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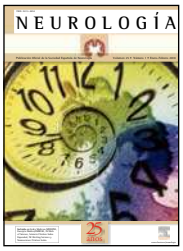

ORIGINAL ARTICLE

Do cerebral venous thrombosis risk factors influence the development of an associated venous infarction?

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KEYWORDS
Venous infarction;
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Abstract
Introduction: Cerebral venous thrombosis (CVT) is a multifactorial process with a wide clinical spectrum and many associated risk factors (RF) that could be complicated with venous infarction (VI). We study the influence of RF in the developing of venous infarction in patients with CVT.
Patients and methods: An observational study with consecutive inclusion of patients with CVT diagnosis admitted to the Stroke Unit of a Neurology Department between 1995 and 2007. RF were identified and their distribution according to the presence of VI was analysed.
Results: A total of 52 patients were included (37 female; 71.15%) with mean age of 46.73 years (range 18-78 years). The most frequent RF associated with CVT were thrombophilia (26.92%) and oral contraceptives (OC) (25% of all the patients and in 35.13% of females). The most frequent RF in patients with venous infarction was thrombophilia (40.9%), whilst in the CVT group without venous infarction the use of oral contraceptives predominated (26.7% of the total sample; 38% of females), with thrombophilic states only being detected in 16.5% No cases of venous infarction were found in the group of patients with oral contraceptives but without an associated thrombophilic state.
Conclusion: There appears to be a different profile of associated RF in patients with venous infarction associated to CVT, with the presence of thrombophilia prevailing.

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PALABRAS CLAVE
Infarto venoso;
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Trombofilia;
Anticonceptivos orales

¿Influyen los factores de riesgo de trombosis venosa cerebral en el desarrollo de infarto venoso asociado?

Resumen
Introducción: La trombosis venosa cerebral (TVC) es un proceso multifactorial con amplio espectro clínico y de factores de riesgo (FR), que puede presentar o no infarto venoso. Estudiamos los FR que influyen en el desarrollo del infarto venoso en pacientes con diagnóstico de TVC.
Pacientes y métodos: Estudio observacional con inclusión de pacientes consecutivos con diagnóstico de TVC atendidos por la Unidad de Ictus del servicio de Neurología entre los años 1995 y 2007. Se identifican los FR y se analiza su distribución en función de la presencia del infarto venoso.
Resultados: Se incluyeron 52 pacientes (37 mujeres; 71,15%) con edad media de 46,73 años (18-78 años). Los factores de riesgo de TVC más frecuentes fueron los estados de hipercoagulabilidad hereditarios (26,92%) y el uso de anticonceptivos orales (ACO) (25% del total muestral y 35,13% de las mujeres). Entre los FR identificados en pacientes con infarto venoso predominan los trastornos de hipercoagulabilidad hereditarios (40,9%) mientras que en los casos sin infarto venoso, el factor más frecuente es el uso de ACO (26,7%; 38% de las mujeres), estando presentes los estados de hipercoagulabilidad sólo en el 16,5%. No observamos ningún caso de infarto venoso con tratamiento ACO y sin estado de hipercoagulabilidad asociado.
Conclusiones: En los pacientes con infarto venoso asociado a TVC parece existir un diferente perfil de factores de riesgo asociado, predominando la presencia de estados protrombóticos hereditarios.

Introduction

Cerebral venous thrombosis (CVT) is an infrequent clinical entity (0.5% of the total number of strokes)[1] and comprises the occlusion of the flow in the cerebral venous system and its sinuses.[2,3] From a pathogenic viewpoint, venous thrombosis is considered to be a continuous process in which the balance between the prothrombotic and thrombolytic processes is disturbed, entailing, over time, the formation of a venous thrombus. This formation is due to factors related to Virchow's triad: venous stasis, alterations in vessel walls and changes in blood composition.[3,4]

