Neurología. 2011;**26(5)**:279-284

NEUROLOGÍA

www.elsevier.es/neurologia

ORIGINAL ARTICLE

Cryptogenic stroke in young patients: Long-term prognosis and recurrence

A. Arauz,[a,*] M. Merlos-Benítez,[a] L.F. Roa,[a] B. Hernández-Curiel,[a] C. Cantú,[b] L. Murillo,[c] J. Roldán,[d] J. Vargas-Barrón,[d] F. Barinagarrementeria[e]

[a]*Clínica de Enfermedad Vascular Cerebral, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, México City, Mexico*
[b]*Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México City, Mexico*
[c]*Facultad de Medicina, Universidad Autónoma de Guadalajara, Guadalajara, Mexico*
[d]*Departamento de Ecocardiografía, Instituto Nacional de Cardiología Ignacio Chávez, México City, Mexico*
[e]*Facultad de Medicina, Universidad del Valle de México, Querétaro, Mexico*

Received on 10th July 2010; accepted on 12th October 2010

KEYWORDS
Cryptogenic infarct;
Recurrence;
Outcome

Abstract
Background: Around 40% of strokes in young people are labelled as infarcts of undetermined cause. The aim of this study was to determine the image characteristics, the long-term functional outcome and recurrence after cryptogenic ischaemic stroke.
Methods: We studied ninety-eight patients under 45 years of age during a median follow up of 54 months (range 12-238), with ischaemic stroke of undetermined cause. We registered vascular risk factors, clinical syndrome, laboratory and imaging results. We used Rankin disability score to assess functional outcome. The cases were evaluated with intracranial and extracranial vascular imaging studies, echocardiogram, and at least two determinations of prothrombotic states.
Results: In our hospital 11% of the patients with cerebral infarction under 45 years of age were labelled as cryptogenic. The mean age of the cases was 39.5±5, 48 (49%) were women, 6 (6%) had arterial hypertension, 7 (7%) prior history of migraine, 32 (33%) were active smokers, 11 (11%) had hypercholesterolemia, and 11 (11%) had alcoholism. All cases were treated with aspirin. We observed good functional outcome (Rankin 0-2) in 65 (65%) cases. The anterior circulation was the most affected (partial in 56%, total in 12%). Infarction was unique in 87 (88%) cases. Recurrence was observed in 4 (4%) cases.
Conclusions: In this study cryptogenic cerebral infarctions were mostly single, had low recurrence and good functional outcome in the long-term follow-up. Total anterior circulation infarctions correlated with poor outcome.
© 2010 Sociedad Española de Neurología. Published by Elsevier España, S.L. All rights reserved.

* Corresponding author.
E-mail: arauzg@prodigy.net.mx, arauzg@innn.edu.mx (A. Arauz).

0213-4853X/$ - see front matter © 2010 Sociedad Española de Neurología. Published by Elsevier España, S.L. All rights reserved.

PALABRAS CLAVE
Infarto cerebral en joven;
Pronóstico;
Recurrencia

Infarto cerebral criptogénico en pacientes jóvenes. Pronóstico y recurrencia a largo plazo

Resumen
Antecedentes: En menores de 45 años, el infarto cerebral (IC) criptogénico representa hasta el 40% de los casos. El objetivo de la presente serie es determinar la tasa de recurrencia, la evolución clínica funcional a largo plazo y las características de imagen de pacientes menores de 45 años, con IC criptogénico.
Métodos: 98 pacientes con diagnóstico con f rmado de IC criptogénico fueron seguidos durante una mediana de 54 meses (rango de 12 a 238). Registramos los datos demográf - cos, factores de riesgo, hallazgos clínicos, de laboratorio y de imagen, así como las complicaciones y la evolución funcional. La evaluación de los casos incluyó estudios de imagen vascular intra y extracraneal, ecocardiograma y dos determinaciones de estudios protrombóticos.
Resultados: Esta serie representa el 11% de los casos de IC en jóvenes en nuestro hospital. La edad promedio de los casos fue de 39,5±5, 48 (49%) fueron mujeres, 6 (6%) tenían hipertensión arterial, 11 (11%) hipercolesterolemia, 7 (7%) antecedente de migraña, 32 (33%) de tabaquismo activo y 11 (11%) de alcoholismo. Todos los casos fueron manejados con aspirina. Se observó buen pronóstico funcional (Rankin 0 a 2) en 65 (66%) casos y recurrencia en 4 (4%). La circulación anterior (parcial en 56%, total 12%) fue la más afectada y en 87 (88%) casos el infarto fue único.
Conclusiones: En esta serie, los IC criptogénicos fueron mayoritariamente únicos, con baja recurrencia y buen pronóstico funcional a largo plazo. Los infartos totales de circulación anterior se correlacionaron con mal pronóstico.
© 2010 Sociedad Española de Neurología. Publicado por Elsevier España, S.L. Todos los derechos reservados.

