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Primary Thrombophilia XVI: A Look at the Genotype of the Sticky Platelet Syndrome Phenotype

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Abstract

The sticky platelet syndrome (SPS) was described by Mammen in 1983. Since then, scientists in several countries have identified the condition and published cases or series of patients, thus enabling the description of the prevalence of the inherited condition, its salient clinical features, and the treatment of the disease. The diagnosis of the SPS phenotype requires fresh blood samples and special equipment which is not available in all coagulation laboratories. In the era of molecular biology, up to now it has not been possible to define a clear association of the SPS phenotype with a specific molecular marker. Some molecular changes which have been described in platelet proteins in some persons with the phenotype of the SPS are here discussed. Nowadays, the SPS phenotype may be considered as a risk factor for thrombosis and most cases of the SPS developing vaso-occlussive episodes are the result of its coexistence with other thrombosis-prone conditions, some of the inherited and some of them acquired, thus leading to the concept of multifactorial thrombophilia. Ignoring all these evidence-based concepts is inappropriate, same as stating that the SPS is a nonentity simply because not all laboratories are endowed with adequate equipment to support the diagnosis.

Keywords

platelets, hyperaggregability, thrombosis, thrombophilia

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Introduction

Platelets were first described by the Italian pathologist Giulio Bizzozero in 1882 when he defined these cells as the third morphological element of blood.[1] These small, anucleate cells travel as discoid fragments in the circulation, with an average circulating life span of 8 to 9 days. The development of this cell line is the paragon of an elegant and finely orchestrated series of cellular processes known as megakaryocytopoiesis and thrombopoiesis.[2] Megakaryocyte maturation hinges on nuclear duplication without cell division, resulting in giant cells. Cytoplasmic organelles are then organized into domains representing nascent platelets, demarcated by a network of invaginated plasma membranes; fragmentation of the megakaryocyte cytoplasm into individual platelets results from the shear forces of circulating blood, perhaps largely in the pulmonary circulation.[3] Thrombopoietin is the dominant hormone controlling megakaryocyte development, but many cytokines and hormones also play a role, including interleukins 3, 6, and 11.[4]

Platelets are unique in their structural assembly, and although they lack a nucleus, they contain several mitochondria. Their phospholipid bilayer plasma membrane is the site of expression

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of various surface receptors and lipid rafts that actively participate in many signaling pathways and intracellular trafficking. Platelet reactivity can be heavily influenced by biologically active markers such as CD36, CD41, CD42a, CD42b, and CD61. These include some active surface receptors and platelet secretory products. Platelets tend to alter the expression and signaling of these markers in different disease circumstances, and potentially compromising their prognoses, while also providing a broad field to explore disease progression.[5] To date, we are still missing sufficient information on the physiological role of blood platelets, so an open field is available to clinicians and researchers to analyze and develop innovative findings, particularly in terms of aggregation and in the so-called sticky platelet syndrome (SPS).

A Brief Overview on Platelet Function

Platelets require many integrins and receptors to fulfill their functions. If a vessel is injured, the platelet's proximity to the endothelial wall allows it to reach the subendothelial extracellular matrix exposed after injury, via cell-surface glycoprotein (GP) VI and integrin α2β1, as well as by binding of the von Willebrand factor (vWF) to the platelet's surface GP Ib-IX-V complex.[6] All these events are mediated by different signal pathways that have been discovered, activation of adenosine diphosphate (ADP) and ATP receptors, GP VI collagen receptor, and GP Ib-IX-V.[7] Inhibitory, activator, and negative feedback signals have been described. Inhibitory signals allow platelets to remain in an inactivated state. Nitric oxide (NO) and prostacyclin 12 (PG12) are the main vasoactive activator hormones. NO activates guanylyl cyclase and prostacyclin (PGI2) that in turn, activate cGMP-dependent Protein kinase G, and decrease intracellular calcium thus inducing cAMP production. Activation signals are responsible for platelet aggregation and thrombus formation; the process begins with adhesion receptor-mediated platelet activation, followed by signal-induced activation of G-protein-coupled receptors. Negative feedback signals regulate and control both inhibitory and excitatory signals.[8,9]

