Value of Carotid Intima-Media Thickness and Significant Carotid Stenosis as Markers of Stroke Recurrence

Jaume Roquer, MD, PhD; Tomás Segura, MD, PhD; Joaquín Serena, MD, PhD; Elisa Cuadrado-Godia, MD; Miguel Blanco, MD, PhD; Jorge García-García, MD; José Castillo, MD, PhD; on behalf of the ARTICO Study

Background and Purpose—Data on the predictive value of carotid intima-media thickness (IMT) for stroke recurrence are scarce. We sought to analyze outcome differences in stroke patients with high IMT values compared with patients with significant carotid stenosis (SCS).

Methods—The multicenter observational ARTICO study included 620 independent patients older than 60 years with a first-ever noncardioembolic stroke. Patients were followed-up for 1 year. The primary end point was a composite of cardiovascular events and death. The IMT-ARTICO substudy analyzed ultrasonographic data from 599 patients. After Doppler carotid echography, patients were classified into the SCS group (carotid stenosis ≥50%; 117 cases), high IMT group (patients with the common carotid IMT in the highest quartile ≥1.11 mm and without SCS; 110 cases), and control group (stroke patients with an IMT <1.11 mm and without SCS; 372 cases). We analyzed the impact of both conditions on the primary end point.

Results—During follow-up, 88 patients (14.7%) had an end point event. Univariate analysis showed that male gender, diabetes, symptomatic peripheral arterial disease, ankle brachial index ≤0.9, SCS, and high IMT were related to the primary end point. Cox regression showed that peripheral arterial disease (hazard ratio [HR], 2.06; 95% confidence interval [CI], 1.18–3.59; P=0.011), SCS (HR, 3.02; 95% CI, 1.78–5.13; P=0.0001), and high IMT (HR, 1.86; 95% CI, 1.05–3.29; P=0.032) were related to the primary end point. If patients with scheduled revascularization procedures were excluded from the Cox regression, then ultrasonographic markers were SCS (HR, 1.84; 95% CI, 1.03–3.28; P=0.039) and high IMT (HR, 1.86; 95% CI, 1.06–3.27; P=0.030).

Conclusions—Both SCS and high IMT have an independent impact as markers of major cardiovascular events or death after a first-ever noncardioembolic stroke. (Stroke. 2011;42:3099-3104.)

Key Words: atherosclerosis ■ carotid stenosis ■ intima-media thickness ■ ischemic stroke ■ stroke recurrence

The impact of significant carotid stenosis (SCS) on cardiovascular outcomes and stroke recurrence after an ischemic stroke (IS) has been well-analyzed and its value is well-established in stroke populations.1-3 The relationship between cardiovascular events and other ultrasonographic variables, such as intima media thickness (IMT) or total plaque area, also have been evaluated.4-7 However, this association has not been consistent, mostly because of different methodology across the studies. Moreover, most of the studies have been population-based excluding stroke patients. Total plaque area seems to be a more representative measure of atherosclerotic burden because it shows better predictive power than IMT for cardiovascular events.8-10 However, IMT seems to be a better predictor of stroke than myocardial infarction, but the extent to which these phenotypes predict cardiovascular risk depends, in part, on the population studied.8

IMT traditionally has been considered to be a marker of early atherosclerosis, whereas plaques have been considered to reflect a later stage. However, recent data suggest that IMT and plaque may reflect different genetic and biological aspects of atherogenesis with distinctive relationships to clinical vascular disease.11-13

The ARTICO study, a multicenter prospective study14 of patients who have experienced a noncardioembolic stroke, was designed to evaluate the prognostic value of the pathological (≤0.9) ankle-brachial index, measured on inclusion, for the emergence of new vascular events at 1 year. The ARTICO data indicate that symptomatic, but not asymp-
tomatic, peripheral arterial disease (PAD) identifies a group at high risk for vascular recurrence after a first noncardioembolic stroke and that the increased risk is particularly high in patients with both internal carotid stenosis and PAD. A secondary objective of the ARTICO study was to evaluate the role of the carotid IMT on the primary outcome (IMT-ARTICO substudy). Using these data, we analyze the predictive value of 2 different ultrasonographic values, SCS and high IMT (h-IMT), on outcome after a first noncardioembolic IS.

