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Artículo de revisión

El síndrome de Plaquetas Pegajosas (SPP)

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RESUMEN

Hace tres décadas Holliday y Mammen describieron a pacientes con enfermedades tromboembólicas arteriales y venosas asociadas con hiperreactividad plaquetaria hereditaria. Ellos llamaron a este fenómeno protrombótico "síndrome de plaquetas pegajosas" (SPP). El SPP tiene un rasgo autosómico dominante, definido por un aumento en la agregación plaquetaria inducida por diversas concentraciones de dos agonistas plaquetarios --adenosín difosfato (ADP) y/o epinefrina (EPI). Se han identificado tres variantes de esta enfermedad: hiperagregabilidad a ADP y EPI- tipo I, solo a EPI- tipo II, y solo a ADP- tipo III. La hiperagregabilidad se diagnostica por medio de agregometría plaquetaria, aunque exista controversia al hacer el diagnóstico, ya que la concentración de los agonistas no está estandarizada, y no existe un consenso en el porcentaje de agregación plaquetaria. Es importante tomar en cuenta la hiperagregabilidad de los agonistas ADP y EPI, porque se ha relacionado con varias enfermedades adquiridas, como enfermedades metabólicas (diabetes mellitus, aterosclerosis) y enfermedades inflamatorias (sepsis y enfermedades del sistema inmune). A pesar de que se conoce el fenotipo de la enfermedad, el genotipò no ha podido definirse. Los fármacos antiplaquetarios, como la aspirina y el clopidogrel revierten la hiperreactividad plaquetaria de los pacientes con SPP, lo que resulta en disminución de la tasa de retrombosis.

ABSTRACT

Three decades ago Holiday and Mammen described patients with arterial or venous thromboembolic disease associated with inherited platelet hyper reactivity and named this prothrombotic state ¨sticky platelet syndrome¨ (SPS). SPS has an autosomal dominant trait, defined by increased platelet aggregation in response to low concentrations of 2 platelet agonists - adenosine diphosphate (ADP) and / or epinephrine (EPI). There are 3 distinct types (hyperaggregability to ADP and EPI - type I, to EPI alone - type II, to ADP alone - type III), which can be identified. Hyper reactivity is diagnosed by platelet aggregometry, although there has been controversy in diagnosing SPS because the concentration of agonists are not standardized, and there is no consensus on the percent of platelet aggregation that would be considered positive. It is important to bear in mind the platelet hyperaggregability agonists, EPI and ADP, because they have been described in several acquired disorders, such as complex metabolic disease (diabetes mellitus, atherosclerosis) and inflammatory disorders (sepsis, systemic immune diseases). Despite the fact that the phenotype if the disease is well known, its genotype has not been defined. Antiplatelet drugs, such as aspirin and clopidogrel, have reverted the platelet hyperreactivity of patients with SPS, translating this into a substantial decrease of their re-thrombosis rate.

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DEFINITION AND PREVALENCE

It is now three decades ago when Holiday and Mammen described patients with arterial or venous thromboembolic disease associated with inherited platelet hyper reactivity and named this prothrombotic state ¨sticky platelet syndrome¨ (SPS)[1]. In his description of SPS, Mammen emphasizes the distinction between acquired platelet hyperaggregability and SPS, which he considered an inherited, autosomal dominant disorder (an observation supported by latter publications) and suggested that aspirin could be used to prevent further thrombosis [2-5]. Interestingly, thrombotic events occur in both arterial and venous beds and are characteristically associated to stressful situations[3,6,7,8].

Hyper reactivity is diagnosed by platelet aggregometry, using concentrations of agonists (adenosine diphosphate

[ADP] and/or epinephrine) that are lower than those used in routine platelet aggregation studies, and do not by definition induce aggregation in healthy control platelets (a normal control must be included every time the test is performed). SPS is classified as type I, II, or III based on the agonist to which platelets overreact (both ADP and epinephrine, ADP alone, or epinephrine alone, respectively). When making a diagnosis of SPS, one must take into account that there are multiple transient or persistent acquired factors that induce a hyper reactive platelet phenotype[2,9]. Thus, in order to make a diagnosis of hereditary SPS, platelet hyper reactivity must be shown to persist over time (there are no set definitions on when the test should be repeated), and to be present in at least one otherwise healthy family member. Acquired causes of platelet hyper reactivity must also be ruled out before establishing a firm diagnosis of SPS.

Key factors that have caused controversy in diagnosing SPS are that the concentration of agonists are not standardized, and there is no consensus on the percent of platelet aggregation above which the test would be considered positive. Accordingly, if the agonists are not sufficiently diluted, then a variable percentage of healthy individuals will be considered to have hyper reactive platelets. In our hands, using a concentration of epinephrine of 0.5µM which is used in the original descriptions of SPS, will indeed induce aggregation of platelets in 10 to 20% of apparently healthy individuals with no family history of thrombosis[10]. We have not found aggregation at this dilution with ADP. Others have also shown varying platelet aggregation responses over time in healthy individuals[11] It is noteworthy that the hyper reactive phenotype may not be restricted to ADP and or epinephrine as shown by Yee et al. who demonstrated that in healthy individuals there is a subset that may have hyper reactive platelets, and that in vitro hyper reactivity to one agonist tended to demonstrate a similar response to others, including collagen, collagen-related peptide, and ristocetin, suggesting that hyper reactivity is a global characteristic of platelets[12].