Platelets play a primordial role in the mechanisms of hemostasis and thrombosis through aggregation and adhesion to the damaged vascular endothelium. This step requires the interaction between environmental factors and other platelets,[10] triggering a complex process on the surface of the platelet membrane via specific receptors. Finally, the activation of platelets is strictly dependent on the interaction between the external and internal environment of the cell, and is mediated through membrane receptors; in terms of platelet adhesion, the most interesting receptors due to their critical roles, are the GP on the membrane surface, which are listed from the largest to the smallest size as I through IX.[11] These GP belong to the integrin family and are α/β heterodimeric protein complexes.[12] The most abundant platelet-specific integrin receptor on the surface of platelets is the IIb/IIIa (αIIb/β3) receptor, responsible for the binding of platelets to fibrinogen, collagen, prothrombin, vWF, thrombospondin, and vitronectin; its activity is one of the main promoters of platelet aggregation.[13]

In addition, primary hemostasis relies on platelet adhesion, activation, secretion, and aggregation. The initial stimulus that initiates platelet adhesion is injury to the endothelium that consequently, mainly exposes collagen fibers and vWF; the interaction of platelets with these substrates provides the surface for platelet adhesion and serves as a key point for platelet activation.[14] The binding of platelet surface receptors with their ligands activates various biochemical intracellular signaling pathways through second messengers, such as tyrosine kinase, calcium, phospholipase C, phosphoinositol-3-kinase, and cyclic AMP, among others.[15] These lead to 4 essential changes in platelets:

- Modification of the actin cytoskeleton, whereby the originally discoid shape of the platelet changes into a sphere with long membrane projections[16]
- Membrane phospholipase A2 activity is stimulated by increased calcium concentrations within the platelets, which leads to the release of arachidonic acid (AA) from membrane phospholipids. Cyclooxygenase-1 converts AA to prostaglandin H2, an intermediate product that is further metabolized by thromboxane synthase into TXA2.[3]
- Release of the content of both alpha (integral membrane proteins, coagulants, anticoagulants, fibrinolytic proteins, adhesion proteins) and dense intracellular platelet granules (cations, phosphates, bioactive amines, and nucleotides) into the canalicular system.[17]
- Increased expression of GP IIb/IIIa on the platelet membrane, which allows its binding to soluble fibrinogen and promotes further platelet aggregation.[18]

In summary, platelet aggregation is regulated primarily by the binding of GP IIb/IIIa to fibrinogen, and to a lesser extent, vWF, and fibronectin. Both molecules simultaneously act as a bridge between several platelets. This platelet–fibrinogen–platelet junction activates the platelet to initiate the clot aggregation process.[15]

Some Molecular Features of the Platelet Function

Many efforts have been made to explore the impact of micro ribonucleic acids (miRNAs) on the expression of genes directed to fine-tune and decrease noise in protein expression, and in proteins that are active in the physiology and pathophysiology of platelets.[19] Platelets contain many miRNAs, but few studies have established a connection between individual platelet miRNAs and platelet function. To date, specific functions of most miRNAs within platelets remain unexplored.[20] Over the past several years, many reports have suggested that platelet miRNAs are biologically and clinically relevant: (i) they are tools to understand platelet physiology and MK gene expression; (ii) they are potential regulators of platelet RNA and

protein expression; and (iii) they are a source of circulating miRNAs.[21]

The first human platelet miRNA profiling was reported as part of a study testing the differential expression of miRNA in patients with polycythemia vera and established that miR-26b was significantly increased in these cases. Platelet reactivity is another disorder in which miR-96 was shown to down-regulate vesicle-associated membrane protein 8 mRNA expression and protein levels.[22] miR-21 has recently been shown to attenuate platelet release of transforming growth factor β-1, a master regulator of fibrosis.[23] Follow-up studies have varied considerably in terms of the most common miRNAs in platelets, miR-223-3p has been described as the most abundant platelet miRNA in numerous studies suggesting that it plays a role in disease. In previous reports, Elgheznawy et al[24] found that miR-223 is decreased in diabetic subjects, while Stratz *et al*[25] reported the opposite in patients with type 2 diabetes. In other studies, mice that are deficient in miR-223 exhibited shorter bleeding times, larger FeCl3-induced thrombi, greater sensitivity to low doses of thrombin, and impaired clot retraction; another report referred that platelet miR-223 expression appears to be decreased in subjects with increased on-clopidogrel activity.[21]

These are only a few examples of what represent new opportunities for future research. Table 1 summarizes the top 10 expressed miRNAs in mouse megakaryocytes and their precursors referred in several studies.[26] These miRNAs open the door to progressively acquire new insights into the relationship between disease and platelet physiology.