Subjects and Methods
ARTICO included independent patients aged 60 years or older with a recent (<3 months) noncardioembolic ischemic stroke. All patients were evaluated by a neurologist before inclusion in the study to confirm the nature of the event under a standardized etiologic protocol, including a complete personal and family medical history of vascular risk factors and a clinical examination including height, weight, waist circumference, and arterial blood pressure. Routine blood and coagulation tests and brain CT or MRI were performed on all patients.

Of the 620 participants in the ARTICO study, 21 were excluded from the IMT-ARTICO substudy (17 because of incomplete IMT records and 4 who were lost to follow-up). Patients were classified using the evidence-based classification algorithm for acute ischemic stroke (SSS-TOAST) criteria: probable atherothrombosis or possible atherothrombosis (n=364), lacunar (n=120), and undetermined cause of stroke (n=115). Follow-up evaluations were performed at 6 and 12 months in every center by a vascular neurologist involved in the study. The primary composite end point included: the first occurrence of any stroke or transient ischemic attack; myocardial infarction or unstable angina; hospitalization for symptomatic PAD, extremity amputation, or a revascularization procedure (coronary, cerebral, or peripheral); and death from any cause within the first year after stroke.

Carotid Ultrasonography Study
B-mode color Doppler carotid echography was performed on all stroke patients within the first 7 days of IS. These studies were performed by a trained sonologist blinded to clinical data. All centers used the same standardized current international recommendations.

Figure. Cox proportional hazards models. Accumulative survival curves according to echographic groups after controlling for confounders. A, Cox analysis including all outcome events. B, Cox analysis after excluding patients with scheduled revascularization procedures. High intima-media thickness (h-IMT; IMT ≥ 1.11), significant carotid stenosis (SCS; carotid stenosis > 50%.)
IMT was measured in a still image during diastole in both common carotid arteries at the far wall and at least 1 cm below the bifurcation on a 1-cm plaque-free segment. To differentiate plaques from increased IMT, a plaque was defined as a focal structure that encroaches into the arterial lumen at least 0.5 mm or 50% of the surrounding IMT value, or demonstrates a thickness >1.5 mm as measured from the media-adventitia interface to the intima lumen interface. The highest value of 6 common carotid artery measurements was taken as the final IMT. To define internal carotid artery stenosis ≥50%, we used the systolic velocity (>125 cm/sec), and for the internal carotid artery/common carotid artery we used the systolic velocity ratio (>2). If necessary, additional neurovascular explorations were performed. IMT measurement was performed at each center. All the ultrasonographic variables were included in a case report form that was analyzed in the coordinating center.

**Statistical Analysis**

Proportions between groups were compared with the χ² test. Continuous variables were expressed as mean±standard deviation or median and quartiles and were compared by the Student t test or the Mann-Whitney U test, as appropriate. IMT distribution was categorized in quartiles because of the non-normal distribution shown by Kolmogorov-Smirnov and Shapiro-Wilk tests. Kaplan-Meier univariate outcome analysis was performed and a pair-wise log-rank test was computed between quartiles of IMT, showing no differences between the first 3 quartiles. Therefore, IMT was categorized in 2 groups using 1.11 mm as the cut-off point that separates the fourth quartile from the rest. Differences in the risk of new vascular events according to the study variables were evaluated in a univariate analysis. Complementary univariate analyses of IMT and SCS categorized into 2 groups (>1.10 mm and >50%, respectively) and of vascular risk factors were performed to rule out confounding factors.

Variables whose association with outcome and study variables (IMT or SCS) reached P<0.10 were included in a Cox regression analysis as possible confounding variables. A Cox multivariate model was used to assess independent association of study variables and the primary end point, adjusting for possible confounding variables. Interaction between IMT and SCS was explored in a separate model that included IMT and SCS as independent variables (data not shown). Hazard ratio (HR) was verified for both models: one with IMT and SCS as independent variables (P=0.2781) and one with the 3-group variable (P=0.463). Because of collinearity between ankle-brachial index and symptomatic PAD, ankle-brachial index was removed from the analysis. Statistical significance was set at P<0.05.

