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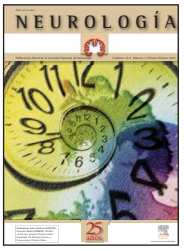

ORIGINAL ARTICLE

Hypercoagulability and ischemic stroke in young patients

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KEYWORDS
Hypercoagulability;
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Abstract
Introduction: Hypercoagulable states have been reported as an established risk factor for cerebral venous thrombosis, but they have also been proposed as a predisposing factor for cerebral ischemia of arterial origin, especially among young patients. This may have implications on therapeutic management and secondary prevention. We have studied the frequency of prothrombotic abnormalities in young patients with ischaemic stroke, as other classic risk factors are less common in this group.
Materials and methods: Observational study with sequential inclusion of patients under 55 with stroke or transient ischaemic attack (TIA) admitted to the Stroke Unit from January 2005 through December 2007. We analysed demographic data, severity and subtype of stroke, risk factors, including the presence of hypercoagulable states, and outcome.
Results: We included 100 patients, of whom 65 were men. The mean age was 42.6±8.9 years, 46% with a hypercoagulable state, and no sex differences. Acquired hyperhomocysteinemia was the most common abnormality (18%), followed by protein C or S deficiency (8%), factor V Leiden mutation (5%) and methylenetetrahydrofolate reductase (MTHFR) C677T mutation (5%). Other findings included anticardiolipin antibodies (3%), presence of lupus anticoagulant (2%), thrombocytosis (3%) and G20210A prothrombin gene mutation (3%). No association was found between these states and the presence of other vascular risk factors, or more severe stroke or worse outcomes. There was an increased presence of these abnormalities in patients who were classified as atherothrombotic stroke (p=0.04).
Conclusions: The hypercoagulable states are common in young patients with ischaemic stroke, being present in up to 46% of them.

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PALABRAS CLAVE
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Estados de hipercoagulabilidad e ictus isquémico en pacientes jóvenes

Resumen
Introducción: Los estados de hipercoagulabilidad se han estudiado como una de las posibles etiologías de la trombosis venosa cerebral y, desde hace unos años, también como factor predisponente de isquemia cerebral de origen arterial, especialmente en pacientes jóvenes. Esto podría tener implicaciones en el manejo terapéutico y la prevención secundaria, por lo que nos proponemos estudiar la frecuencia de anomalías protrombóticas en pacientes jóvenes con ictus isquémico, subgrupo en que otros factores de riesgo clásicos son menos habituales.
Material y métodos: Estudio observacional con inclusión secuencial de los pacientes menores de 55 años con infarto cerebral o ataque isquémico transitorio ingresados en la unidad de ictus desde enero de 2005 hasta diciembre de 2007. Se analizaron datos demográficos, gravedad y subtipo de ictus, factores de riesgo, incluidos los estados de hipercoagulabilidad, y evolución.
Resultados: Se incluyó a 100 pacientes, de los que 65 eran varones, con una media ± desviación estándar de edad de 42,6 ± 8,9 años. El 46%presentó estado de hipercoagulabilidad, sin diferencia por sexo. La hiperhomocisteinemia adquirida fue la alteración más frecuente (18%), seguida del déficit de proteína C o S (8%), la mutación para el factor V de Leiden (5%) y la mutación C677T del gen de la metiltetrahidrofolato reductasa (MTHFR) (5%). Otras alteraciones procoagulantes fueron síndrome antifosfolípido (3%), anticoagulante lúpico (2%), trombocitosis (3%) y mutación 20210A del gen de la protrombina (3%). No se encontró relación de estas alteraciones con otros factores de riesgo vascular, como tampoco se relacionó la hipercoagulabilidad con el ictus de mayor gravedad o peor evolución. Se observó una mayor presencia de estas alteraciones en los pacientes catalogados de ictus de origen aterotrombótico (p = 0,04).
Conclusiones: Los estados de hipercoagulabilidad son frecuentes en los pacientes menores de 55 años con ictus isquémico, encontrándose hasta en el 46%de ellos.

Introduction

Hypercoagulability states have mainly been studied in relation to cerebral venous thrombosis, where they are present in up to one third of cases.[1,2] However, although their involvement in the pathogenesis of arterial ischemia has been studied less, it has seemed increasingly clear for some years, presenting values of up to 5-10% in young people without other concomitant stroke risk factors depending on the series.[3,4] In up to one third of these patients, the stroke is classified by its origin as indeterminate or cryptogenic,[5] and the discovery of these disorders would make an aetiological orientation possible.[3] This would thus lead to the possibility of implementing appropriate secondary prevention measures.

