Paciente joven con accidente cerebrovascular isquémico: ¿Se debe buscar una trombofilia?

Ischemic stroke in a young patient, is it needed to look for a thrombophilia?

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Abstract

Acute ischemic stroke is a pathology of great complexity due to the implications and impact on the quality of life of the affected population. The incidence of this pathology is higher in older adults and in people with cardiovascular risk factors. There is a group of young patients with no risk factors who present these events. Therefore, in clinical practice, hereditary thrombophilias tend to be frequently evaluated as the main etiological factor for this age group. However, there are few cases where a disorder of this type is documented and the presence of other etiologies such as cardioembolism and vascular disorders are more frequent. Thus, the evaluation of thrombophilia is complex due to its high cost, technical limitations when evaluating, and its uncertain clinical and therapeutic impact when documented. For this reason, this review is carried out in order to guide the clinician about the relevance of objectifying these conditions in young patient with acute ischemic stroke

Key words: Acute CVA, young patient, thrombophilia.

Resumen

El accidente cerebrovascular isquémico es un evento de gran importancia debido a las implicaciones y el impacto en la calidad de vida de la población afectada. Su incidencia es más alta en adultos mayores y en personas con factores de riesgo cardiovascular. Existe un grupo de pacientes jóvenes (18-

44 años) sin factores de riesgo que presentan dicho evento, por lo que, en la práctica clínica, se tiende a evaluar rutinariamente las trombofilias hereditarias y adquiridas como factor etiológico principal para los eventos isquémicos en este grupo etario. No obstante, son pocos los casos donde se documenta algún trastorno de este tipo, ya que es más frecuente la presencia de otras etiologías como el cardioembolismo y trastornos vasculares. La evaluación de las trombofilias es compleja, dado el alto costo, las limitaciones técnicas para hacerlo y el impacto clínico y terapéutico incierto al documentarse estos estados. Se realiza esta revisión de tema con el fin de orientar al clínico acerca de la pertinencia de objetivar estas condiciones en el paciente joven con accidente cerebrovascular isquémico.

Palabras clave: ACV agudo, paciente joven, trombofilia.

Introduction

Ischemic stroke accounts for about 87% of all cerebrovascular events (1). Worldwide, more than 11 million ischemic strokes occur each year and most occur in low- and middle-income countries. Genetic, social, cultural, and technological factors, as well as the opportunity to access the health care system, determine its level of impact (2). Hospitalizations for this condition have increased significantly for both men and women and, strikingly, with ages between 18-54 years (3). For this group, different etiologies have been described, including the use of illicit drugs and a greater presence of cardiovascular risk factors (4). However, finding the etiology in the young patient without cardiovascular risk factors remains a clinical challenge.

In the clinical setting, the study of thrombophilias or procoagulant states as causal agents of the ischemic event is frequent. However, they only explain between 1% and 4% of CVA in this age group (5) and little is known about how to evaluate these alterations or the existence of diagnostic algorithms that help in the routine study of these states. For this reason, we conducted this review on the relationship of probable thrombophilia in young patients with ischemic CVA.

«Descriptive studies and case reports or articles that did not have the full text available or were not related to the objective of this review were excluded.»

Methodology

The following databases were considered for this review: PubMed, Google Scholar and SciELO, without language restriction and establishing a time range from 1990 to current date. The keywords used were Acute ischemic stroke, young patient, thrombophilia, which were combined with the Boolean term "AND". A total of 35 articles were selected from the mentioned search, including systematic reviews, case-control studies and clinical trials that included in their main title or abstract the previously mentioned keywords. Descriptive studies and case reports or articles that did not have the full text available or were not related to the objective of this review were excluded.

Definition and etiology

CVA in a young patient is defined as a person between 18 and 44 years of age who suffers an acute ischemic event (6,7). For this group of patients, the etiology tends to be determined based on the classification of the TOAST (Trial of Org 10172 in Acute Stroke Treatment) multicenter study (Table 1).

Table 1. Causes of stroke. Adapted from TOAST classification (6).

Causes of stroke				
1. Large-artery atherosclerosis	2. Cardioembolism	3. Small-vessel occlusion (lacune)	4. Stroke of other determined etiology: 4a. Hypercoagulable states 4b. Hematologic disorders 4c. Nonatherosclerotic vasculopathies	5. Stroke of undetermined etiology: 5a. Two or more causes identified 5b. Negative evaluation 5c. Incomplete evaluation

Cardioembolic origin is the main cause, since it represents between 20% and 35% of cases, followed by non-atherosclerotic vascular disorders (dissection of extracranial arteries) with 6% to 25% (8). Regarding hypercoagulable states, only 1 to 4 % have been documented as the causal agent (5), although this may vary depending on the population under study. Kittner et al. report 5 to 10 % of CVA associated with a thrombophilic state, while Tapia et al. report between 8 and 15 % (9,10).

Epidemiology

Incidence and prevalence data in young patients with ischemic CVA are limited. It has been established that the incidence of ischemic CVA increases exponentially with age, the most important nonmodifiable risk factor for all types of strokes. Studies show that 75-89% of strokes occur in those over 65 years of age. Of these, 50% occur in people over 70 years of age and almost 25% occur in individuals over 85 years of age. Meanwhile, the prevalence is low in young and middle-aged adults with reports of 2.4 per 100,000 for persons between 20 and 24 years of age and 20 per 100,000 for persons between 35 and 44 years of age (8). Regarding prevalence, a retrospective cross-sectional study in Brazil found that thrombophilia tests were positive in 13.7% of patients between 18 and 45 years of age, although thrombophilia was determined to be the causative mechanism in only 3.7% of patients (12).

