealed by the modifications of Peak Systolic Velocity (PSV) (Friedman-ANOVA test, $p < 0.001$). The pairwise post-hoc analysis showed a statistically significant difference between PSV at T0 and PSV at T3 ($p = 0.005$) and between PSV at T0 and PSV at T4 ($p < 0.001$) being PSV at T3 and T4 lower than PSV at T0. Seven patients had a new event in the first 12 months.

Conclusions The high rate of recurrent stroke or death among ICAD patients seems to be independent of progressive arterial narrowing. A wide multicenter follow-up study is needed in order to identify the factors that, alongside the hemodynamic features, contribute to the high risk of recurrent stroke among patient with symptomatic ICAD.

Keywords Ischemic stroke · Intracranial atherosclerotic disease · Arterial stenosis · Transcranial color-coded duplex sonography Ultrasound

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Introduction

Intracranial atherosclerotic disease (ICAD) causes 5–10% of strokes in Caucasian, 15–29% of TIA/strokes in black, and up to 30–50% of strokes in Asian subjects [1]. The presence of ICAD-related stenosis is associated to high rates of recurrent stroke [2, 3]. Angiography is the gold-standard for the diagnosis of stenosis; however, considering the associated risks and costs, the primary use of a non-invasive exam is preferred. Therefore, transcranial color-coded duplex sonography (TCCS), transcranial Doppler (TCD), MR-angiography, and CT-angiography may replace angiography in daily clinical practice [4–7]. However, MR-angiography and CT-angiography have major limitations in long-term follow-up due to high-costs and patient compliance; therefore, TCCS may be a useful technique in the follow-up of patients [5, 8].

To our knowledge, no long-term instrumental follow-up study of patients with symptomatic ICAD is actually available. Therefore, the objective of our study was to describe the evolution of symptomatic ICAD investigated by a validated, low-cost and non-invasive method such as TCCS.

Methods

This is a prospective single-center cohort long-term follow-up study. From October 2014 to January 2017, we consecutively enrolled patients with a clinical diagnosis of acute ischemic stroke or TIA and symptomatic ICAD, detected by TCCS and confirmed by MR-angiography and/or CT-angiography.

Ethics approval was obtained from the "Policlinico Gemelli" Ethics Committee and written informed consent was obtained from patients.

We define symptomatic ICAD as a stenosis > 50% of an artery that supplies the vascular territory in which the stroke or TIA occurred [9].

Baumgartner et al. proposed TCCS criteria that provide an accurate detection of > 50% stenosis, if compared with angiography; cut-offs of peak systolic velocity (PSV) for the anterior, middle, posterior, basilar, and vertebral cerebral arteries were found [5]. We also considered a PSV > 140 cm/s as a marker of stenosis of the intracranial tract of the internal carotid artery [10]. Being stenosis with a severe impairment of the flux not standardized [11], we enrolled patients with symptomatic ICAD diagnosed by CT-angiography and/or MR-angiography associated with minimal, blunted or dampened flux at TCCS, in order to avoid a selection bias (excluding patients with ICAD but without increased PSV).

Patients inclusion criteria were: clinically defined stroke or TIA according to WHO definition; AIAS > 50% [5] confirmed by MR-angiography and/or CT-angiography; AIAS diagnosed by CT-angiography and/or MR-angiography associated with minimal, blunted, or dampened flux at TCCS [11], large artery atherosclerosis according to TOAST criteria [9].

Patients exclusion criteria were: other etiologies according to TOAST criteria, in particular small vessel disease (radiological features) and cardioembolic stroke (including history of atrial fibrillation or detection of AF during the hospital stay or the follow-up period, heart failure with extremely low ejection fraction); no MRI-/CT-angiography confirmation of the > 50% AIAS detected by TCCS.

In particular cases, as young patients, our stroke work-up included autoimmunity tests, screening for coagulopathies, transesophageal echocardiogram, genetic tests (e.g., Fabry's disease, CADASIL, and collagenopathies). When performed, no one of these tests revealed different etiologies for the enrolled patients.

The first evaluation was performed during the hospital stay (T0) and the neurosonological follow-up was set at three (T1), six (T2), twelve (T3), and twenty-four (T4) months. The same operator performed TCCS. During the follow-up, we registered recurrent strokes or deaths.

The statistical analysis was carried out using the SPSS software package for Windows (12.0).

We excluded from the statistical analysis patients lost at follow-up, dead, and with a still-ongoing follow-up.

