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Artículo original

Primary thrombophilia in México VIII: Description of five kindreds of familial sticky platelet syndrome phenotype

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RESUMEN

Antecedentes: el síndrome de las plaquetas pegajosas es la segunda trombofilia identificada en México, sólo superada por la mutación 677 C- >T en el gen 5,10 –metien-tetrahidrofolato-reductasa. Aproximadamente el 50% de los mestizos mexicanos con un marcador clínico de trombofilia hereditaria tienen el fenotipo del síndrome de las plaquetas pegajosas, frecuentemente asociado con otras trombofilias
Objetivo: presentar cinco casos de pacientes con fenotipo de las plaquetas pegajosas en varios miembros de dos generaciones.
Material y métodos: se estudiaron los *propositii* porque tuvieron marcadores clínicos de un estado trombofílico primario y, además, habían padecido un episodio vaso-oclusivo.
Resultados: el fenotipo MSF se estudió prospectivamente en dos generaciones en estos cinco *propositii*, en algunos casos asociados con otras enfermedades proclives a la trombosis.
Conclusiones: los estudios de la familia sugieren que el síndrome de las plaquetas pegajosas puede tener un origen genético y heredarse como un rasgo autosómico dominante.
Palabras clave: síndrome de plaquetas pegajosas, trombofilia, México, hereditaria.

ABSTRACT

Background: The sticky platelet syndrome (SPS) phenotype is the second most frequent thrombophilic condition identified in Mexican mestizos with a clinical marker of thrombophilia, only surpassed by the 677 C->T mutation in the 5,10-methylen-tetrahydrofolate-reductase gene; approximately 50% of Mexican mestizo patients with a clinical maker of thrombophilia display the SPS phenotype, frequently associated with other thrombophilic conditions.
Objective: To present five kindreds of persons in whom the SPS phenotype presented in several family members.
Material and methods: The kindreds were studied because proposition in each one had clinical markers of thrombophilia and had suffered a vaso-occlusive episode.
Results: The SPS phenotype was prospectively found in two generations in these five kindreds, in some instances associated with other thrombosis-prone conditions.
Key words: Thrombophilia, platelets, aggregation, sticky platelet syndrome, familial.

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The sticky platelet syndrome (SPS) was first described in 1983;[1] however, not until later did its prevalence receive significant recognition in the medical literature.[2-26] The SPS seems to be a rather common cause of arterial and venous thrombosis[2-6] since it accounts for about 20% of otherwise unexplained arterial events and 13% of unexplained venous events.[2-8] Three forms of the SPS have been identified: Type I is marked by platelet hyperaggregability with adenosin-diphosphate (ADP) and epinephrine, whereas type II evidences hyperaggregability only with epinephrine and type III only with ADP.[3-6] The platelet abnormality seems to be con-

genital and the precise nature of the defect is at present not known.[4] The congenital nature of the SPS has been suggested previously.[2-5] We describe herein five kindreds of persons in which the SPS was shown to be present in several family members. These observations may further support the genetic nature of the condition.

a) Description of the kindreds:

1) Kindred one: The *propositus* was a 56 year old male who was studied as a result of a cerebrovascular episode. A full laboratory workup for thrombophilia was conducted including the investigation of the SPS phenotype, the activated protein C resistance (aPCR) phenotype, coagulation protein C activity and antigen, coagulation protein S, antithrombin III, plasminogen, tissue-type plasminogen activator activity, plasminogen activator inhibitor activity, plasminogen activator inhibitor type 1, IgG and IgM isotypes of antiphospholipid antibodies, lupus anticoagulants, homocysteine levels, the factor V gene Leiden, Cambridge, Hong Kong, and Liverpool mutations, the 677 C-->T mutation in the 5,10-methylenetetrahydrofolatereductase (MTHFR), the G20210A polymorphism in the 3'-untranslated region of the prothrombin gene and the investigation of the V617F *JAK2* gene mutation (26-27, 34). The screening disclosed type I SPS, heterozygous G20210A mutation in the 3´-untranslated region of the factor II gene, homozygous 677 C->T mutation in the MTHFR gene, lupus anticoagulant and both IgG and IgM anti-phospholipid antibodies. The SPS was also shown in three relatives in two generations of the kindred, whereas the MTHFR gene mutation was present in other family members (see figure). Treatment with aspirin failed to revert the platelet hyperaggregability and accordingly the patient was switched to anagrelide; he was also given folic acid and oral rivaroxaban and has remained thrombii-free for 24 months months.

