Genetic origin of the sticky platelet syndrome.

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Abstract
The sticky platelet syndrome (SPS) is a prothrombotic platelet disorder, associated with increased platelet aggregability with both adenosine diphosphate (ADP) and epinephrine (EPI). Type I of the disorder is the most common phenotype in Mexican mestizos and SPS is even reported to be the second most common hereditary thrombophilic state in this particular population. It accounts for 48% of all thrombophilic disorders diagnosed in patients with unprovoked thromboembolic events. SPS is detected in patients with arterial and venous thrombotic episodes, and these can even be present concomitantly in one person or his/her relatives. The syndrome contributes more often to arterial than to venous thrombosis (21% of unexplained arterial thrombotic events vs 13% of otherwise unexplained venous thromboembolic episodes). SPS is also the most frequent thrombophilia contributing to arterial thrombotic events and possibly the leading cause of thrombosis in the atypical parts of the circulation. Several families with SPS have been described; the affected members of one family may not express the same SPS type and there are even the cases of the negativity of their family history. Various mutations of one or more genes contribute to similar SPS phenotype. Additionally, platelets of the patients with atherosclerosis, autoimmune and renal diseases showed hyperaggregability after the addition of EPI or other agonists, pointing to the possible acquired forms of SPS. Moreover, the diagnosis of SPS is based on clinical manifestation and laboratory parameters, not on the results of genetic analysis. Therefore, currently we cannot state that SPS is inherited exactly in autosomal dominant trait, as it was originally proposed.

KEYWORDS: platelet aggregation; membrane glycoprotein; sticky platelet syndrome; single nucleotide polymorphism; mutation

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El origen genético del síndrome de plaquetas pegajosas

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Resumen
El síndrome de plaquetas pegajosas es una enfermedad protrombótica plaquetaria, asociada con agregabilidad plaquetaria aumentada, en respuesta

BACKGROUND

The sticky platelet syndrome (SPS) is a prothrombotic platelet disorder, associated with increased platelet aggregability with both adenosine diphosphate (ADP) and epinephrine (EPI) (type I), only EPI (type II), or only ADP (type III). The type I of the disorder is the most common phenotype in Mexican mestizos and SPS is even reported to be the second most common hereditary thrombophilic state in this particular population. It accounts for 48% of all thrombophilic disorders diagnosed in patients with unprovoked thromboembolic events. And these can even be present concomitantly in one person or his/her relatives. The syndrome contributes more often to arterial than to venous thrombosis (21% of unexplained arterial thrombotic events vs 13.2% of otherwise unexplained venous thromboembolic episodes). SPS is also the most frequent thrombophilia contributing to arterial thrombotic events and possibly the leading cause of thrombosis in the atypical parts of the circulation.

We read with a great interest the articles of the authors Ruiz-Argüelles et al. and were pleased to see the increasing amount of data regarding the characteristics of SPS. The results of the com-

a adenosín difosfato (ADP) y epinefrina. El tipo I de la enfermedad es el fenotipo más común en mestizos mexicanos y el síndrome de plaquetas pegajosas incluso se reporta como la segunda causa más común de trombophilia hereditaria en esta población en particular. Constituye 48% de todas las enfermedades trombofilicas diagnosticadas en pacientes con eventos tromboembólicos sin causa aparente. El síndrome de plaquetas pegajosas se detecta en pacientes con episodios trombóticos venosos y arteriales y éstos incluso pueden manifestarse de manera concomitante en una persona o sus familiares. El síndrome contribuye más a una trombosis arterial que a una trombosis venosa (21% de los eventos de trombosis arterial sin causa aparente versus 13% de episodios tromboembólicos venosos sin causa aparente). El síndrome de plaquetas pegajosas es también la causa más frecuente de trombofilía que contribuye a eventos trombóticos arteriales y la primera causa de trombosis en sitios inusuales. Se han descrito muchas familias que padecen el síndrome de plaquetas pegajosas, los miembros afectados de una familia podrían no expresar el mismo tipo de la enfermedad e incluso se han descrito casos de negatividad de la enfermedad en la historia familiar. Varias mutaciones de uno o mas genes contribuyen a un fenotipo similar del síndrome de plaquetas pegajosas. Además, los pacientes con aterosclerosis, enfermedades autoinmunitarias y renales muestran hiperagregabilidad plaquetaria después de la administración de epinefrina u otros agonistas, lo que apunta a la posibilidad de una forma adquirida del síndrome de plaquetas pegajosas. El diagnóstico de este síndrome se basa en las manifestaciones clínicas y parámetros de laboratorio y no en los resultados de estudios genéticos. Por ello actualmente no puede afirmarse que el síndrome de plaquetas pegajosas es una enfermedad hereditaria autosómica dominante, como se había propuesto en un principio.