Salient Features of the SPS Phenotype

The SPS phenotype is a qualitative platelet disorder with familial occurrence (an autosomal dominant trait affecting both genders), defined by increased *in vitro* platelet aggregation after the addition of very low concentrations of ADP and/or epinephrine (EPI).[27] This disorder remains multifactorial and predisposes to, rather than causes, thrombosis and often remains silent until a second insult to the coagulation system or vasculature occurs.[28] Since thrombosis is a complex disorder involving the interaction between many different types of genes with environmental factors, and these processes culminate in the development and coexistence of more than 1 thrombosis-prone conditions (which can be inherited and some of them acquired), the term of multifactorial thrombophilia may be used.[29]

Table 1. Top miRNAs Expressed in Mice.

Rank	CMPs	MEP	Megakaryocytes
1	miR-720	miR-720	miR-720
2	miR-16	miR-142-3p	miR-142-3p
3	miR-142-3p	miR-16	miR-16
4	miR-30b	let-7	miR-223
5	miR-706	miR-709	miR-98
6	miR-136	miR-19b	miR-18a
7	miR-98	miR-106a	miR-709
8	miR-18a	miR-19a	miR-15b
9	miR-15a	miR-15b	miR-706
10	miR-19b	miR-25	miR-19b

Abbreviations: MEP, megakaryocyte–erythroid progenitors; CMPs, common myeloid progenitors.
Source: Ref.[26]

There is no characteristic clinical pattern to the SPS. Although clinical findings are very similar to those typically seen in patients with any other hereditary or secondary thrombophilia.[30] Some authors have described that arterial thrombosis is the most common clinical manifestation of the syndrome. These observations have led to constant research on SPS since its discovery in 1983, in an attempt to weave a biologically plausible mechanism explaining the complexities of this pathological entity (Table 2).[31] According to Bick *et al*, the SPS may be considered as a frequent cause of unexplained arterial thrombosis.[41] Beside these reports, SPS is remarked as a risk factor to the development of venous or arterial thrombosis, migraine, graft-versus-host disease (GVHD), and pregnancy complications, particularly in states of physiological stress that exacerbate the risk of developing a thrombotic episode. However, not all patients with SPS are symptomatic or develop thrombotic complications.[50]

The exact prevalence of SPS is unknown due to the lack of studies focused on exploring the presence of this entity. Only a few countries have published studies on this syndrome, including Mexico, where it represents the second most frequent inherited thrombophilic condition identified in Mexican mestizos.[51] SPS has been identified and published worldwide: A total of 1783 patients have been published from different parts of the world between 1988 and 2019 and informed that cases have increased in the last 10 years, most of them have been identified in Slovakia, the United States, Mexico, Germany, and Russia.[48]

Overview of the Diagnosis of SPS

There has been extensive discussion over the years of whether SPS is a real entity due to the fact that there are multiple transient or persistent acquired factors which may induce a hyperreactive platelet phenotype. To establish a diagnosis of hereditary SPS, one must prove that the platelet hyperreactivity persists over time and that another family member expresses the same phenotype. Another controversial factor is the fact that the concentrations of agonists used have not been fully standardized, nor is the percent of platelet aggregation which is considered positive. The usual percent of platelet aggregation which is considered normal at full concentrations of agonist is greater than 60%. If this cutoff is reduced, or if the agonists are not sufficiently diluted, then a higher percentage of individuals will be considered to have hyperreactive platelets.[52]

The most widely used method in order to prove platelet hyperaggregability is that described by Mammen (diagnostic criteria are described in Table 3).[38] And according to the aggregation pattern, 3 types of the syndrome can be identified. Type II is the most common (hyperaggregability to EPI alone), followed by type I

Table 2. Most Relevant Published Studies on Platelet Function and SPS (Adapted from Ref[31]).