Many risk factors have been identified in association with CVT as having additive effects in such a way that CVT is, in the final analysis, a multifactorial process.[5,6] In fact, the presence of more than one risk factor ha been shown in up to 44% of patients.[7] Those most frequently associated with CVT are the use of oral contraceptives and hereditary hypercoagulability states.[3] In addition, some studies have suggested that the combination of oral contraceptives and thrombophilias considerably increases the risk of CVT.[6,8-10]

Bearing in mind the wide spectrum of risk factors, the clinical heterogeneity of CVT in terms of both their presenting pattern (acute, sub-acute or chronic) and the accompanying symptoms, with or without the presence of venous infarctions, it is possible that some risk factors may be particularly involved in the development of the latter. On the other hand, there are so far no studies specifically analyzing the presence of different mutations constraining a prothrombotic state in patients with CVT when comparing patients with and without venous infarction.

The purpose of the present paper is to identify the risk factors influencing the development of venous infarctions in patients with CVT.

Patients and methods

Observational study with the inclusion of consecutive patients diagnosed as having CVT and seen by the Stroke Unit in the Neurology Department of our hospital between 1995 and 2007. The sources for identifying patients has been the Stroke Unit's database and the case histories of the patients admitted to the Neurology Department with a diagnosis of CVT.

For all patients, a note was taken of the following variables: age, gender, symptoms and the presence of the following risk factors: systemic infections or infections in nearby structures (head and neck), mechanical triggers (neurosurgery, cranioencephalic trauma and lumbar punctures performed in the month prior to the start of clinical symptoms), infections, neoplasias, haematological alterations: thrombocytosis (platelet figures in excess of 400,000/mcL), polyglobulia (haematocrit above 50%), anaemia (presence of fewer than 4.2×10^6 erythrocytes per mm^3 in males or fewer than $3.6 \times 10^6/mm^3$ in females), hereditary and acquired prothrombotic states, vasculitis, systemic inflammatory diseases, pregnancy, puerperium,

infections, consumption of medicinal or other drugs, and dehydration. The hypercoagulability study included the determination of hyperhomocysteinaemia, anti-phospholipid antibodies, deficit of protein S, deficit of protein C, resistance to activated protein C, deficit of antithrombin III, deficit of factor II, presence of factor V Leyden, mutation G20210A in prothrombin and mutation C667T in methylene tetrahydrofolate reductase (MTHFR). In some cases, no hypercoagulability study was conducted at the criterion of the physician responsible for the patient as other grounds had been identified for the CVT. Patients were considered to have anti-phospholipid syndrome when they presented positive anti-phospholipid antibodies (anticardiolipin or lupus anticoagulant), potentially also associate with a history of miscarriages. The diagnosis of venous infarction was based on the criteria of the Cerebrovascular Diseases Study Group of the Spanish Neurology Society.[11] The neuroimaging techniques used for diagnosis were computed tomography with contrast, cerebral magnetic resonance, cerebral magnetic resonance angiography or cerebral arteriography using digital subtraction depending on each case and the criterion of the physician responsible for the patient.

All the data were included in a database (Microsoft® office Excel 2003) specifically designed for this study.

Statistical analysis

First of all, the results of the descriptive analysis are presented for the series, expressing the qualitative variables as numbers and percentage and the quantitative variables as mean, median, range and mode. Subsequently, a comparative analysis is given for the presence of risk factors depending on the presence of venous infarction using the Chi-square test.

Results

Fifty-two patients diagnosed as having CVT and seen during the study period were recruited. Most of them, 37 (71.15%), were female. The mean age of the patients was 46.73 years (range 18-87 years). The sub-acute presenting form was the most frequent in 29 cases (55.77%), and cephalea the most frequent symptom in 43 cases (82.69%), followed by other symptoms (nausea, vomiting, sensory deficit, dizziness, alterations in language, involvement of non-oculomotor cranial nerves) in 36 cases (69.23%). Twenty-four cases (46.15%) presented intracranial hypertension; venous infarction was present in 22 cases (42.30%), of which 11 cases (50%) were associated with bleeding (table 1). The characteristics of the neuroimaging studies carried out and the findings in these are reflected in table 2.