**Variables Analyzed**

To define different phenotypes and to assess the potential predictive capacity of h-IMT in the absence of SCS in the clinical setting, patients were classified into 3 groups: SCS (patients with carotid stenosis ≥50% in symptomatic or asymptomatic carotid artery, independently of the IMT value), h-IMT (patients without SCS and with common carotid IMT ≥1.11 mm, the highest quartile), and control group (no SCS and IMT <1.11 mm).

**Results**

The final cohort was 599 patients. Mean age was 71.2 (7.4) years, and 406 (67.8%) were men. Diabetes mellitus was present in 35.3% of patients, arterial hypertension was present in 76.2%, dyslipidemia was present in 44.9%, coronary artery disease was present in 11.3%, PAD was present in 8.9%, and current smoking was present in 18.9%. Microalbuminuria was observed in 22.5% of cases, and ankle-brachial index was ≤0.9 in 28.2%. Median IMT (Q1–Q3) was 0.90 (0.70–1.11). After the ultrasonographic stratification, 110 patients (18.4%) were in the h-IMT group, 117 patients (19.5%) were in the SCS group, and 372 (62.1%) were in the control group. In the SCS group, 82 patients (70.1%) had stenosis ≥70%, including 30 carotid occlusions. In almost all patients, the greater stenosis was in the symptomatic carotid artery. Stroke etiology was atherothrombotic in 364 (60.8%) cases, lacunar in 120 (20.0%) cases, and undetermined in 115 (19.9%) cases.

In univariate analysis, IMT in all quartiles was associated with age (P=0.022), diabetes (P=0.033), hypertension (P=0.016), and dyslipidemia (P=0.027). However, SCS was associated with male gender (P=0.011) and PAD (P=0.009).

A total of 88 patients (14.7%) experienced an end-point event during follow-up. After ultrasonographic stratification, the risk was greater in the SCS group (29.1%) and h-IMT group (18.2%) than in the control group (9.1%; P<0.0001). Univariate analysis for the development of any end-point event is shown in Table 1. Male gender (odds ratio [OR], 1.88; 95% CI, 1.09–3.22; P=0.026), diabetes (OR, 1.66; 95% CI, 1.05–2.62; P=0.030), PAD (OR, 2.90; 95% CI, 1.53–5.50; P=0.002), ankle-brachial index ≤0.9 (OR, 2.99; 95% CI, 1.86–4.82; P=0.0001), the echographic group (P=0.0001), and the etiologic group (P=0.021) were the variables associated with the end point.

Table 2 shows the results of the Cox regression analysis. The variables independently associated with the emergence of new vascular events or death were PAD (HR, 2.06; 95% CI, 1.33–4.62; P=0.004), SCS (HR, 3.02; 95% CI, 1.78–5.13; P<0.0001), and h-IMT (HR, 1.86; 95% CI, 1.05–3.29; P=0.032).

If the 16 patients treated with scheduled revascularization procedures during follow-up were excluded from the study to limit overestimation of the rate of recurrent events, then the Cox regression analysis showed that the variables independently associated with the emergence of new vascular events or death were: PAD (HR, 2.07; 95% CI, 1.10–3.91; P=0.024); diabetes mellitus (HR, 1.64; 95% CI, 1.02–2.61; P=0.039); SCS (HR, 1.84; 95% CI, 1.03–3.28; P<0.039); and h-IMT (HR, 1.86; 95% CI, 1.06–3.27; P=0.030; see Figure).

We found no interaction between IMT and SCS or between these variables and the other study variables in a second model that analyzed IMT categorized in 2 groups independently from SCS (data not shown). Including variables associated with IMT or SCS in the univariate analysis did not change the results.

If patients with scheduled revascularization procedures after index stroke were excluded, then there were no clear differences in the type of primary end point between patients in the h-IMT group and those with SCS (Table 3).