The Shapiro-Wilk test was used to assess the normality of the distributions. We used the Friedman-ANOVA test to detect differences among the values of PSV during the follow-up. Friedman post-hoc pairwise comparisons between observations were performed. Moreover, we performed the Friedman-ANOVA test in a subgroup selected after excluding seven patients: five patients with a PSV normalization by T1 were excluded being possible a cardioembolic stroke etiology even if no embolic source was detected; two patients with minimal flux in each observation were excluded because they could have an occlusion with slow recanalization. To evaluate the group effect (thrombolysis/non-thrombolysis) on PSV at T0, we performed the Mann–Whitney U test, being PSV values not normally distributed in the two groups. P value was set at $p < 0.05$.

Results

We consecutively enrolled forty-eight patients with symptomatic ICAD. Twelve patients with ICAD at T0 were successively excluded because atrial fibrillation was detected. Among the remaining thirty-six patients, four patients were lost at follow-up (one at T1, two at T2, and one at T3), two patients died, and three patients had a still-ongoing follow-up. Table 1 shows the main demographic and clinical features of the enrolled patients. We observed that PSV values were changing during the 2-year follow-up (Friedman-ANOVA test, $p < 0.001$). The pairwise post-hoc analysis showed a statistically significant difference between PSV at T0 and PSV at T3 ($p = 0.005$) and between PSV at T0 and PSV at T4 ($p < 0.001$). Figure 1 shows the Friedman's two-way analysis of variance by ranks, the box plots and PSV plotted over time for each case. In the subgroup analysis, we found similar results (Friedman-ANOVA test, $p < 0.001$). The pairwise post-hoc analysis showed difference between T0 and T3 ($p = 0.03$) and between T0 and T4 ($p = 0.001$). We found no effect of thrombolysis on PSV at T0.

In the first 12 months, five patients presented a recurrent event and two patients died (19.4%).

Regarding the therapy the patients received during the follow-up, we treated patients with double antiplatelet therapy following these criteria, because of the lack of guidelines: no disabling symptoms at discharge; no intralesional bleedings; no microbleeds detected at MRI; no history of peptic ulcer or other hemorrhagic diathesis [12, 13]. Otherwise, we treated

Table 1 Population overview

	Number/ total	%	Median (range)
Male	24/36	66.6	–
Female	12/36	33.4	–
Age	–	–	65 (26–86)
NIHSS at presentation	–	–	4 (0–31)
Hypertension	24/36	66.6	–
Dyslipidemia	11/36	30.5	–
Smokers	5/36	13.9	–
Omolateral internal carotid stenosis > 70%	4/36	11.1	–
Carotid atherosclerosis	22/36	61.1	–
Double antiplatelet therapy at discharge	15/36	41.7	–
Single antiplatelet therapy at discharge	21/36	58.3	–
New stroke	5/36	13.9	–
Death	2/36	5.5	–
Patient with concomitant non-symptomatic ICAD	3/36	8.3	–

patients with aspirin or clopidogrel alone. If needed, all patients were discharged with a cholesterol-lowering therapy (atorvastatin 40/80 mg daily) and appropriate antidiabetic and antihypertensive therapy. In particular, twenty-one patients received single antiplatelet therapy at discharge (sixteen aspirin, five clopidogrel); fifteen patients received double antiplatelet therapy until 3 months after the event and then continued aspirin alone. Twenty-six patients received statins (atorvastatin 40/80 mg). Twenty-one patients were treated with antihypertensive drugs (sixteen of them received a combination of them: seven patients received ACE-inhibitors, twelve angiotensin receptor blockers, eight Calcium-channel