2) Kindred two: The *propositus* was a 22 year old female who was studied as a result of a pulmonary thromboembolism which presented while receiving oral contraceptives. The full laboratory workup for thrombophilia[26,27,34] disclosed type III sticky platelet syndrome, which was also shown in four members of two generations of the kindred (see figure). Treatment with aspirin resulted in disappearance of the platelet hyperaggegability.

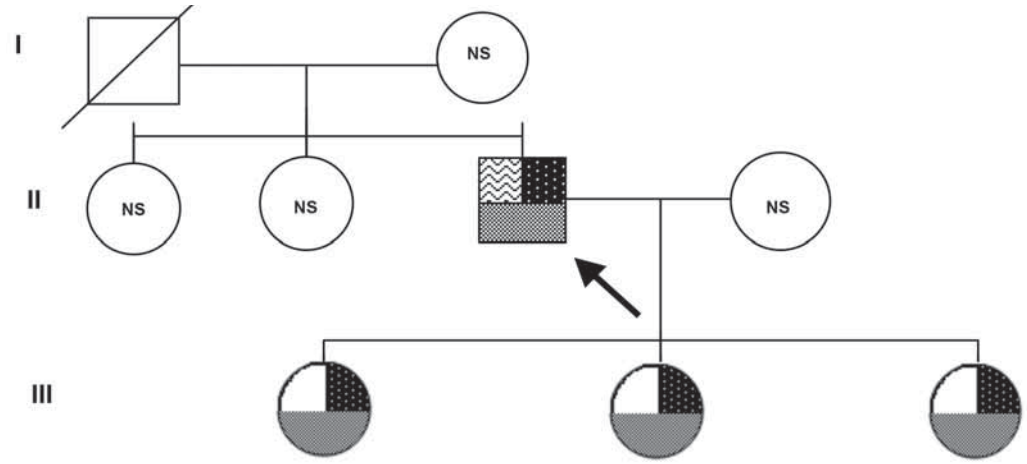
3) Kindred three: The *propositus* was a 24-year old female who was studied as a result of a ileofemoral thrombophlebitis and pulmonary embolism. The full laboratory workup for thrombophilia[26,27,34] disclosed type II sticky platelet syndrome, which was also found in a female sibling. Heterozygous beta thalasemia was also identified in the propositus, one sibling and the father (see figure). Treatment with aspirin reverted the platelet hyperaggegability.

4) Kindred four: The propositus was a 31 year old female who was studied as a result of an ileofemoral thrombophlebitis and pulmonary embolism. The full laboratory workup for thrombophilia (26-27, 34) disclosed type III sticky platelet syndrome and heterozygous 677 C->T mutation in the MTHFR gene, which was also shown in two siblings (see figure): the patient was given aspirin and folic acid supplements.

5) Kindred five: The *propositus* was a 56-year old male who was studied as a result of a cerebrovascular episode. The full laboratory workup for thrombophilia[26,27,34] disclosed type I sticky platelet syndrome and heterozygous 677 C->T mutation in the MTHFR gene. The SPS was identified in thre family members of two generations, whereas the MTHFR mutation was also shown in other family members (see figure). The patient was treated with aspirin and folic acid and has remained free of thrombi.

b) Assessment of the sticky platelet syndrome phenotype: The method described by Mammen et al[2,4] was used: Blood was drawn, usually between 8:30 and 10:30 am, by clean venipuncture using no. 19 or no. 21 butterfly needles. After venipuncture the tourniquet is released. The first 5 mL is discarded. Then 18 mL of blood is aspirated into a 20 mL syringe containing 2 mL of 3.8% sodium citrate solution. The anticoagulated blood is centrifuged as soon as possible for 10 min at 100 g at room

KINDRED 1



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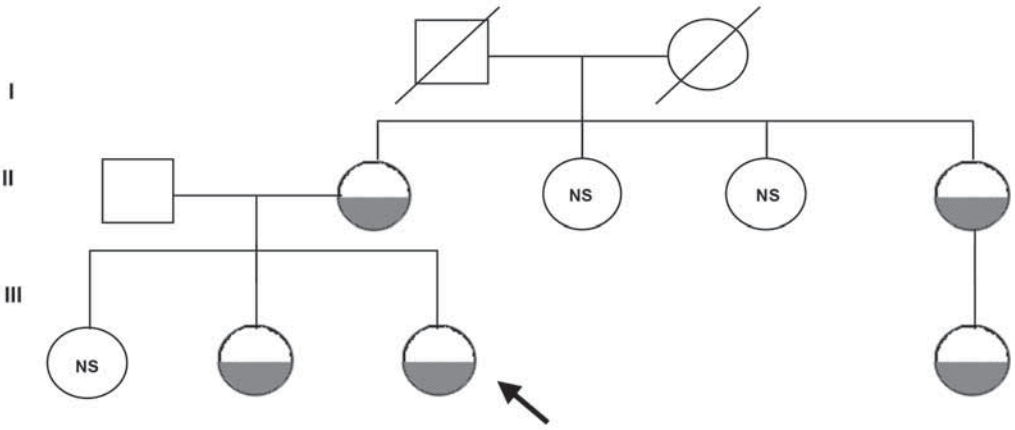