Introduction

Establishing the cause of a cerebral infarction (CI) is important to determine the functional prognosis and reduce the recurrence risk by choosing appropriate secondary preventative measures. In clinical practice, CI aetiology can be identi f ed with routine diagnostic procedures in more than half of cases. However , despite an exhaustive study , the cause of a CI cannot be determined in between 30% to 40% of cases, especially in patients under 45 years of age. [1]

Despite important advances in vascular , cerebral and cardiac imaging methods, and a greater recognition of haematological disorders, an important number of ischemic strokes continue having an unknown aetiology .[2] Cerebral infarctions classi f ed as cryptogenic have been considered benign and with a low recurrence rate when compared to other CI subtypes.[1,3] However, the most recently published series reports a recurrence rate near to 30% during the f rst follow-up year, a clear contradiction to other studies where the recurrence rate, after 2 years of follow-up, was found to be from 10% to 20%. [4] P revious studies related to cryptogenic CI have included patients over 45 years old, with risk factors of atherosclerosis and with probable CI causes, such as patent foramen ovale (PFO), which is why their results have not been conclusive.[1,3-7]

In this series, we analysed a group of patients of up to 45 years of age with CI of undetermined cause despite a full study and long term follow-up, with the aim of determining the recurrence rate and functional clinical evolution, and to detail neuroimaging f ndings.

Patients and methods

We analysed data from 127 patients under 45 years old with a conf rmed diagnosis of CI of undetermined aetiology . We used data that was prospectively included in our institution's stroke register, following standard protocol. Our database register was started in 1987 and includes 156 variables with demographic data, vascular risk factors, clinical f ndings from laboratory or imaging, together with complications and functional prognosis upon hospital discharge and during evolution. Currently, the register includes 4,600 cases with a mean age of 52.3±19 years, of which 20% (914 cases) correspond to CI in people under 45 years of age.

In the cases included, we also recorded a history of previous vascular or neurological events and the imaging results from magnetic resonance (MRI) or computerised tomography (CT). All cases were studied during the f rst month of the stroke and treated in the general neurological department. The following conditions were considered def ned CI causes and were therefore excluded: *a*) large-vessel atherosclerosis (at least 50% stenosis or occlusion of the affected vessel); *b*) lacunar infarction of at least 15mm diameter in patients with traditional clinical lacunar syndromes, without any evidence of cortical affectation and with a history of hypertension and diabetes; *c*) potential emboligenic heart disease, such as atrial f brillation (AF), inactive rheumatic heart disease, mechanical valve prosthesis, atrial thrombus, sick sinus syndrome, recent myocardial infarction, atrial myxoma, akinetic left ventricular segment and dilated cardiomyopathy, as well as

possible causes such as PFO, atrial septal aneurysm (ASA) or mitral valve prolapse; and *d*) other defined CI causes, such as arterial dissection, muscle fibrodysplasia, coagulopathies or antiphospholipid syndrome.

The results for each patient, from clinical findings of laboratory and imaging studies, were reviewed by neurologists with training in cerebral vascular disease.

Classification of a cerebral infarction

We used the TOAST[8] classification to determine CI aetiology, taking the subtype infarction of undetermined aetiology with complete or negative assessment for this analysis. We defined as cryptogenic CI those cases with: *a*) acute neurological deficit lasting more than 24h, *b*) a brain CT scan or MRI that corroborated CI as per the patient's symptoms and *c*) absence of carotid lesion by atherosclerosis or non-atherosclerotic vascular disease, from sources of emboligenic heart disease and hypercoagulable states responsible for the CI.[9]

Clinical and topographic classification

The clinical and imaging characteristics (CT or MRI) of the CI were listed according to the Oxfordshire Community Stroke Project classification in: *a*) total anterior circulation infarction (TACI); *b*) lacunar infarction (LACI); *c*) partial anterior circulation infarction (PACI), and *d*) posterior circulation infarction (POCI).[10]

Other studies

A Doppler of the neck vessels was carried out in all cases, together with at least one of the following studies: Transcranial Doppler, magnetic resonance angiography (MRA), computerised tomography angiography (CTA) or conventional cerebral angiography, to assess the intracranial and extracranial arteries.