The relationship between echocardiographic phenotypes and TOAST subtypes in relation to the outcome events was also analyzed. For the h-IMT group, 75% of events were experienced by patients with the atherothrombotic subtype and by 25% with undetermined cause of stroke subtype. For the SCS >50% group, all events were of the atherothrombotic subtype. For the control group, 47.1% of events were of the atherothrombotic subtype, 38.2% were of the lacunar subtype, and 14.7% were of the undetermined cause of stroke subtype.
The identification of markers of high cardiovascular risk in the general population, particularly in those considered to be at high risk, is an area of continued interest. Among these markers, carotid ultrasonographic data have been extensively studied. It is well-established that patients with a high degree of carotid stenosis, especially those who are symptomatic, are at high risk for cardiovascular events, mainly stroke.1–3 With regard to other ultrasonographic variables, it has been suggested that total plaque area is the strongest predictor of cardiovascular risk of the ultrasound phenotypes.9,13 Plaque echogenicity also predicts future strokes independently of plaque size.11 In patients with symptomatic carotid stenosis, the risk of IS increases for echolucent versus echo-rich plaques.18

A recent meta-analysis concluded that IMT is a modest but independent predictor of coronary artery disease that adds little information to coronary artery disease prediction by classical risk factors. In the case of stroke, IMT is a stronger independent predictor, although there are little data on the value of incremental IMT as a predictor of stroke beyond the classical risk factors.19 Few studies have analyzed the predictive value of IMT for stroke recurrence. The first published one, which analyzed 238 patients with first-ever IS, showed that patients who experienced recurrent cerebrovascular

### Table 1. Univariate Analysis of Patients According to the Emergence of New Vascular Events or Death

<table>
<thead>
<tr>
<th>Variable</th>
<th>Yes (n=88)</th>
<th>No (n=511)</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (men), n (%)</td>
<td>69/88 (78.4)</td>
<td>337/511 (65.9)</td>
<td>0.026*</td>
<td>1.88 (1.09–3.22)</td>
</tr>
<tr>
<td>Sex (women), n (%)</td>
<td>19/88 (21.6)</td>
<td>174/511 (34.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y (SD)</td>
<td>71.6 (8.0)</td>
<td>71.1 (7.2)</td>
<td>0.569</td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>40/88 (45.5)</td>
<td>169/505 (33.5)</td>
<td>0.039*</td>
<td>1.66 (1.05–2.62)</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>60/88 (69.8)</td>
<td>365/502 (72.7)</td>
<td>0.603</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>44/87 (50.6)</td>
<td>218/497 (43.9)</td>
<td>0.293</td>
<td></td>
</tr>
<tr>
<td>Symptomatic PAD, n (%)</td>
<td>16/87 (18.4)</td>
<td>36/499 (7.2)</td>
<td>0.002*</td>
<td>2.90 (1.53–5.50)</td>
</tr>
<tr>
<td>ABI ≤0.9, n (%)</td>
<td>43/83 (51.8)</td>
<td>125/473 (26.4)</td>
<td>0.0001</td>
<td>2.99 (1.86–4.82)</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>14/87 (16.1)</td>
<td>53/507 (10.5)</td>
<td>0.141</td>
<td></td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>17/86 (19.8)</td>
<td>94/502 (18.7)</td>
<td>0.881</td>
<td></td>
</tr>
<tr>
<td>Waist circumference (men)</td>
<td>100.6 (14.5)</td>
<td>100.1 (12.0)</td>
<td>0.779</td>
<td></td>
</tr>
<tr>
<td>Waist circumference (women)</td>
<td>101.9 (13.3)</td>
<td>99.9 (14.8)</td>
<td>0.578</td>
<td></td>
</tr>
<tr>
<td>Statin pretreatment</td>
<td>23 (32.4)</td>
<td>122 (27.1)</td>
<td>0.393</td>
<td></td>
</tr>
<tr>
<td>Microalbuminuria, n (%)</td>
<td>12/73 (16.4)</td>
<td>195/448 (23.4)</td>
<td>0.226</td>
<td></td>
</tr>
</tbody>
</table>

ECographic group 0.0001*

<table>
<thead>
<tr>
<th>Variable</th>
<th>P</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>0.198</td>
<td>1.41 (0.84–2.37)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.091</td>
<td>1.44 (0.94–2.21)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>0.011</td>
<td>2.06 (1.18–3.59)</td>
</tr>
<tr>
<td>Stroke etiological group</td>
<td>0.546</td>
<td></td>
</tr>
<tr>
<td>h-IMT group</td>
<td>0.032</td>
<td>1.86 (1.05–3.29)</td>
</tr>
<tr>
<td>SCS group</td>
<td>0.0001</td>
<td>3.02 (1.78–5.13)</td>
</tr>
</tbody>
</table>