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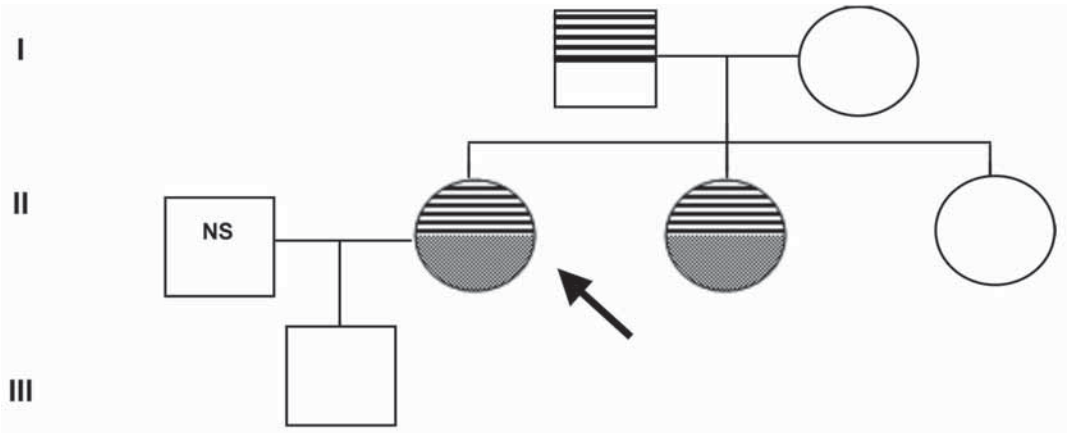

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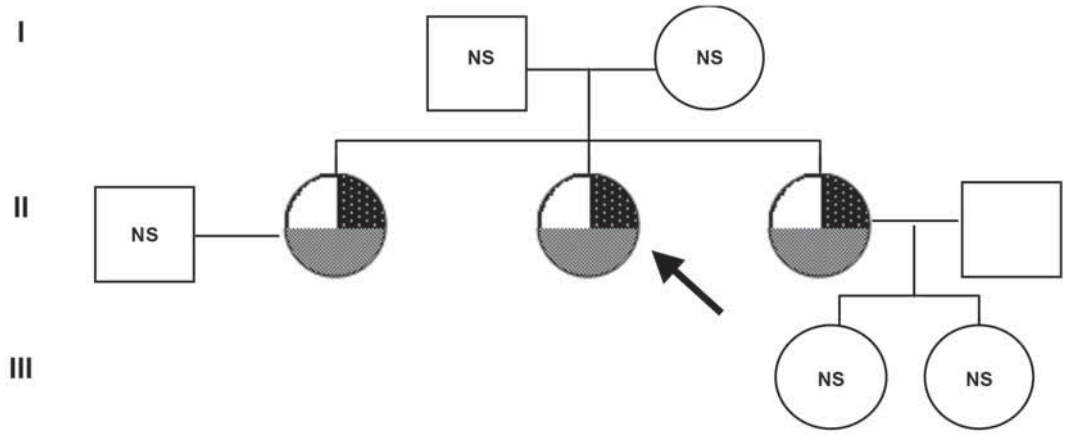

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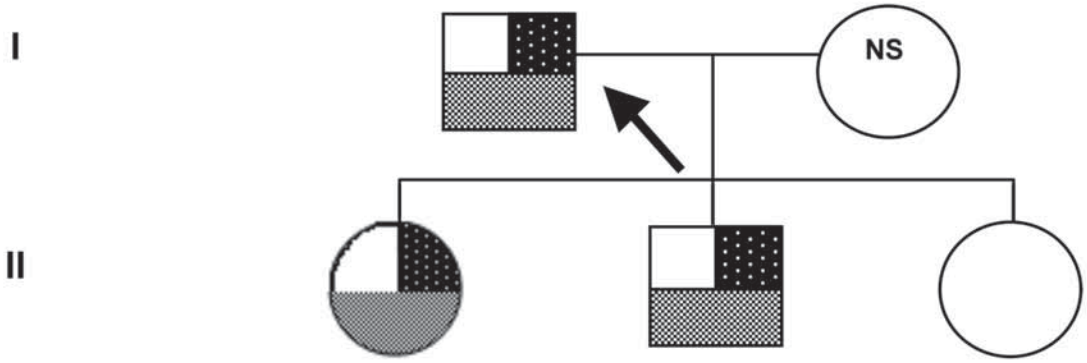