Although there are no studies that collect population data on the frequency of individual procoagulant alterations in the same adult population, analysis in children and reviews of cases in adult series point out the high frequency of the different hypercoagulability states in relation to the development of cerebral stroke.[4,6]

We intend to conduct a descriptive study to analyse the frequency of these disorders in young patients with cerebral stroke and transient ischemic attack (TIA) admitted to a stroke unit.

Patients and methods

This was an observational study with sequential inclusion of patients admitted to the stroke unit of our neurology department between January 2005 and December 2007. We selected patients under 55 with cerebral stroke or TIA. The data were obtained from the medical records of patients and were included prospectively in a stroke database.

The parameters analysed were: *a*) demographic data such as age and gender; *b*) aetiological subtype of cerebral stroke according to the classification of the Group for Cerebrovascular Disease Study of the Spanish Neurology Society (GEECVSEN)[7] (cardioembolic, atherothrombotic, lacunar stroke or stroke with unusual cause or of undetermined origin); *c*) previous vascular risk factors: arterial hypertension (AHT), diabetes mellitus (DM), hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia); *d*) smoking; *e*) alcohol abuse; *f*) use of other drugs; *g*) previous diagnosis of migraine, defined according to the criteria of the International Headache Society;[8] and *h*) permeable foramen ovale objectified by transthoracic and/or transesophageal echocardiography.

The severity of stroke was evaluated as measured by the Canadian Stroke Scale (CSS), taking a value of 6 points as the cutoff level to differentiate between severe (CSS<6) and mild stroke. We used the modified Rankin Scale (mRS) to assess the

functional status at discharge, dichotomising values according to the degree of patient dependence (values <2 were indicative of good functional recovery and independence).

Comparative analysis was performed by classifying patients into two groups according to the presence or not of alterations in the hypercoagulability study.

During hospitalisation, the study and treatment program were administered to all patients at the stroke unit. In addition to monitoring vital signs during their stay in the unit, it included at least one brain imaging test (computed tomography and/or MRI), blood and biochemical laboratory study, chest radiograph, electrocardiogram, carotid, transcranial and vertebrobasilar system Doppler/duplex study, monitoring with transcranial Doppler to detect left-right shunt and transthoracic echocardiography (TTE) with contrast. In cases with suspected right-left short-circuit, a transesophageal echocardiogram was performed to confirm the presence of permeable foramen ovale.

Patients under 55 underwent, during hospitalisation, a complete blood study to detect genetic and acquired coagulation alterations, including the determination of the G1691 mutation of Leiden factor V, G20210A mutation of the prothrombin gene, C677T mutation of the methylenetetrahydrofolate reductase gene (MTHFR), concentrations of proteins C and S, lupus anticoagulant, anticardiolipin antibodies, resistance to activated protein C, plasma homocysteine levels and platelet counts.

Haematological findings were classified according to their degree of evidence as factors aetiologically related to stroke, into "major" alterations (with strong evidence of association) and "minor" alterations (with some evidence), based on the review proposed by Levine.[4] In turn, we differentiated subgroups depending on whether they were acquired or genetic hypercoagulability states.

The study of hypercoagulability factors was repeated after 3 months to rule out false positives due to deterioration caused by the acute phase of stroke[3]. The data included in the study were the definitive at 3 months.

Statistical analysis was carried out using SPSS 15.0 for Windows. Univariate analysis was developed with the χ^2 test or Fisher exact test for dichotomous variables. Values were considered statistically significant when $p<0.05$. The results are presented with a confidence interval (CI) of 95%.

Results

From a total of 120 patients who met the inclusion criteria (diagnosis of cerebral stroke or TIA in patients younger than 55), 20 did not undergo haematological study to detect

Table 1 Demographic data, vascular risk factors and stroke subtypes according to hypercoagulability state

Variables	Hypercoagulability (n=47)	No hypercoagulability (n=53)	P
Demographic data			
Males	32 (68.1)	33 (62.3)	0.69
Age (years)	42.2±9.9	43.1±8.17	0.64
Vascular risk factors			
Obesity	6 (12.8)	2 (3.8)	0.14
Arterial hypertension	13 (27.7)	9 (17.3)	0.22
Diabetes mellitus	3 (6.4)	3 (5.7)	1
Dyslipidemia	7 (14.9)	8 (15.1)	0.98
Prior stroke	3 (6.4)	6 (11.3)	0.5
Prior TIA	1 (2.1)	3 (5.7)	0.62
Migraine	8 (17)	10 (18.9)	0.81
Ischemic cardiopathy	1 (2.1)	3 (5.7)	0.62
Active smoker	17 (36.2)	28 (52.8)	0.1
Alcoholism	10 (21.3)	6 (11.3)	0.18
Other drugs	1 (2.1)	3 (5.7)	0.62
Type of ischemic stroke			
TIA	12 (25.5)	18 (34)	0.36
Cerebral stroke	35 (74.4)	35 (66)	1
Aetiological subtype of cerebral ischemia			
Cardioembolic	6 (12.8)	5 (9.4)	0.6
Atherothrombotic	8 (17)	2 (3.8)	0.04
Lacunar	10 (21.3)	17 (32.1)	0.23
Of unusual cause*	5 (10.6)	1 (1.9)	0.1
Of undetermined cause	6 (12.8)	10 (18.9)	0.41