Table 2. Cox Regression Analysis: Variables Related to the Emergence of New Vascular Events or Death

<table>
<thead>
<tr>
<th>Event</th>
<th>SCS Group (n=117)</th>
<th>h-IMT Group (n=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke recurrence</td>
<td>7 (6.0%)</td>
<td>10 (9.1%)</td>
</tr>
<tr>
<td>Carotid revascularization procedures</td>
<td>16 (13.7%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Other CV events</td>
<td>4 (3.4%)</td>
<td>3 (2.7%)</td>
</tr>
<tr>
<td>Death</td>
<td>7 (6.0%)</td>
<td>6 (5.5%)</td>
</tr>
</tbody>
</table>

CV indicates cardiovascular; h-IMT, high intima-media thickness; SCS, significant carotid stenosis.
Events had higher IMT values than subjects who were free of stroke recurrence, and after adjustment for baseline characteristics, risk factors, stroke subtypes, and secondary prevention therapies, increasing IMT was found to be an independent predictor of stroke recurrence. For each increment of 0.1 mm in IMT, the probability of experiencing recurrent stroke increased by 18.0%. A second study with a similar cohort (284 patients with a first-ever IS during a 1-year follow-up) showed that IMT adjusted for confounding factors was the only independent predictor of stroke recurrence (HR, 1.65; 95% CI, 1.11–2.46).

To the best of our knowledge, no previous studies have assessed the value of carotid IMT compared with SCS in predicting stroke recurrence. This is of potential interest not only because the data on the relationship between IMT and stroke recurrence are scarce but also because there is increasing evidence suggesting that IMT and plaques may be different phenotypes of the atherosclerotic process. This hypothesis is supported by certain differences between IMT and atherosclerotic plaques. From a histopathological point of view, IMT is approximately 80% media (smooth muscle cells) and 20% intima (endothelial layer, basal lamina, and subendothelial matrix), whereas atherosclerosis is largely an intimal process (with deposition of cholesterol, inflammation, and cell infiltration). Second, from a physiopathologic point of view, IMT mainly reflects a hypertensive hypertrophic response of the medial cells, which seems to be related to changes in local shear stress and probably represents a part of the arterial remodeling at early stages of atherosclerosis, whereas athero sclerotic plaques represent a later stage of atherogenesis related to inflammation, oxidation, endothelial dysfunction, and/or smooth muscle cell proliferation. Epidemiologically, carotid plaques measured in the carotid bulb or internal carotid arteries are more strongly related to hyperlipidemia and smoking and are a stronger predictor for myocardial infarction, whereas the IMT has been related to hypertension and ischemic stroke.

The results of our study of patients with a first noncardioembolic IS show that both ultrasonographic variables, h-IMT and SCS, were predictors of new vascular events, with an independent effect that was greater in the SCS group than in the h-IMT group (HR, 3.02 and 1.86, respectively) in the Cox regression analysis. If patients with planned revascularization procedures were excluded from analysis, then the HR was similar between the 2 groups (HR, 1.84 in the SCS group and 1.86 in the h-IMT group). Except for the revascularization procedures, there was no difference in the subtypes of end points experienced by patients from the h-IMT and SCS groups (Table 3). These findings suggest that h-IMT is an important determinant of outcome in non-SCS patients. It is possible that SCS and h-IMT may develop together in some cases, but their impact on the clinical course of patients might be independent. We see a certain agreement between our results and previous data, suggesting that the presence of high IMT values should not be considered to be only an initial stage of the atherosclerotic process but rather as probably representing a different phenotype of this process.

In addition, symptomatic PAD was independently associated with the composite end point formed by cardiovascular recurrences and mortality. PAD has been previously described as a poor prognostic marker after IS, and it is a powerful indicator of atherosclerotic burden.