Echocardiogram

Echocardiographic assessment was carried out on all patients to look for emboligenic sources, such as PFO and/or ASA. The echocardiogram was carried out in only one centre (National Cardiology Institute of Mexico), with two cardiologists taking part that had training in echocardiograms and followed previously established protocol for young patients with CI. The protocol was started with a transthoracic approach, once the possible structural changes related to an embolism of cardiac origin had been dismissed, we proceeded with the administration through the peripheral vein of microbubbles obtained from shaking saline solution.[11] The study was carried out while resting and with Valsalva manoeuvres; in case of doubtful or substandard studies in assessing the correct or negative morphological score for PFO diagnosis, we proceeded to complement the study with a transesophageal approach and administered a new amount of agitated saline solution[12]. In all the cases included, any potential emboligenic heart disease and lesser causes or possible cerebral embolisms, such as PFO or ASA were dismissed.

Haematological rating

Routine blood biochemical and prothrombotic studies were performed, with determination of protein S, protein C, antithrombin III, antiphospholipid antibodies (IgG, IgM) and anti-β2 glycoprotein (IgG, IgM). In some cases, these studies were carried out during the acute phase of the stroke; however, and given that the values tend to change during this stage, we took into account the studies performed at 3 and 6 months after the CI for the purpose of this series. There were no abnormalities in the studies in any of the cases.

Monitoring

The patients were assessed on average every 6 months. Any medical and/or neurological complications seen during the acute phase and in the follow-up were recorded. All patients received secondary prevention management with aspirin.[13]

The following events were recorded during the follow-up; recurrent CI (defined as an occurrence of new neurological signs lasting more than 24h in a different location to the previous event) or a worsening of the existing neurological deficit, being documented by imaging studies, new lesions or extensions of the previous ones. Any vascular, cardiac or peripheral events were also recorded.

Functional evolution was assessed using the modified Rankin scale (mRS)[14] at each consultation; a favourable prognosis was considered Rankin score of 0 to 2.

Statistical analysis

A descriptive analysis was performed on all the variables collected, with a percentage calculation for the qualitative variables and a measurement calculation of centralisation and dispersion for the numeric variables. The percentage comparison among groups was carried out using the chi-square test or the exact Fisher test, as appropriate.

The statistical analysis was performed using the SPSS 17 programme for Windows. All tests were carried out with a bilateral approach. Values of $P<.05$ were considered significant.

Results

From a total of 127 cases listed initially as idiopathic, we excluded 29: there were 12 who did not have a complete study and 17 lost after hospital discharge or during follow-up who could not be located to record recurrence or death. The study population was made up of 98 patients (50 males, 48 females), with a mean age of 39.5±5 (range, 21-45 years).

The basal characteristics of the patients are shown in table 1. The most common risk factors were smoking (33%), arterial hypertension (6%), migraine (7%), hypercholesterolemia (11%) and alcoholism (11%). In 2 cases, the CI was associated to acute alcohol intake, while no cases reported a documented history of peripheral venous thrombosis, drug consumption, repetitive abortions or previous CI.

Table 1 Demographic and imaging characteristics and evolution of patients

Variable	N=98 (%)
Age	39.5±5
Males	50 (51)
History	
Arterial hypertension	6 (6)
Migraine	7 (7)
Hypercholesterolemia	11 (11)
Alcoholism	11 (11)
Smoking	32 (33)
Imaging characteristics	
Left	46 (47)
Bilateral	8 (8)
P ACI	55 (56)
POCI	27 (28)
T ACI	12 (12)
LACI	4 (4)
Evolution	
Rankin score 0 to 2	65 (66)
R ecurrence	4 (4)
Death	1 (1)

LACI: lacunar infarction; P ACI: partial anterior circulation infarction; POCI: posterior circulation infarction; TACI: total anterior circulation infarction.

A brain CT scan was carried out in all cases; in 87 (87%), an MRI was also undertaken. A Doppler in the neck vessels was performed and the extracranial and intracranial vessels were also studied, with one of the following methods: MRA in 33 (33%), CTA in 6 (6%), digital subtraction angiography in 59 (59%) and transcranial Doppler in 59 (59%) All cases were studied with a transthoracic echocardiogram and 70 (70%) required an additional transesophageal one.

There was no rtP a administered in any case and 3 (3%) required decompressive craniectomy during the acute phase.