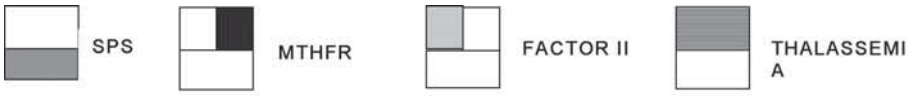

NS = not studied. SPS = Sticky platelet syndrome phenotype. MTHFR = 677 C-->T mutation in the 5,10-methylenetetrahydrofolatereductase gene; factor II = G20210A mutation in the 3'-untranslated region of the prothrombin gene; thalassemia = heterozygous beta thalassemia. Arrow denotes the *propositus.*

temperature to obtain platelet-rich plasma (PRP). About one-half of this PRP is recentrifuged at 2 000 g for 20 min at room temperature to obtain platelet-poor plasma (PPP). For aggregation the PRP is diluted with the PPP to give a platelet count of 200 x 10^9/L. Platelet aggregation is measured in an aggregometer (ChronoLog Corporation, Havertown, PA, U.S.A.), employing the technique originally described by Born and Cross.[29] Changes in optical density were recorded on a Chrono Log recorder (model 703). While keeping temperature (37ºC) and stirrer speed constant, aggregation is induced by three concentrations of ADP (2.34, 1.17, and 0.58 u*M*), and by three concentration of epinephrine (11, 1.1, and 0.55 u*M*), (final concentration in the PRP cuvette). Maximal aggregation was expressed as percentage of 100% light transmission, calibrated for each specimen. Normal control were studied for each case. Abnormal results for platelet aggregation with three concentrations of ADP (2.34, 1.17, and 0.58 u*M*) were found to be above 55, 36 and 12%, whereas for the three concentrations of epinephrine (11, 1.1, and 0.55 u*M*) were above 80, 27 and 20%.

DISCUSSION

There is clinical and experimental evidence that changes in the hemostasis system can lead to a hypercoagulable or thrombogenic state in the circulation that can foster thrombus formation. In the last years, we have been interested in analyzing the changes in the hemostatic system of Mexican Mestizos, which can result in thrombophilia, and accordingly, we have found different abnormalcies in the natural anti-thrombotic mechanisms. [6,26-27,31-34] In these studies, it has been clear that the SPS phenotype is the second most frequent thrombophilic condition identified in Mexican mestizos with a clinical marker of thrombophilia,[6, 26-27] only surpassed by the 677 C->T mutation in the MTHFR, which may not be by itself a fully recognized thrombophiic condition; probably when associated with other thrombosis-prone conditions. [26,27] In México, we [6, 26-27] and others[25] have found that approximately 50% of Mexican mestizo patients with a clinical maker of thrombophilia display the SPS phenotype. Most patients with the SPS display other thrombosis-prone conditions, but there are also instances of the SPS identified as the single thrombophilia marker;[6,26,27] accordingly, it is possible that this platelet abnormality may contribute to the so-called "multifactorial thrombophilia".[26]

The platelet abnormality in the SPS seems to be congenital but the nature of the defect is at present unknown;[4] it is supposed that glycoprotein receptors on the platelet surface membrane may be involved, its abnormality leading into platelet hyperfunction.[7,8] The genetic nature of the SPS has been suggested but not proven; an autosomal dominant inheritance has been proposed.[2-5] The data which we present here in these five kindreds support a genetic origin of the condition inherited probably as an autosomal dominant trait, since the platelet hyperaggregability identified in the five *propositii* was also shown to be present in other family members belonging to at least two generations. Studies to define the precise origin of the SPS are in progress: The glycoprotein (GP) IIIa $PL^{A1/A2}$ polymorphism[7] and the growth arrest-specific gene 6 (Gas6; Gas6 c. 834 + 7G > A) polymorphisms[8] have been studied. We have found that the glycoprotein IIIa $PL^{A1/A2}$ polymorphism may result in the SPS phenotype;[35] interestingly, these two kindreds of persons with the SPS phenotype did not display mutations in the GPIIa $PL^{A1/A1}$ gene.

In summary, we have presented five kindreds of persons displaying the SPS phenotype; they were studied because the *propositii* in each kindred had clinical markers of thrombophilia, in two cases associated with other thrombosis-prone conditions but not in the other one. These family studies suggest that the SPS phenotype may have a genetic origin; additional studies are needed to clarify the true nature of this entity.

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