In Colombia, a precise registry has not yet been documented, probably due to underreporting or limitations to identify and study a specific etiology. A cross-sectional descriptive study carried out in Bogotá found that, although the most common etiology in this study population corresponded to "undetermined cause", 3.2 % was associated with antiphospholipid antibody syndrome (7).

Is it necessary to look for thrombophilia in young patients with CVA?

It is recommended to initiate the study of a possible thrombophilia in a patient under 50 years of age with an arterial thrombotic event, in the absence of cardiovascular risk factors and especially in those with a history of venous thromboembolism and in whom the predisposing factors are not well known as the cause of the event (13,14). Within the anamnesis it is important to ask for a family history of thrombophilia or autoimmune diseases (15).

On the other hand, some centers do not perform thrombophilia tests, because only 40% have at least one positive thrombophilia test and only 1% to 8% of them have a modification or change in clinical behavior, in addition to the high costs of measuring a certain thrombophilia (16.17). A retrospective study conducted in two European centers to determine the different etiologies of ischemic CVA concludes that the role of immunological screening in young patients is questionable, except for testing for antiphospholipid syndrome, which should be performed in case of high cli-

nical suspicion given its high association with recurrent arterial or venous thrombosis, transient cerebral ischemia, and probably ischemic stroke (18). Currently, screening tests for thrombophilia are not recommended as a first measure in these patients, given the limitations in measurement and the limited impact on therapeutic behaviors when documenting them (19).

What type of thrombophilia should be looked for in a young patient with CVA, if there is suspicion?

The case of a young patient with an ischemic event can be catastrophic from the functional point of view, so for the clinician, the search for a triggering factor will be the challenge to optimize management and perhaps prevent future events, weighing the therapeutic impact or modifications in subsequent behaviors. In this regard, some prothrombotic conditions, such as hematologic and non-hematologic neoplasms, paroxysmal nocturnal hemoglobinuria, nephrotic syndrome, inflammatory bowel disease and autoimmune diseases, should be taken into account. These conditions should be sought since rarely is a thrombophilia the primary etiologic factor. Subsequently, if a triggering factor has not been identified, the main thrombophilias to be studied are hyperhomocysteinemia and antiphospholipid syndrome (13,20).

Homocysteinemia is derived from elevated homocysteine concentrations, which are aggressive to the arterial endothelium and have been associated with increased atherosclerosis, mainly in the coronary and carotid territory (21,22). A Chinese meta-analysis concludes that high homocysteine levels may be related to most of the etiological causes of the TOAST classification of ischemic CVA (23).

Antiphospholipid syndrome (APS) is recognized as a syndrome that predisposes to present thrombotic events both venous and arterial (26). Approximately 17% of ischemic CVA may be associated with this condition (27). Lupus anticoagulant positivity has been associated with a 5- to 16-fold increased risk for the development of arterial thrombotic events, compared with the presence of anticardiolipin antibodies (28).

Other thrombophilias commonly sought in these patients are deficien-

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cies of natural anticoagulants, such as protein C and S deficiency and the G20210A mutation of the prothrombin gene. However, their low prevalence has limited a significant relationship with ischemic CVA to be established (33,34). Similarly, the direct association of antithrombin deficiency with arterial thrombosis remains controversial, and Factor V of Leyden (FVL) gives the strongest association with venous thrombotic events (32,35).

If there is suspicion, at what point should these alterations be measured?

Several factors can alter the interpretation of some thrombophilia tests and thus favor errors in diagnosis and management of young patients with CVA. For hyperhomocysteinemia, the technique for its collection should be considered. Plasma should be rapidly separated by centrifugation and the samples should be kept cold, with optimal protection from light. It is recommended to obtain vitamin B12 levels, since low levels have been correlated with hyperhomocysteinemia (36).

As for the SAFL, a new measurement of the profile should be performed at 12 weeks to confirm this condition. Hereditary or acquired thrombophilias should be evaluated at least 3 months after the thrombotic event, and these tests should be avoided if the patient is anticoagulated, either with coumarins or heparins, being evaluated at least two days after the suspension of heparins and 15 days after the suspension of coumarins (13).

Secondary prevention of thrombotic event: Should anticoagulation be initiated?

The only condition in which an impact has been demonstrated is antiphospholipid syndrome, with warfarin being the anticoagulant of choice and aiming to obtain INR levels between 3 and 4 as monotherapy (37,38). In contrast, direct anticoagulants have failed to demonstrate benefit, since there is no decrease in the occurrence of thrombotic events, and they have been associated with a higher risk of bleeding (38). Currently, there is no determined or established time for anticoagulation, so long-term or definitive anticoagulation therapy is considered (39, 40). Anticoagulation should be initiated according to the patient's profile and severity of the event as assessed by the NIHSS scale.

Conclusion

The young patient with ischemic CVA and no cardiovascular risk factors remains a challenge in clinical practice. The usual etiological approach in the hospital setting should be guided by the search for thrombophilias, despite

the low percentage of association with ischemic CVA. Therefore, the search for other more common etiologies should be considered. The routine search for thrombophilia as an etiologic factor in this group is uncertain and has little impact on patient prognosis. Antiphospholipid syndrome and hyperhomocysteinemia could be primarily evaluated, with the previously mentioned considerations, as the most common etiologies in this age group.

Conflict of interest:

The authors declare that they have no conflicts of interest.

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