Risk factors were identified in 40 cases (76.92%), of which 23 (44.23%) had two or more (fig. 1). The most frequent factor was the presence of hereditary prothrombotic states (26.92%); followed by the use of oral contraceptives, which appeared in 13 patients (25% of the total and 35.13% of the group of women and therefore the most frequent in this group) (table 3).

Table 1 Clinical characteristics of the patients

	N° (%) patients (N = 52)
Mean age	46.7 years (range: 18-87 years)
Females/ males	37 (71.1%) / 15 (28.8%)
Presentation form	
Acute	21 (40.4%)
Sub-acute	29 (55.8%)
Chronic	2 (3.8%)
Neurological manifestations	
Cephalea	43 (82.7%)
Visual alterations	7 (13.5%)
Pappiloedema	17 (32%)
Paralysis of oculomotor nerves	7 (13.5%)
Alteration in the level of consciousness	8 (15.4%)
Alteration in behaviour	5 (9.6%)
Hemiparesis	13 (25%)
Partial crises	0 (0%)
Generalized crises	14 (26.9%)
Others	36 (69.2%)
Venous infarction/ no venous infarction	22 (42.3%) / 30 (57.7%)

Table 2 Neuroimaging data

	N° (%) of patients
Neuroimaging techniques used for diagnosis	
Magnetic resonance Angio-magnetic resonance	49 (94.1%)
Arteriography	2 (3.8%)
Contrast-enhanced computed tomography	1 (1.9%)
Venous structures affected	
Superior longitudinal sinus	20 (38.4%)
Inferior longitudinal sinus	0 (0.0%)
Left transverse sinus	26 (50.0%)
Left sagittal sinus	14 (26.9%)
Left jugular sinus	6 (11.5%)
Right transverse sinus	15 (28.8%)
Right sagittal sinus	7 (13.4%)
Right jugular sinus	3 (5.7%)
Straight sinus	15 (28.8%)
Deep cerebral veins	5 (9.6%)
Cortical veins	2 (3.8%)
Others (collateral, cerebellous veins)	8 (15.3%)
Patients with involvement of several venous structures	37 (71.1%)
Cerebral infarction N=22 (42.3%)	
Left hemisphere cerebral infarction	11 (21.1%)
Right hemisphere cerebral infarction	7 (13.4%)
Bilateral cerebral infarction	2 (3.8%)
Cerebellous infarction	2 (3.8%)

Table 3 Risk factors identified in connection with cerebral venous thrombosis

Risk factor	N° (%) patients
Local infection	2 (3.8%)
Systemic infections	2 (3.8%)
Cranioencephalic trauma	2 (3.8%)
Surgery less than 1 month previously	1 (1.9%)
Pregnancy	2 (3.8%)
After miscarriage	1 (1.9%)
Previous miscarriages	2 (3.8%)
Use of oral contraceptives (total)	13 (25%)
Females	13 (35.1%)
Cancer	1 (1.9%)
Thrombocytosis	2 (3.8%)
Anaemia	5 (9.6%)
Polyglobulia	6 (11.5%)
Inflammatory bowel disease	4 (7.6%)
Vasculitis (Behçet's disease, lupus)	2 (3.8%)
Thrombosis in another location	5 (9.6%)
Drug use	1 (1.9%)
Hyperhomocysteinaemia	4 (7.6%)
Anti-phospholipid antibodies	2 (3.8%)
Hereditary hypercoagulability	14 (26.9%)
Increased factor VIII	1 (1.9%)
Deficit of S protein	2 (3.8%)
Deficit of factor II	1 (1.9%)
Factor V Leyden	2 (3.8%)
Mutation G20210A in prothrombin	4 (7.6%)
Mutation C667T in MTHFR	4 (7.6%)
Deficit of antithrombin III	0 (0.0%)