The nature of the defect that causes platelet hyper reactivity is still unknown. Human platelets express both adrenergic and dopaminergic receptors that are influenced by different catecholamines, yet definite abnormalities in these receptors have not been detected[13]. Recently Kubisz et al. reported four haplotypes in glycloprotein 6 gene which may be associated with the platelet hyperaggregability in SPS[14]. The glycoprotein IIIa PLA1/A2 polymorphism is not associated with the sticky platelet syndrome phenotype [13], and vitamin K-dependent growth arrest-specific 6 gene (Gas6) polymorphisms have been proposed to be implicated [15]. The fact that high fibrinogen levels correlate with this phenotype in healthy women suggests that either platelet or plasma factors may be responsible for the increased platelet aggregation. In conclusion, SPS is a prothrombotic disease of unknown etiology, inherited as an autosomal dominant trait, in which thrombosis in any vascular bed can occur and is frequently associated with a stressful event; the diagnosis is made by the finding of hyperaggregable platelets at low agonist concentrations.

Regarding prevalence in the general population, there are no hard data, since as noted above, the criteria for the definition of SPS are not strictly defined, and large studies where aggregometry is repeated in those with hyper reactive platelets are not available. There are more data for the prevalence of platelet hyper reactivity amongst individuals with a confirmed thrombotic event, yet the confirmation of definite SPS would require repeat aggregometry, confirmation of family members with the same platelet phenotype, and ruling out associated acquired causes for the abnormal platelet aggregation. Despite these caveats there are interesting reports pointing to hyper aggregation as a real and frequent finding in patients with hereditary thrombophilia. For example, in a small group of selected individuals with likely hereditary thrombophilia (arterial or venous thrombosis, age under 40, family history of thrombosis, recurrent idiopathic thrombosis without overt prothrombotic risk factors, thrombosis in unusual vascular beds), aggregometry detected hyper reactivity at the lowest agonist dilutions in 6/10 individuals[16].; this initial observation was later on confirmed in a group of 100 individuals using the same criteria [17]. Other studies that report a high prevalence of platelet hyper aggregability do not meet all criteria for the strict diagnosis of SPS. For the most part these studies have concomitant diseases that may induce acquired abnormal platelet reactivity [8,18]. In conclusion, the prevalence of SPS in the general population has not been studied. In the subgroup of individuals with clinical suggestion of primary thrombophilia, close to halve the patients show platelet hyperaggregability. Larger studies must be done in different populations to corroborate these findings.

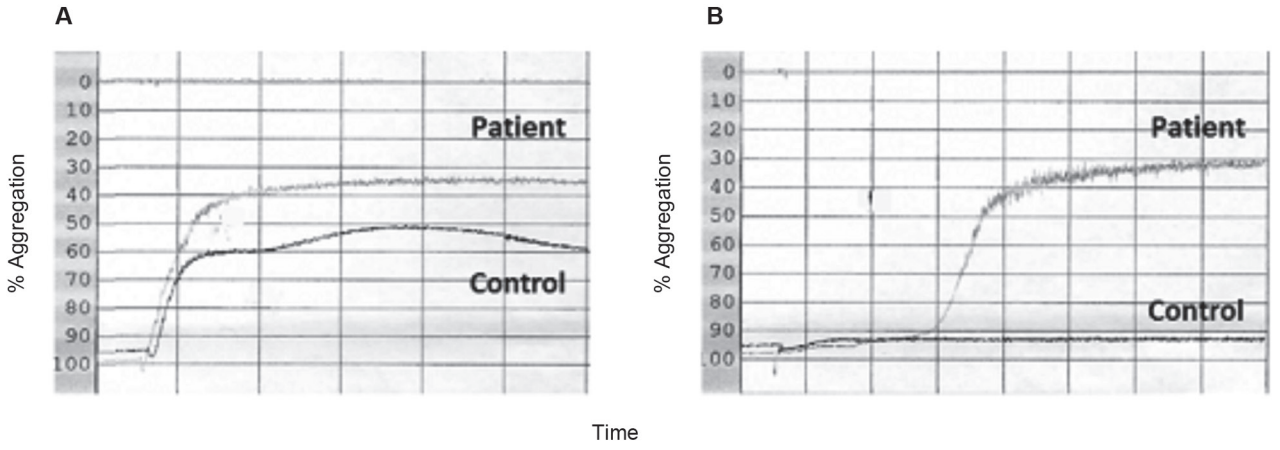

Figure 1. Platelet aggregometry using epinephrine at the standard concentration 1 µM (A), or with progressive dilutions 0.5 µM (B). Curves depict percent aggregation for patient or control platelet rich plasma. At the lower concentration of epinephrine only patient platelets aggregate (70%), while control platelets remain below 10% aggregation. For reference: routine platelet aggregation for platelet function studies is carried out using 10 µM of either ADP or epinephrine.