Imaging characteristics of cerebral infractions

The radiological characteristics of CI are shown in table 1. In 46 (47%) of cases, the affected side was the left one; in 44 (45%), the right; and in 8 (8%), it was bilateral. In 87 (88%) patients, the stroke was the only one; in 11(11%), it was multiple. The stroke location, according to the Oxfordshire classif cation, was as follows: PACI in 55 (56%) patients, POCI in 27 (28%), TACI in 12 (12%) and LACI in 4 (4%).

Evolution and recurrence

One of the patients died during the acute phase. After an average follow-up of 54 months (range from 12 to 238 months), 65 (66%) patients evolved with a mRS score of from 0 to 2. Total anterior circulation infarctions were associated with poor prognosis (P=.0001).

During the follow-up, there were 4 (4%) cases of relapse. The mean age of the recurrent cases was 33 years. In 2 cases, the recurrence presented itself 13 months into the follow-up, in 1 case at 12 months and another at 13 years. In 3 cases, the cerebral area initially affected was the vertebrobasilar (POCI) and the recurrence occurred in the same location. In the case of anterior circulation, the recurrence presented itself in the contralateral hemisphere. Evolution after recurrence was favourable in 3 cases with posterior circulation affectation and unfavourable (Rankin score of 3) in the case of anterior circulation (PACI).

The recurrence was not related in any of the cases to bad treatment adherence, which in all cases consisted of a daily average aspirin dose of 100mg. The 4 patients were once again studied with the same study protocol, concluding again with cryptogenic CI.

Discussion

Epidemiologic review of ischemic strokes suggests that, unlike CI caused by a speci f c cause, patients with cryptogenic CI are younger and have traditional vascular risk factors less frequently . In this series, cryptogenic CI represented 11% of our sample total, the average age of the cases was 39 years old and similar to other series, and the main risk factor was active smoking.[1,3,5,15,16] Our cases were studied using a protocol and prospectively , which can explain the lesser frequency of cryptogenic CI observed.[1,3,5,15-18]

In our hospital stroke register, the mean age of the cases is notable (52 years), which is explained by the epidemiological circumstances of our institution where admittance criteria of patients attended in our centre favours younger patients. Our register was started more than 20 years ago, a time where there was no MRA or CTA, which is why many of the patients were studied with an angiogram.

In the cases that we included, we eliminated premature atherosclerosis as a possible aetiology , as well as non-atherosclerotic vascular disease, potential emboligenic heart disease and the most common hypercoagulable states. However, genetic studies were not undertaken and Factor V Leiden, prothrombin gene 20210 A and MTHFR C677T mutations were therefore not determined. Previous studies have suggested that CI could have a polygenic basis, but identifying genetic susceptibility and associated risks have been hampered by the con f icting results of case-control series.[19] A meta-analysis of the genetic studies in CI showed that some genes could increase the risk of CI, although only moderately.[20]

The PFO and ASA have been identi f ed as potential risk factors, particularly in young patients with idiopathic CI. Some studies have found an association between short circuit level, foramen size orASA presence and the risk of CI. The evidence available from a systematic review and meta-analysis suggests that the relative recurrence risk is similar in young patients with idiopathic CI, with or without PFO. [21] We included patients with no cardiac abnormalities in our series and our results are similar to those described in other published studies.[12,21]

There are some situations that, although hypothetical, have to be taken into account when trying to explain the

Table 2 Cerebral stroke recurrence in different studies

Author, year	Age	No.	Monitoring	Cryptogenic	Recurrence
Sacco, 1989[1]	17-99	1,273 NM		39.9%	NM
Barinagarrementeria, 1996[15]	11-40	300	3 months to 7 years	32%	5.1%
Kittner, 1998[16]	15-44	428	3 years	34.3%	33.3%
Petty, 2000[18]	Average 31.5 years	442	5 years	36%	33.2%
Bang, 2003[3]	37-87	204	<3 months to 1 year	18%	30%
Otero, 2007[17]	18-45	93	2 years	37.6%	NM
Putaala, 2009[5]	15-49	1,008 NM		22.4%	NM
Arauz, 2010	21-45	914	12 to 238 months	11%	4%

NM: not mentioned.

cause of CI in these patients: *a*) transitory or reversible causes, and that diagnostic assessment was not able to determine the aetiology in the proper time, and *b*) that some stroke causes continue to be unknown. Among the first, we can mention: *a*) atrial fibrillation (AF) and *b*) transient and reversible cerebral vasospasm.