Sticky platelet syndrome throughout history		
XIX century	1873	**Bizzozero and Osler**: Platelets as separate components of blood were recognized in pioneering studies.
	1880	The first quantitative and qualitative platelet disorders were described.[32]
XX century	1900-1910	**Hayem and Duke**: The role of platelets in hemostasis was further demonstrated in several clinical studies.
	1962	**Born and O'Brienin**: Introduction of turbidimetric platelet aggregometry.[33,34]
	1978	**Ten Cate et al**: Described platelet aggregation in a cohort of 50 patients with transient ischemic attack (TIA) or cerebral infarction. They proposed a possible platelet defect as the cause of these events.[35]
	1979	**Weiss et al**: Publication of the first treaty on the prothrombotic qualitative platelet disorder.[36]
		Mefty et al: Described 22 patients with transient ischemic attack (TIA), all showing on repeated testing, an increase in platelet adhesion and/or aggregation; they suggested that this platelet hyperaggregability could be the underlying cause of TIA in those individuals.
	1983	**Holiday et al**: The first recognition of SPS as a distinct disorder of hemostasis, at the 9th International Conference on Stroke and Cerebral Circulation in Arizona.[37]
	1984	**Mammen**: Published a case report of a 24-year-old woman that suffered an acute MI while pregnant. There were no identifiable risk factors or disease.[38]
	1988	**Mammen et al**: Published the first large series of patients with the sticky platelet syndrome (SPS).
	1995	**Mammen et al**: Summed up their 10-year experience with this most probably inherited platelet defect characterized by increased platelet aggregability with ADP and/or EPI.[38]
	1996	**Mammen et al**: In studies including over 200 patients, they identified 2 types of patients: one with the classic hyperaggregability of platelets to ADP and epinephrine, now referred to as type I, and the other, with hyperaggregability only with epinephrine, type II.[39]
	1997	**Berg-Dammer et al**: In a case report of 2 patients in Germany with cerebrovascular thromboses, therapy with low-dose aspirin normalized the hyperaggregable platelet state.[40]
	1998	**-Chittoor et al:** Reported the case of a 30-year-old woman who initially suffered thrombosis of the superior sagittal sinus manifested as sudden visual disturbances. **-Bick:** Was among the first to describe SPS in patients with venous thrombosis.[41] **-Andersen**: Reported her experience with 195 prospectively screened patients with arterial, venous, or mixed thromboses.[42]
	1999	**Chaturvedi and Dzieczkowski**: The first to describe the occurrence of SPS in association with other inherited thrombophilic disorders in the same individual.[43]
XXI century	2004	**Lewerenz et al**: SPS as a cause of cutaneous changes.
	2007	**Mûhtfeld et al**: SPS as a cause of graft dysfunction (kidney).
	2010	**Kubisz et al and Ruiz Argüelles et al**: SNP's of PLT proteins studied in SPS.
	2013	**Ruiz Argüelles et al**: The first prospective study on the treatment of SPS.
	2017	**Sokol et al**: Recommendations for the standardization of aggregometry, SPS diagnostic criteria.[44]
		Fejes Z et al: Association between miR-223, miR-26b, and miR-126, and dysregulation of platelet function[45]
	2019	**Peter Kubisz et al**: Sticky Platelet Syndrome: 35 Years of Growing Evidence.[27]
		Yagmur et al: Demonstration of the clinical and diagnostic relevance of platelet hyperaggregability in women with infertility and a history of miscarriage, in a study conducted in Germany.[46]
		García-Navarrete YI et al: Antithrombotic treatment of sticky platelet syndrome worldwide.[47]
		Vallejo-Villalobos et al: Primary Thrombophilia XIV: Worldwide Identification of the Sticky Platelet Syndrome.[48]
	2020	**Vadelova L et al**: Possible association of miR-96 in patients with SPS and pregnancy complications.[49]

(hyperaggregability to ADP and EPI), whereas type III (hyperaggregability to ADP alone) is infrequent[53] (see Figure 1).[54]

SPS and Current Management

Treatment of SPS relies on attenuate the abnormal platelet hyperaggregability with antiplatelet drugs. In most cases, acetylsalicylic acid (ASA) appears to be an adequate option but there are situations in which other antiplatelet drugs are needed.[47] Patients that are allergic or intolerant to aspirin can be managed with clopidogrel, and in cases in which platelet hyperreactivity persists over an established time period, the combination of ASA and clopidogrel at the usual doses appears to provide good results. For example, in a study published in 2015 which analyzed the results of treatment in 55 patients with SPS

Table 3. Diagnostic Criteria for SPS.