PALABRAS CLAVE: agregación plaquetaria, glucoproteína de membrana; síndrome de plaquetas pegajosas, polimorfismos de nucleotido único, mutación.
Comprensive prospective study of these experts confirm the coexistence of two or more thrombophilic states in one patient without any mutual association. Therefore, it is proposed that primary thrombophilia is potentially a multifactorial disorder.\textsuperscript{5,9} Mutations of membrane glycoproteins have been discussed as the cause of the syndrome.\textsuperscript{1,3,7}

Platelet aggregation is initiated by the binding of fibrinogen or von Willebrand factor to the activated platelet glycoprotein IIb/IIIa (GP IIb/IIia).\textsuperscript{10} PI(A2) variant of PL(A1/A2) polymorphism causes a decreased threshold for platelet activation.\textsuperscript{7,10} Therefore, platelets heterozygous for PI(A) allele showed increased sensitivity to acetylsalicylic acid and GP IIb/IIIa antagonist abciximab, indicating to the thrombogenic potential of the mutation and higher risk for cardiovascular diseases.\textsuperscript{10,11} However, later it was confirmed that GP IIIa PL(A1/A2) polymorphism is not associated with the development of thrombotic complications in patients with SPS.\textsuperscript{12,13}

Growth arrest-specific gene 6 (Gas6) encodes Gas6 protein, stored in \(\alpha\)-granules. It represents a member of the family of vitamin K-dependent proteins, structurally highly homologous with protein S. Gas6 is involved in the platelet activation by modulating the function of alpha2-adrenergic and ADP receptors, and activating of endothelial and vascular smooth muscle cells.\textsuperscript{3} The A allele of the GAS6 c.834 + 7AA polymorphism, more highlighted in the concomitant presence of CACA haplotype is less frequent in individuals with stroke, proposing a protective function of this particular haplotype for stroke.\textsuperscript{14} Anyway, single nucleotide polymorphism (SNP) rs9550270 of GAS6 gene is more frequent in SPS patients with previous pregnancy loss. Higher risk for abortion was proved in carriers of the rs7400002 polymorphism of GAS6 gene.\textsuperscript{15}

Glycoprotein VI (GPVI) is a platelet membrane glycoprotein acting as a physiological receptor for collagen. Interaction of platelets with collagen mediated by this receptor leads to the platelet activation, subsequent adhesion and platelet aggregation on a collagen surface.\textsuperscript{1,16} The increased frequency of major haplotype TTGTGA and two minor haplotypes CGATAA and TTGTGG of GP6 gene in 77 individuals with SPS manifested by ischemic stroke was detected. The allele G of SNP rs12610286 and major haplotype TTGTGA were significantly increased in patients with SPS type I and stroke.\textsuperscript{17}

The significantly increased occurrence of SNPs 1613662 and 1654419 in SPS patients with history of VTE was noticed. In comparison with the control group, polymorphisms rs1671153 and rs1654419 were significantly more common in SPS type II.\textsuperscript{18}

SNPs 1671153, 1613662 and 1654419 were more frequent in patients with SPS and pregnancy loss. Significantly increased presence of CTGAG in haplotype 5 and CGATAG in haplotype 6 in women in this patient population was confirmed.\textsuperscript{19} Last but not least, an increased frequency of SNPs rs1671152, rs1654433 and rs1671215 in women with platelet hyperaggregability and experience of miscarriage was recently revealed. Significantly higher prevalence of haplotypes ACGG and CCGT was simultaneously detected.\textsuperscript{20}

Platelet endothelial aggregation receptor-1 (PEAR1) is a transmembrane protein of the epidermal growth factor–like domain protein group, considered to be a receptor for contact between the platelets.\textsuperscript{21} The study of 23 patients with SPS and spontaneous abortion confirmed increased prevalence between SNPs rs12566888 and rs12041331 of PEAR1 gene and platelet aggregability. On the contrary, the T allele of PEAR1 c. -9-4663G>T polymorphism seems to have a protective role for fetal loss.\textsuperscript{15}
In relation to platelet aggregation, further loci have been studied (glycoprotein Ia/IIa and Ib/V/IX, alpha2-adrenergic receptors for EPI, P2Y and P2Y12 receptors for ADP, jumonji domain containing 1C, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma, sonic hedgehog or murine retrovirus integration site 1 homolog), but the exact underlying cause of the syndrome has not been established yet.2,3,7

The affected members of one family may not express the same SPS type and there are even the cases of the negativity of their family history. As shown by all the results of genetic studies described above, various mutations of one or more genes contribute to similar SPS phenotype. Additionally, platelets of the patients with atherosclerosis, autoimmune and renal diseases showed hyperaggregability after the addition of EPI or other agonists, pointing to the possible acquired forms of SPS.2,3 Moreover, the diagnosis of SPS is based on clinical manifestation and laboratory parameters, not on the results of genetic analysis.2 Therefore, currently we cannot state that SPS is inherited exactly in autosomal dominant trait, as it was originally proposed.1,2

These facts only underline the need to study not only the genetic background, but also the epidemiology, clinical symptoms and the treatment response more comprehensively to better predict and prevent the development of thrombotic episodes, and manage the existing complications of the disorder. Finally, SPS should be taken into account when differentially diagnosing the patient with unknown cause of thrombotic event.3

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