With regards to AF, this is frequently not diagnosed and can be intermittent in 30% of patients with CI.[22,23] However, it is clear that its prevalence increases after the age of 50 and is rare in younger people. It has been suggested that recent and excessive alcohol intake could trigger arrhythmias, considering it an independent risk factor for stroke. The most frequently associated arrhythmia in these cases is AF, not only with acute alcohol intake but with chronic alcoholism.[24] Two of our cases developed neurological symptoms relating to alcohol intake and chronic intake of alcohol was reported in the history in 11 cases. There were no arrhythmias in the acute phase or during the follow-up in any of the cases. However, the same as with other series, imaging characteristics of our cases suggested an embolic aetiology,[17,25] which emphasises the need to intentionally look for the presence of arrhythmias.

Transient cerebral vasospasm has been reported in isolated cases of migraine, vasculitis and eclampsia. Extracranial vasoconstriction can be secondary to mechanical manipulations, punctures, and catheterisation and associated to the use of ergot. In 1998, Arming et al [26] were able to document the presence of a extracranial vasospasm in a 32-year-old female with no vascular risk factors and for which a cause was not found. We had previously suspected that extracranial vasospasm could be important in migrainous CI, but this possibility has not been confirmed. In our series, 7% of cases had a history of migraine, but all studies of intracranial and extracranial vessels were normal and none fulfilled the criteria for migrainous stroke.

The possibilities of transient cerebral vasospasm and AF suggest that in young patients with CI, an early assessment of cerebral circulation is important, as well as the search for cardiac arrhythmias.

Independently or together with conventional risk factors, acute or chronic infections can hasten CI through accelerated atherosclerosis or immunological disorders. Although their direct contribution in CI risk is small, association to conventional risk factors and genetic predisposition significantly increases the risk.[27] In our series, atherosclerosis was dismissed in all cases. The determination of inflammatory or genetic markers and their contribution to a CI risk could be a reason for future research.

Previous studies suggest the theory that CI is induced by stress, where stress can hypothetically induce episodic and systemic activation of platelets and hypercoagulability; this promotes transient formation of clots and subsequent embolisation.[28] This theory has not yet been proved.

When compared to other series, the recurrence rate in ours was low. In table 2, we can see the recurrence percentage reported in different studies. The ranges vary widely, from 4% in our series to 33% in the Kittner et al [16] series, reported in 1998. The decrease in the recurrence is probably explained by the different times the cases were reviewed and by identifying new mechanisms of CI production, which are mainly haematological.

Functional long term prognosis was good in 66% of cases, which could be correlated to the low frequency of the risk factors and comorbidities, and certainly with the age of the patients.

To conclude, the vast majority of strokes of undetermined cause were unique and had a low recurrence and favourable long-term functional prognosis. Total anterior circulation infarctions were associated with poor prognosis.

Conflict of interest

The authors declare no conflict of interest.

References

1. Sacco R, Ellenberg J, Mohr J, Tatemichi T, Hier D, Price T, Wolf P. Infarcts of undetermined cause: The NINCDS Stroke Data Bank. Ann Neurol. 1989;25:382-90.
2. Barinagarrementerria F, González A, Cantú C. Estados protrombóticos e isquemia cerebral. Rev Neurol. 1998;26:85-91.
3. Bang O, Lee P, Joo S, Lee J, Joo I, Huh K. Frequency and mechanisms of stroke recurrence after cryptogenic stroke.Ann Neurol. 2003;54:227-34.
4. Waje-Andreassen U, Naess H, Thomassen L, Eide G, Vedeler C. Arterial Events after Ischemic Stroke at a Young Age: A Cross-Sectional Long-Term Follow-Up of Patients and Controls in Western Norway. Cerebrovasc Dis. 2007;24:277-82.