Laboratory Classification:

- Type I: Hyperaggregability with EPI and with ADP
- Type II: Hyperaggregability with EPI only
- Type III: Hyperaggregability with ADP onlySuggestive of diagnosis: Hyperaggregability with only 1 reagent and only 1 concentration, and a history of thrombosis Firm diagnosis: *History of thrombosis plus:

1. Platelet hyperaggregability with 2 concentrations and 2 different reagents
2. Hyperaggregability at 1 concentration with 2 different reagents
3. Abnormalities with a single concentration and with 1 reagent on 2 occasions

Abbreviations: SPS, sticky platelet syndrome; EPI, epinephrine; ADP, adenosine diphosphate.
Source: Ref.[53]

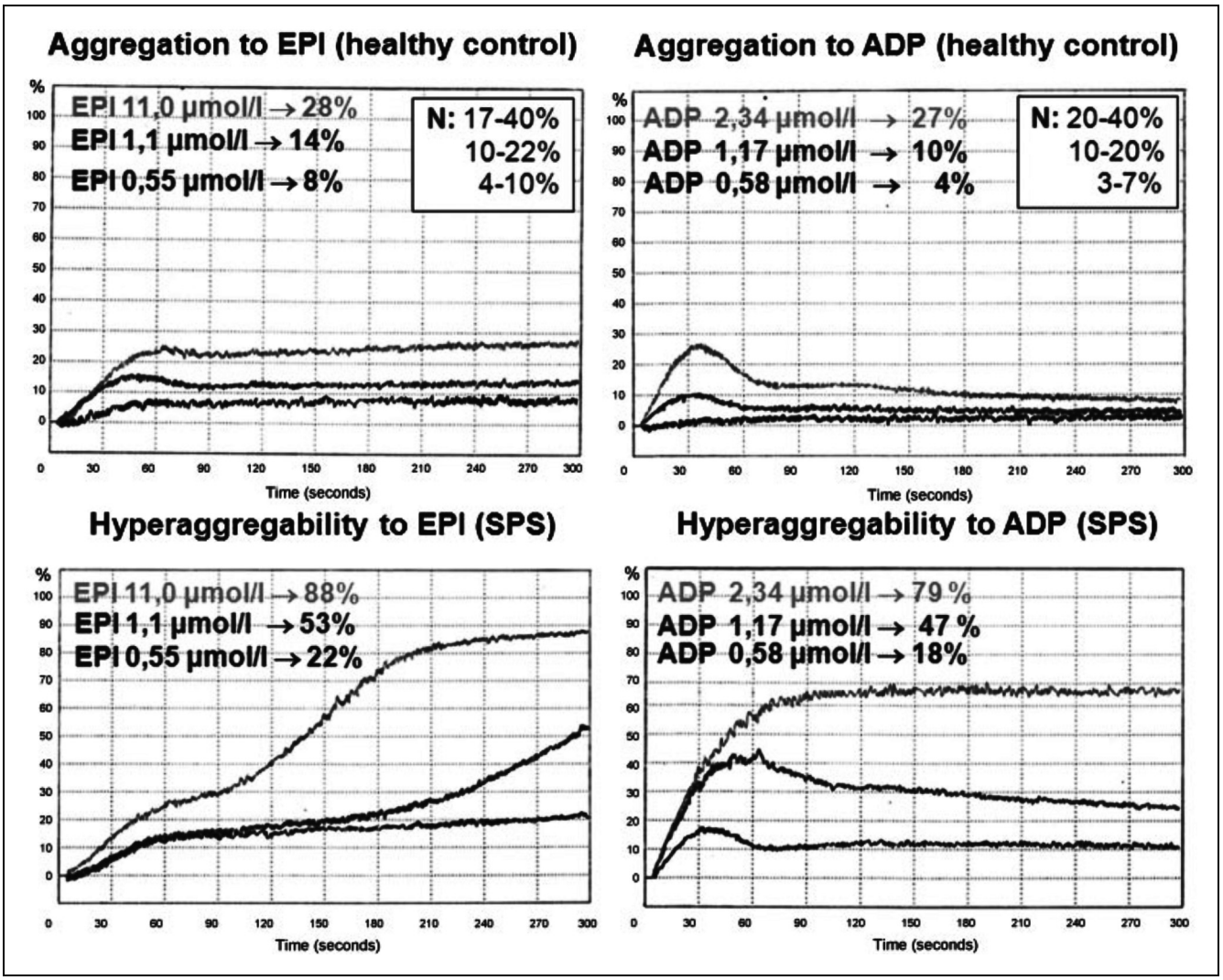

Figure 1. Patterns of hyperaggregability between healthy individuals and sticky platelet syndrome (SPS) patients (took from Peter Kubisz et al[54]).