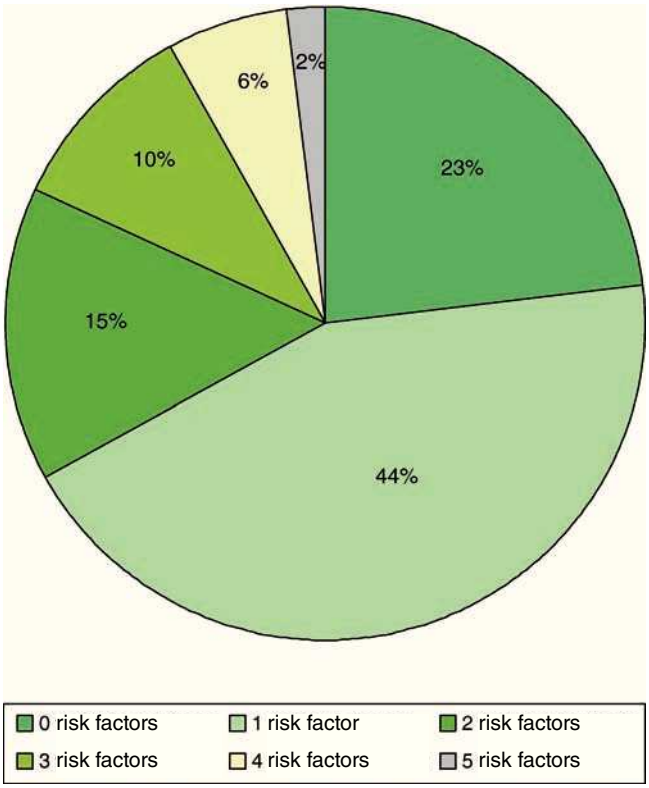

Figure 1 Distribution by number of risk factors identified.

A hypercoagulability study was carried out in 42 cases (80.77%). The most hereditary prothrombotic disorders were mutation C677T in the MTHFR gene and mutation G20210A in the prothrombin gene, present in 4 patients each. More than one mutation was detected in two cases (4.76%): a combination of factor V Leyden and mutation

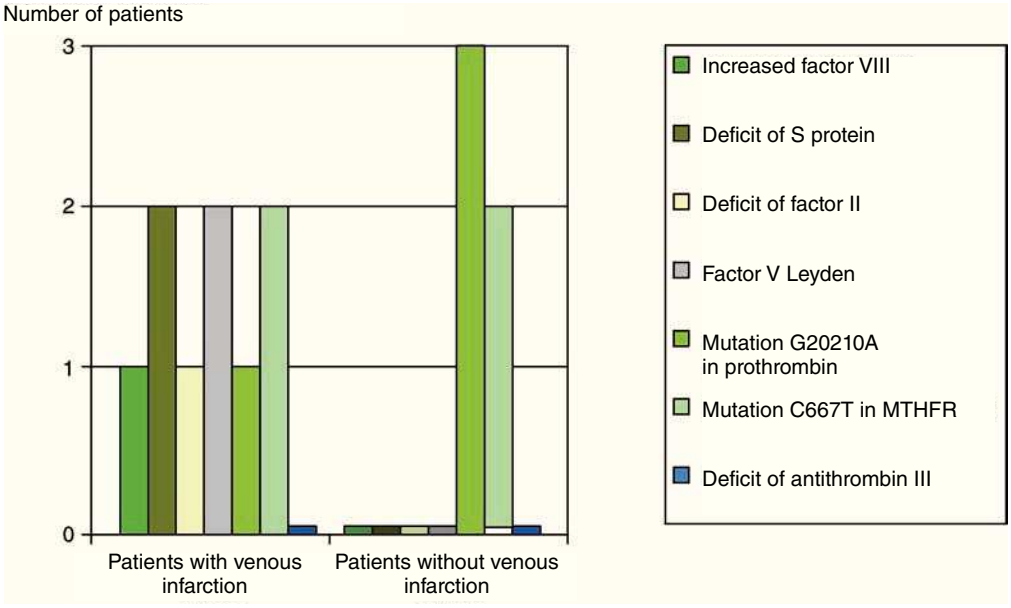

Figure 2 Distribution of prothrombotic factors according to the presence or otherwise of venous infarction.