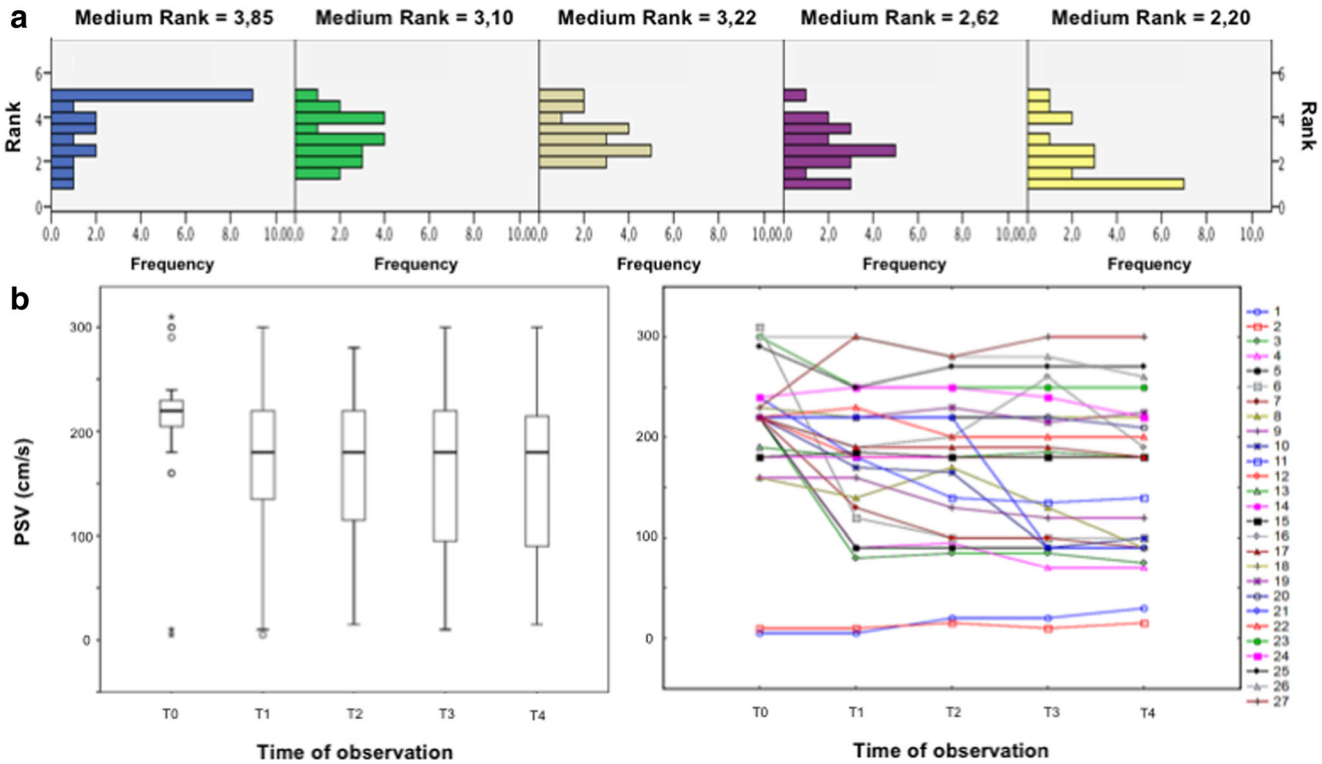

Fig. 1 PSV variations at different follow-up times. **a** This section shows the Friedman's two-way analysis of variance by ranks of PSV at different follow-up times (T0, T1, T2, T3, and T4, from left to right). **b** This section shows on the left the box plots of PSV, on the right the PSV plotted over time for each patient

blockers, and eleven other classes). Six patients needed an antidiabetic therapy (oral hypoglycemic drugs and/or insulin).

Discussion

Although symptomatic ICAD are associated to a high risk of recurrent stroke or death [1–3, 12, 13] our observations suggest that the hemodynamic effect unexpectedly decreases after 6 months as revealed by a statistically significant reduction of PSV. Given this, the high rate of a second event among our patients may not be influenced by a progressive narrowing of the stenosis, but probably by the combination of different mechanisms that, put together with the ICAD, compromise the vascular territory supplied by the stenotic vessel. Moreover, we cannot exclude that an "unstable" plaque may have caused a new stroke in the downstream territory with an artery-to-artery embolism [14].

Considering the causes that determined the observed modifications of the hemodynamic features of the stenosis, alongside spontaneous qualitative and quantitative changes of the plaque itself, we cannot exclude the effect of the medications. In fact, almost all enrolled patients received statin and antihypertensive therapy during the follow-up [15–18].

Although the small sample size recruited in a single center might influence the results, we think that the robust inclusion/exclusion criteria we adopted may reduce the confounders. Moreover, no instrumental long-term follow-up studies are nowadays available and, in this view, our study may contribute to enrich our knowledge on ICAD. Furthermore, PSV reduction at T3 and T4 may be linked to the variability of repeated measurements at different times; however, we consider this possibility not likely since all subjects were evaluated by the same operator.

Conclusions

In our study, we detected a stability of the hemodynamic features of symptomatic ICAD in the first 6 months followed by a reduction of PSV at the 12-month follow-up. Therefore, the high rate of recurrent stroke or death is unlikely related to a progressive arterial narrowing. In this view, the answer might lie in a multifactorial etiology of stroke recurrence among this category of patients. Given this, our pilot study highlights the need of a multicenter follow-up evaluation to investigate the factors that, alongside the hemodynamic features, contribute to the high risk of recurrent stroke among ICAD patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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