Table 4. Genes Related to the Sticky Platelet Syndrome[56].

Symbol	Description
GP6	Glycoprotein VI Platelet
GAS6	Growth Arrest Specific 6
F5	Coagulation Factor V
ITGB3	Integrin Subunit Beta 3
PEAR1	Platelet Endothelial Aggregation Receptor 1
SERPINC1	Serpin Family C Member 1
SERPIN E1	Serpin Family E Member 1

Malacards.org. (referred on May 6, 2021). Available at: https://www.malacards.org/card/sticky_platelet_syndrome.

followed for a median of 129 months, the authors found that after the administration of antiplatelet drugs, particularly ASA platelet hyperreactivity in patients with the SPS phenotype could be reverted, leading to a substantial decrease in the rate of rethrombosis. All 55 patients included in the study had at least 1 episode of thrombosis before starting treatment, but once administered, rethrombosis episodes decreased to 3.6% at 129 months.[55]

New Molecular Insights and Their Relationship with Other Conditions

After more than 30 years of research, the definition of the SPS requires an update since this syndrome has a multifactorial etiology in which genetic and environmental factors may play an active role.[33] Table 4 shows the most common genes associated to the condition.[56] The genetic origin proposed for some authors as we previously mentioned, relies on the mutations on the membrane GPs, mainly the GP6 gene mutation which encodes GPVI: a crucial platelet membrane GP important for an adequate platelet activation, adhesion, and aggregation.[57,58]

In a recent study, there was found an increased frequency of major haplotype TTGTGA and 2 minor haplotypes CGATAA

Table 5. Salient Features of the Sticky Platelet Syndrome.

1. The sticky platelet syndrome (SPS) is a phenotype of platelet hyperaggregability, defined by increased *in vitro* platelet aggregation after the addition of very low concentrations of adenosine diphosphate and/or epinephrine. The concentrations and dilutions of the agents are relatively well standardized.
2. The genotype is currently unknown, but several observations on the genes of platelets proteins are being studied: platelet glycoprotein IIIa PLA1/A2; platelet glycoprotein 6, growth arrest specific 6, coagulation factor V, integrin subunit beta 3, platelet endothelial aggregation receptor 1, serpin family C member 1, serpin family E member 1.
3. The SPS phenotype is probably the expression of genetic conditions interacting with other medical conditions or environmental factors, such as diabetes mellitus, hormonal therapy, pregnancy, and others.
4. The SPS may lead into both arterial and venous thrombosis, the latter being more frequent.
5. The SPS is an hereditary autosomal dominant trait.
6. The SPS is the most frequent cause of hereditary thrombophilia in México and probably in other countries.
7. Patients with the SPS have been identified and treated in all continents of the world.
8. The SPS is a frequent cause on miscarriages and obstetric complications.
9. The SPS usually needs another thrombophilic condition to fully express as a thrombotic episode. It has recently been described as a risk factor for thrombosis during COVID-19.
10. The hyperaggregability of the SPS reverts employing antiplatelet drugs and the rethrombosis rate of persons with the syndrome is very low while being on treatment. Most patients revert the hyperaggregability with aspirin, but around one quarter need 2 antiplatelet drugs. It is therefore advisable to assess the SPS phenotype after starting the antiplatelet drug, in order to define further treatment. Treating persons with the SPS with oral anticoagulants does not reduce the rethrombosis rate.
11. Claiming that the SPS is a nonentity indicates that it is not being assessed properly and may also be detrimental for the patients, since the consequences of defining is a simple, cheap, and effective treatment, tolerated by most persons, which is the use of low-doses of aspirin and other antiplatelet drugs.