Table 4 Risk factors identified in connection with cerebral venous thrombosis whether or not associated with venous infarction

Associated risk factor	Patients with venous infarction (N = 22)		Patients without venous infarction (N = 30)		p
	N° of patients	%	N° of patients	%	
Local infection	0	0%	2	6.7%	NS
Systemic infections	1	4.5%	1	3.3%	NS
Cranioencephalic trauma	2	9.09%	0	0%	NS
Surgery less than 1 month previously	0	0%	1	3.3%	NS
Pregnancy	0	0%	2	6.7%	NS
After miscarriage	1	4.5%	1	3.3%	NS
Previous miscarriages	1	4.5%	1	3.3%	NS
Use of oral contraceptives	5	22.7%	8	26.7%	NS
Use of oral contraceptives (females)	5	31.2%	8	38%	NS
Cancer	1	4.5%	0	0%	NS
Thrombocytosis	2	9%	0	0%	NS
Anaemia	3	13.6%	2	6.7%	p=0,056
Polyglobulia	5	22.7%	1	3.3%	NS
Inflammatory bowel disease	2	9.0%	2	6.7%	NS
Vasculitis	0	0%	2	6.7%	NS
Venous thrombosis in another location	2	9.0%	3	0.1%	NS
Drug use	0	0%	1	3.3%	NS
Hyperhomocysteinaemia	2	9.0%	2	6.7%	NS
Anti-phospholipid syndrome	1	4.5%	1	3.3%	NS
Hereditary hypercoagulability disorder	9	40.9%	5	16.7%	p=0,051
Oral contraceptives and associated hypercoagulability disorder (females)	5	31.2%	2	9.6%	p<0,05
Oral contraceptives without associated hypercoagulability disorder (females)	0	0%	6	28.5%	NS

G20210A in prothrombin, and mutation G20210A in prothrombin and C677T in MTHFR.

The combination of risk factors most frequently associated with cerebral venous thromboses involved the use of oral contraceptives together with the presence of hereditary thrombophilias (such as the presence of the factor V Leyden, mutation G20210A in prothrombin, mutation C677T in MTHFR, resistance to activated protein C and deficit of protein S), which appeared in 7 cases (13.46% with respect to the total number of patients and in 18.92% of women).

When analyzing the distribution of the risk factors in the existence or otherwise of cerebral venous infarction, we see that the most frequent factor for patients with venous infarction was the presence of hereditary prothrombotic states (40.9%), which were only present in 16.7% of patients without venous infarction; the most frequent risk factor in this group was the use of oral contraceptives (table 4).

It should be pointed out that all females with a venous infarction who were also taking oral contraceptives were associated, in addition, to a hereditary hypercoagulability disorder (5/5), versus only 2/8 cases with cerebral venous thrombosis without venous infarction ($p<0.05$).

No mutations (deficit of protein S, increase in factor VIII, deficit of factor II, presence of factor V Leyden and deficit of antithrombin III) were found in the patients who did not develop venous infarction (fig. 2).

Discussion

So far, the most complete analysis of risk factors for CVT comes from the international ISCVT study[3] which collated data on 624 patients from 89 centres in 21 countries. The most frequent was the use of oral contraceptives (54.30% in females), followed by the presence of hereditary thrombophilias (22.40%). Nonetheless, there was no specific analysis of the type of thrombophilia and there were differences in the pattern of risk factors in those patients who developed venous infarction.