5. Putaala J, Metso A, Metso T, Konkola N, Kraemer Y, Haapaniemi E, et al. Analysis of 1008 consecutive patients aged 15 to 49 with first-ever ischemic stroke: The Helsinki Young Stroke Registry. Stroke. 2009;40:1195-203.
6. Rodés-Cabau J, Noël M, Marrero A, Rivest D, Mackey A, Houde C, et al. Atherosclerotic burden findings in young cryptogenic stroke patients with and without a patent foramen ovale. Stroke. 2009;40:419-425.
7. Knebel F, Masuhr F, Von Hausen W, Walde T, Dreger H, Raab V, et al. Transesophageal echocardiography in patients with cryptogenic cerebral ischemia. Cardiovascular Ultrasound. 2009;07:15-22.
8. Adams H, Bendixen B, Kappelle L, Biller J, Love B, Gordon D, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24:35-41.
9. Kizer J. Evaluation of the patient with unexplained stroke. Coron Artery Dis. 2008;19:535-40.
10. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet. 1991;337:1521-6.
11. Attaran R, Ata I, Kudithipudi V, Foster L, Sorrel V. Protocol for optimal detection and exclusion of a patent foramen ovale using transthoracic echocardiography with agitated saline microbubbles. Echocardiography. 2006;23:616-22.
12. Mas J, Zuber M. Recurrent cerebrovascular events in patients with patent foramen ovale, atrial septal aneurysm, or both and cryptogenic stroke or transient ischemic attack. French a study group on patent foramen ovale and atrial septal aneurysm. Am Heart J. 1995;130:1083-8.
13. Sacco R, Adams R, Albers G, Alberts M, Benavente O, Furie K, et al. Guidelines for Prevention of Stroke in Patients with Ischemic Stroke or Transient Ischemic Attack: A Statement for Healthcare Professionals from the American Heart Association/ American Stroke Association Council on Stroke. Circulation. 2006;113:e409-449.
14. De Haan R, Limburg M, Bossuyt P, Van der Meulen J, Aaronson N. The clinical meaning of Rankin "handicap" grades after stroke. Stroke. 1995;26:2027-30.
15. Barinagarrementeria F, Figueroa T, Huebe J, Cantú C. Cerebral infarction in people under 40 years etiologic analysis of 300 cases prospectively evaluated. Cerebrovasc Dis. 1996;6:75-9.
16. Kittner S, Stern B, Wozniak M, Buchholz D, Earley C, Feeser B, et al. Cerebral infarction in young adults. The Baltimore-Washington Cooperative Young Stroke Study. Neurology. 1998;50:890-4.
17. Otero M, Barbagelata C. Subtipos etiológicos de accidente cerebrovascular isquémico en adultos entre 18 y 45 años: Estudio de una serie de 93 pacientes. Rev Clin Esp. 2007;207:158-65.
18. Petty G, Brown R, Whisnant J, Sicks J, O'Fallon, Wiebers D. Ischemic stroke subtypes: A population-based study of functional outcome, survival, and recurrence. Stroke. 2000;31:1062-8.
19. Voetsch B, Damasceno BP, Camargo EC, Massaro A, Bacheschi LA, Scaff M, et al. Inherited thrombophilia as a risk factor for the development of ischemic stroke in young adults. Thromb Haemost. 2000;83:229-33.
20. Casas J, Hingorani A, Baustista L, Sharma P. Meta-analysis of genetic studies in ischemic stroke thirty-two genes involving approximately 18,000 cases and 58,000 controls. Arch Neurol. 2004;61:1652-61.
21. Almekhlaf MA, Wilton SB, Rabi DM, Ghali WA, Lorenzetti DK, Hill MD. Recurrent cerebral ischemia in medically treated patent foramen ovale: a meta-analysis. Neurology. 2009;73:89-97.
22. Guercini F, Acciarresi M, Agnelli G, Paciaroni M. Cryptogenic stroke: time to determine aetiology. J Thromb Haemost. 2008;6:549-54.
23. Todo K, Moriwaki H, Saito K, Naritomi H. Frequent Premature atrial contractions in stroke of undetermined etiology. Eur Neurol. 2009;61:285-8.
24. Hillbom M, Numminem H, Juvela S. Recent heavy drinking of alcohol and embolic stroke. Stroke. 1999;30:2307-12.
25. Lamy C, Giannesini C, Zuber M, Arquizan C, Meder J, Trystram D, et al. Clinical and imaging findings in cryptogenic stroke patients with and without patent foramen ovale: The PFO-ASA Study. Stroke. 2002;33:706-11.
26. Arming C, Schrattenholzer A, Lachenmayer L. Cervical carotid artery vasospasm causing cerebral ischemia. Stroke. 1998;29:1063-6.
27. Ionita C, Siddiqui A, Levy E, Hopkins L, Snyder K, Gibbons K. Acute ischemic stroke and infections. J Stroke Cerebrovasc Dis. 2010. En prensa.
28. Eggers A. A new theory of cryptogenic stroke and its relationship to patent foramen ovale; or , the puzzle of the missing extra risk. Medical Hypotheses. 2006;67:1072-5.