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ETIOLOGY AND PATHOLOGY OF THE SPS. CLINICAL SYMPTOMS, POSSIBLE DEFECTS RESPONSIBLE FOR THE DISORDER AND PATIENT REGISTER

The sticky platelet syndrome (SPS) is a thrombophilic thrombocytopathy with familial occurrence and autosomal dominant trait, defined by increased in vitro platelet aggregation in response to low concentrations of 2 platelet agonists - adenosine diphosphate (ADP) and / or epinephrine (EPI).[1,2] According to laboratory findings, 3 distinct types (hyperaggregability to ADP and EPI - type I, to EPI alone - type II, to ADP alone - type III) can be identified.[1-3] Due to the limited published data (mostly case reports or case series) the prevalence of the syndrome in general population is not known. But, as shown by Bick, SPS is relatively frequent among patients with thrombotic events unexplained by common acquired and inherited thrombophilias [3]. Although in the initial reports SPS was found to be an isolated hemostatic defect, with the increased number of affected individuals combinations with other inherited or acquired thrombophilic disorders have been reported.[4] Clinically, the syndrome is characterized by thrombotic events, both venous and arterial (though arterial, namely stroke and coronary syndromes, prevail), and pregnancy-associated complications (fetal growth retardation, fetal loss) in women. Interestingly, both arterial and venous thrombosis could occur in the same patient. Although the clinical symptoms of SPS are in general similar to thromboembolism from other causes, certain distinct features could be identified: the first thrombotic event usually occurs in young individuals (< 40 years, even in children) without prominent acquired risk factors, rather frequently in atypical localization (e. g. retinal veins, cerebral sinuses), thrombosis may reoccur despite of adequate anticoagulant treatment (vitamin K antagonists), and some family members - both men and women - in several generations may be affected. Several authors recognized an association between stressful situations and thrombotic events. In women, the first thrombotic event is usually associated with pregnancy or the use of hormonal contraception. Although the hereditary nature of SPS is well documented by several family studies,[5,6] the exact genetic defect has not been identified so far. Hypothetically, abnormalities of platelet receptors or regulatory proteins involved in platelet activation and aggregation were labeled as a possible cause. Several of them – GPIIIa HPA-1 polymorphism, Gas6 c. 834+7G>A polymorphism, and various GP6 polymorphisms among others - have been evaluated in recent years. In general, all studies failed to prove any of these mutations to be a single genetic defect responsible for SPS and did not find a consistent relation to SPS and its types. In a case of GPVI, 3 SNPs appeared to be more frequent in patients with SPS (rs1671153, rs1654419, rs1613662), particularly among those with SPS type II and in whom the syndrome manifested by venous thromboembolism or fetal loss.[7] Thus, although not the underlying disorder, these polymorphisms could have a modulating effect on the clinical presentation of the syndrome. The observed discrepancy in genetic studies as well as laboratory heterogeneity of SPS might suggest a multifactorial genetics, similarly to some other hemostatic disorders. Furthermore, it is important to bear in mind that platelet hyperaggregability to natural agonists including EPI and ADP was described in several acquired disorders, such as complex metabolic (diabetes mellitus, atherosclerosis) and inflammatory (sepsis, systemic immune diseases) disorders.[8,9] Therefore, further complex studies focused on individuals not likely to be affected by aforementioned disorders – young adults and children – are needed for the deeper understanding of the syndrome's genetics. The aim of the lecture is to summarize present knowledge on the clinical symptoms and etiology of SPS and to document distinct clinical and pathological features of the syndrome on the author's own cohort of more than 300 cases.

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TREATMENT OF THE SPS

Introduction: The sticky platelet syndrome (SPS) is a common cause of thrombosis. There are no prospective studies concerning treatment.

Objective: To analyze changes in platelet hyperaggregability of SPS patients given antiplatelet drugs and to asses its association with re-thrombosis.

Methods: Fifty-five patients with a history of thrombosis and SPS phenotype were prospectively studied, before and after treatment with aspirin and / or clopidogrel.

Results: Patients were followed for 1 to 129 months, median 13. Forty received aspirin, 13 aspirin + clopidogrel and 2 only clopìdogrel. The platelet aggregation response to adenosine diphosphate and epinephrine significantly diminished after treatment and only two developed another thrombosis, 52 and 259 months after starting therapy, the freedom from rethrombosis rate of the patients being 96.4% at 129 months.

Conclusion: By using antiplatelet drugs the platelet hyperreactivity of patients with the SPS phenotype was reverted; this translated into a substantial decrease of the re-thrombosis rate.

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