Other studies analyzing the frequency of these risk factors in specific geographical areas such as the Lebanon, Brazil, Canada, Germany and Britain coincide in the importance given to hereditary prothrombotic states, with the most frequent being mutation C667T in MTHFR (33-50%), factor V Leyden (13-31%) and mutation G20210A in prothrombin (8-23%).[12-17] In Spain, there are data from a series studied in Gran Canaria showing a dominance of the G20210A mutation in prothrombin (28%).[17] Another series in Ciudad Real showed a wide variety of aetiologies, with the most frequent being the relationship with puerperium and, within this, only one patient was found to have a deficit of factor V Leyden.[18] In another study in Madrid, the most frequent risk factor found was hereditary prothrombotic disorders (20.3%) and, among these, the most frequent

were mutation G20210A in prothrombin (12.7%) and factor V Leyden (3.8%).[19] Our study confirmed the important association with hereditary thrombophilic disorders in patients with CVT (mutation C667T in MTHFR and mutation G20210A in prothrombin were the most frequent) as well as the influence of taking oral contraceptives in the female group.

The use of oral contraceptives is present in a large percentage of women with cerebral venous thrombosis (12-84%).[8,12,14,17,20] However, the association between taking oral contraceptives with hereditary prothrombotic states and the onset of CVT and venous infarction has not been specifically analyzed.

The main finding of our study is the verification of a different profile of risk factors in the cases of CVT with venous infarction; hereditary prothrombotic factors predominate, appearing in up to 40% of cases. On the other hand, even though no significant differences are seen in the percentage of women under treatment with oral contraceptives suffering from CVT with or without venous infarction, it is striking that only those cases associating the use of oral contraceptives and hereditary hypercoagulability disorders presented venous infarction. This suggests that the use of oral contraceptives might not be a sufficient factor to trigger venous infarctions in patients with CVT, but might require association with a hereditary prothrombotic factor.

Prior series have described the importance of thrombophilias and the use of oral contraceptives as factors related to CVT, but they had not specifically analyzed the presence of venous infarctions associated with these, nor the relationship between venous infarctions and risk factors[6,8-10] This is important as the presence of venous infarctions, particularly haemorrhagic infarctions, are predictors for a poor prognosis in terms of both mortality and morbidity of CVT[4,20,21] and they may entail a lower survival and the presence of greater sequelae.

Furthermore, we have observed that resistance to activated protein C, deficit of protein S, deficit of factor II and factor V Leyden only appear in patients with venous infarction, suggesting that there might be a different distribution profile for thrombophilic alterations in patients with and without venous infarction. Nonetheless, in order to be able to verify this, it would be necessary to conduct a study with a larger sample size. In addition, it would have been interesting to carry out a multi-variant study to evaluate whether there is any influence by other factors on the development of venous infarction, but this was not possible because of the small size of the series.

The tendency to a greater presence of anaemia in the group of patients with venous infarction (13.6%) than without it (6.7%) is noteworthy. Although anaemia is a known cause of cerebral venous thrombosis appearing in up to 9.2% of cases,[3] there are no data relating it specifically to the development or otherwise of venous infarction.

Although previous studies have pointed to the importance of the use of oral contraceptives as a risk factor, our study adds the observation that it is probably necessary to suffer simultaneously from prothrombotic disorders for the development of venous infarctions. To this end, it would be recommendable to conduct hypercoagulability studies in patients in whom treatment with oral contraceptives is going to be started. Studies with a larger sample size might offer more insight into a possible association between CVT in venous infarctions and hypercoagulability states, as well as the role of the use of oral contraceptives in their onset.

In conclusion, the most frequent risk factor for the development of venous infarction associated with CVT is the existence of a hereditary prothrombotic state (in up to 40% of patients). The risk of oral contraceptives seems to be determined by co-existence alongside a hypercoagulability state that would boost the prothrombotic effects.

Conflict of interest

The authors declare they have no conflict of interest.

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