TIA: transient ischemic attack.
*Strokes classified as of unusual cause before completion of the hypercoagulability study.
The data express n (%) or mean ± standard deviation.

Table 2 Hypercoagulability states by gender

Hypercoagulability states	Total (n=100)	Males (n=65)	Females (n=35)	P
A. Major, n (%)	25	15 (23.1)	10 (28.6)	0.55
A.1. Genetic, n (%)	16	9 (13.8)	7 (20)	0.42
G2120A mutation of prothrombin gene[a], n (%)	3	1 (1.5)	2 (5.7)	0.28
G1691A mutation of factor V gene[b], n (%)	5	2 (3.1)	3 (8.6)	0.34
Protein C or S deficit[c], n (%)	8	6 (9.2)	2 (5.7)	0.71
A.2. Acquired, n (%)	9	6 (9.2)	3 (8.6)	1
Antiphospholipid syndrome[d], n (%)	3	3 (4.6)	1 (2.9)	1
Lupus anticoagulant, n (%)	3	1 (1.5)	2 (5.7)	0.28
Thrombocytosis, n (%)	3	2 (3.1)	1 (2.9)	1
Polycytemia vera, n (%)	1	1 (1.5)	0	1
B. Minor, n (%)	23	17 (26.2)	5 (14.3)	0.17
B.1. Genetic, n (%)	4	4 (6.2)	0	0.3
C677T mutation of MTHFR gene, n (%)	6	5 (7.7)	1 (2.9)	0.66
Heterozygous, n (%)	2	2 (3.1)	0	0.54
Homozygous, n (%)	4	3 (4.6)	1 (2.9)	1
B. 2. Acquired, n (%)	18	13 (20)	5 (14.3)	0.48
Oral contraceptives, n (%)	2	0	2 (5.7)	0.18
Substitutive hormonal therapy, n (%)	1	0	1 (5.7)	1
Cancer[e], n (%)	1	1 (1.5)	0	1
Hyperhomocysteinemia[f], n (%)	18	15 (23.1)	3 (8.6)	0.1

MTHFR: methylenetetrahydrofolate reductase.
[a]Heterozygous in all cases, 2 patients associated homozygous for the C677T mutation of the MTHFR gene.
[b]Heterozygous in all cases. One patient associated hyperhomocysteinemia.
[c]One case associated hyperhomocysteinemia.
[d]Two cases associated lupus anticoagulant.
[e]One case associated thrombocytosis.
[f]Not associated with the C677T mutation of MTHFR.

coagulation abnormalities, so they were excluded from the analysis. This gave a total of 100 analysed patients (70 with cerebral stroke and 30 with TIA).

The characteristics of the sample of patients included in the study are listed in table 1. We did not observe significant differences in the distribution of vascular risk factors between groups with or without associated hypercoagulability status.

In 46% of patients, we found a hypercoagulability state; with a genetic basis in 20% and with an acquired basis in 27%. A combination of both forms was presented by 20%.

The distribution of the different findings in the blood cell study is detailed in table 2. The most common abnormality found was hyperhomocysteinemia, either acquired (18%) or by mutation of the MTHFR gene (5%); this was followed by a deficit of protein S or C (8%) and factor V Leiden mutation (5%).

We also observed the combination of more than one procoagulant disorder in 7% of patients. Hyperhomocysteinemia was the alteration most frequently associated with others.

We found a relationship between hypercoagulability states in general ($p = 0.04$) and stroke classified as atherothrombotic. This was not demonstrated for the presence of isolated hyperhomocysteinemia, although it has been reported that this alteration is related to the affectation of large arteries and, to a lesser extent, to lacunar stroke.[9] This does not imply differences in the characteristics of patients, who did not present greater stenosis in the Doppler study.