Our study has several limitations. The principle one is the low number of events, mostly because of the relatively short follow-up. Nevertheless, we were able to find statistically significant differences in the risk of midterm outcome according to our study variables. Another limitation is that ultrasonographic studies were not centralized. However, all participating centers had previous experience in IMT measurement and all used the same standardized current international recommendations.

In summary, high IMT values after a noncardioembolic ischemic stroke should be considered a predictor of poor outcome, independently of the presence of carotid or peripheral arterial atherosclerosis.

Appendix

List of ARTICO Registry Investigators

Enrique Jiménez Caballero (Hospital Virgen de la Salud, Toledo); Jaume Roquer Gonzalez (Hospital del Mar, Barcelona); Mercedes Romero (Hospital de Valme, Sevilla); María Jiménez (Hospital Universitario Dr Josep Trueta, Girona); Jorge García García (Hospital General Universitario, Albacete); Miguel Blanco (Hospital Clínico Universitario, Santiago de Compostela); Vicente Medrano Martínez (Hospital General de Elda, Alicante); José Mª Ramírez (Hospital San Pedro Alcántara, Cáceres); Exuperio Díez Tejedor (Hospital Universitario La Paz, Madrid); Sergio Calleja (Hospital Central de Asturias, Oviedo); Adrián Arboix Damunt (Hospital Sagrat Cor, Barcelona); Luis García-Tuñón Villahuguen (Hospital de León); Jose A. Egido Herrero (Hospital Clínico Universitario San Carlos, Madrid); Covadonga Fernández Maiztegui (Hospital de Cruces, Barakaldo); Jaime Masjuan Vallejo (Hospital Ramón y Cajal, Madrid); Rosa Mª Sánchez Pérez (Hospital Marina Baixa, Alicante); José Miguel Pons Amate (Hospital General Universitario, Valencia); Raul Espinosa (Hospital Puerta del Mar, Cádiz); Ángel Fernández Díaz (Hospital Comarcal del Bierzo, León); Ernest Palomeras Soler (Hospital de Mataró, Barcelona); Victoria Mejías (Hospital Torrecárdenas, Almería); Carmen Jiménez Martínez (Hospital Universitario Son Dureta, Palma de Mallorca); Manuel Márquez Martínez (Hospital Clínico Universitario Virgen de la Victoria, Málaga); Alejandro García Escrivá (Hospital de Levante, Alicante); Pere Comas (Hospital de Sant Joan de Deu de Martorell, Barcelona); Jose Tembill Ferrairó (Hospital Universitario La Fe, Valencia); Rosario Gil (Hospital Clínico Universitario, Valencia); Mayte Martínez (Complejo Hospitalario Donostia); Roberto Belvis (USP Institut Universitari Dexeus, Barcelona); Francisco Moniche Álvarez (Hospital Virgen del Rocio, Sevilla); Javier Abella (Hospital Arquitecto Marcide, La Coruña); Gemma Reig Roselló (Hospital Universitario de La Princesa, Madrid); Oscar Fernández Fernández (Hospital Carlos Haya, Málaga); Isabel Campello (Hospital Royo Villanova, Zaragoza); Toni Figuerola (Hospital de Son Llatzer, Palma de Mallorca); Jordi Sanahuja Montesinos (Hospital Universitari Arnau de Vilanova, Lleida); Enrique Botia Paniagua (Complejo Hospitalario La Mancha Centro, Ciudad Real); Jose Manuel Molto Jordá (Hospital Francesc de Borja, Valencia); Josep Lluís Martí Vilalta (Hospital de la Santa Creu i Sant Pau, Barcelona); Jose Mª Ramírez (Hospital Universitario Infanta Cristina, Badajoz); Elena Vila Herrero (Clinica Santa Elena, Málaga); Marta Ferrero Ros (Hospital General, Segovia).

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1 Department of Neurology, Hospital Universitari del Mar, Parc de Salut Mar, Barcelona, Spain; 2 Department of Neurology, Hospital Universitario, Albacete, Spain; 3 Department of Neurology, Hospital Universitari Dr. Josep Trueta, Institut d’Investigació Biomèdica, Girona, Spain; 4 Department of Neurology, Hospital Clínico Universitario, Universidad de Santiago de Compostela, Spain.