Following the completion of a transcranial Doppler with injection of agitated serum for the detection of a possible right-left shunt, we performed transthoracic and/or transesophageal echocardiograph studies in 51 patients with suspected patent foramen ovale (PFO). Only 20 of them showed this structural anomaly, showing no relation of hypercoagulability with the development of stroke (only 35% of patients with PFO presented alterations in the blood study, with no significant differences in the subgroup without them) ($p=0.11$).

With respect to the severity of stroke at admission, patients with hypercoagulability factors tended towards increased frequency of severe stroke (CSS <6) (14.9 versus 9.4%; $p=0.40$). There were no differences in functional outcome, which was good in both groups, according to the mRS at discharge; 90.6% of patients had no procoagulant alterations with a score <2 compared to 82.6% of those who had a hypercoagulability state ($p=0.24$).

Discussion

Hypercoagulability states in patients under 55 years with ischemic stroke are a very common finding, affecting up to

46%, that is, almost one in 2 young patients with cerebral stroke.

Hyperhomocysteinemia, with or without concomitant mutation is the most frequent abnormality, followed by Leiden factor V mutation. This seems to correspond with findings in the general population[10,11] and in other studies on patients with cerebral stroke.[3,6,12]

We found no relationship between haematological disorders and other cerebrovascular risk factors (arterial hypertension, diabetes mellitus, hypercholesterolemia) or drug consumption.

For patients whose stroke was considered as having an atherothrombotic origin, we observed a higher frequency of hypercoagulability states ($p = 0.04$) compared to other aetiological subtypes. However, this did not mean a greater frequency of extracranial or intracranial stenosis or of hyperhomocysteinemia, as indicated by previous studies.[9]

Regarding the presence of migraine, PFO and hypercoagulability states, our analysis could not demonstrate an association between prothrombotic alterations and shunt by interatrial communication in the context of stroke. Likewise, we were unable to demonstrate an increased prevalence of migraine in the group of patients with hypercoagulation, as other studies have indicated.[13]

Although recommended, the utility of blood studies in the search for procoagulant disturbances has been debated as a screening test in cerebral stroke in adults with no personal or family history of thrombosis or venous hypercoagulability states.[3,4,14-17] This is due to the low positive predictive value of these determinations.[11] Their importance in the case of aetiological study of cerebral stroke (and also of venous thrombosis) in children seems more obvious, and they are part of routine laboratory studies in this population.[6,15,18] The frequency found in our sample is higher than those described in previous works,[3,4] which could be due to the fact that our study focused exclusively on patients under 55 years or to the extensive battery of diagnostic tests for hypercoagulability states that we used. However, the identification of hypercoagulability states in this group of patients seems useful and of high diagnostic profit, as they are found in nearly one in 2 young patients with cerebral stroke.

The risk factors and aetiology of ischemic stroke in young people differ significantly from those seen in older patients. There are predisposing factors which, although they should not be unique to this age group, would have more value in it because there would generally be no concomitant risk factors. This represents a diagnostic challenge for neurologists.[5,19]

Stroke of undetermined aetiology, whose frequency varies depending on the series, can represent up to one third of the cases in young populations.[5] In such strokes, the search for prothrombotic states would have even more value, given that the blood study can represent the description of the cause of cerebral ischemia, thus leading to a diagnosis of stroke with unusual cause.[7] In our case, 6 patients, in whom a causal mechanism was not found initially through standard laboratory tests, were diagnosed with stroke of unusual aetiology after finding alterations in the blood study while seeking procoagulant alterations.

However, further studies will be required to determine the role of hypercoagulability states in the pathophysiology of cerebral ischemia, as well as the risk of recurrence, both in isolation and in relation to other factors.

Finding a potential cause in these patients represents a better therapeutic management[10,20,21] and the possibility of reducing the risk of recurrence[22,23] with secondary prevention measures. Although platelet antiaggregation is generally recommended as an effective drug treatment in the prevention of new events (Class IIa, evidence level C), there are circumstances in which oral anticoagulation is indicated in these patients (in cases with a history of deep vein thrombosis and inherited thrombophilia, Class I, evidence level A, or in those with antiphospholipid syndrome associating arterial or venous thrombosis, Class IIa, evidence level B). Other specific treatments proposed, in the case of protein S deficiency, include repeated blood transfusions (Class IIb, evidence level C).

In conclusion, up to 46% of patients younger than 55 years with acute cerebral stroke showed a hypercoagulability state. Therefore, it would be advisable to study hypercoagulability in young patients with ischemic stroke, because this state could contribute to the thrombotic process. Future studies should clarify its influence on the pathophysiology of cerebral ischemia.

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Presentation

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Conflict of interests

The authors declare no conflict of interests.

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