and TTGTGG of GP6 gene in patients with SPS, they also observed that the allele G of a single nucleotide polymorphism (SNP) rs12610286 and major haplotype TTGTGA were significantly increased in patients with SPS type I and stroke.[57,59] Kotuličová et al[58] found in a case-control study an increased occurrence of SNPs 1613662 and 1654419 in patients with SPS and history of deep venous thrombosis (DVT). Also, the risk of developing DVT in patients with SPS is related with the presence of other risk factors, including some gene polymorphisms. On the other hand, Sokol et al found that ADRA2A allele (rs1800545) might be an independent risk factor, and that PEAR1 alleles (rs12041331 and rs12566888) might be an independent protective factors for DVT in patients with SPS type II.[60] In a case-control study SNPs 1671153, 1613662, and 1654419 were more frequent in patients with SPS and pregnancy loss according to Sokol et al.[61] On the other hand, Vadelova et al[49] in a case-control study with 45 patients with SPS and 30 healthy controls, found a considerably increased expression of platelet miR-96 in patients with SPS and pregnancy complications, while miR-223 and miR-126 were not correlated with miscarriages.

In the SPS, there are only a few studies regarding the role of m-RNA in the physiopathology of this condition, most of them related with chronic degenerative diseases and infertility. Diabetes mellitus (DM) is associated with a hypercoagulable state, specifically, signaling pathways in the platelets of diabetic patients are dysregulated, leading to platelet hyperactivation and an increased risk of microcapillary embolization.[62] In a state of hyperglycemia, platelets are more prone to aggregation through nonenzymatic glycation of platelet membrane proteins and consequently increased expression of certain GPs (Ib-IX, IIb/IIIa) and receptors necessary for platelet function.[63] As is well known, DM is related to overexpression of inflammatory cytokines, which may stimulate endothelial expression of factor VIII and vWF, as well as increase vascular cell adhesion molecules, endothelin-1 and E-selectin, and decrease the production of NO and prostacyclin, all contributing to endothelial cell injury and a prothrombotic state.[64] Considering SPS as a state of platelet hyperaggregability, many questions have arisen on its possible role in the complex pathogenesis of diabetic microvascular complications. Hence, different authors have questioned whether DM patients with an early onset of chronic complications should be screened for the presence of the SPS. Several studies have shown that individuals with DM have increased platelet activation, and that this could potentially be explained by an abnormality in miRNA, such as the previously described miR-223, miR-26b, and miR-126 leading to dysregulation in platelet function[45]

Recent investigations have centered on the relationship between the presence of the SPS and infertility and/or miscarriage. Pregnancy is well known to represent a hypercoagulable state which predisposes to the development of thrombi and secondarily, to pregnancy complications and miscarriage. In one of our previous prospective study, we analyzed 108 thrombophilic women and found a relative risk of 2.66 of having a miscarriage in female patients with SPS in comparison with healthy females.[65] Some studies support our data and have shown that recurrent miscarriage and infertility could be related in patients with undiagnosed SPS. Yagmur *et al*[46] studied 208 patients with infertility for 11 years, and found that 33.2% of the patients with SPS had a history of miscarriage. These observations are interesting since a molecular mechanism could be related to that clinical outcome.

Closing Remarks

As a result of our interest in the SPS, we have been able to learn several pieces of information on the SPS which are summarized in Table 5.

The genetic and molecular influence within the pathogenesis of SPS must be a trigger to adopt newer molecular tests to perform new investigations capable of demonstrating the role of new miRNA in the physiopathology of the SPS, and the activation of platelet aggregation. Moreover, and considering the molecular basis of the pathogenesis in SPS in which miR-26b, miR-223, and miR-126 regulated genes play an important role; we could take them as key targets to create new antiplatelet drug therapies in SPS and other hyper aggregation states.

The importance of these studies and the need of further studies lies not only in the establishment of new biomarkers but also in the creation of new therapies and an adequate approach as well as evaluate the possible impact of SPS in other important and frequent conditions.

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References

1. Ribatti D, Crivellato E. Giulio bizzozero and the discovery of platelets. *Leuk Res*. 2007;31(10):1339-1341.
2. Twomey L, Wallace R G, Cummins P M, et al. Platelets: from formation to function, homeostasis - An integrated vision, Fernanda Lasakosvitsch and Sergio Dos Anjos Garnes. . *IntechOpen*. 2018. Available from: https://www.intechopen.com/chapters/64989.
3. James NG. Platelets. *The Lancet*. 2000;355(9214):P1531-15394.
4. Kaushansky K. Thrombopoietin: the primary regulator of platelet production. *Blood*. 1995;86(2):419-431.
5. Ghoshal K, Bhattacharyya M. Overview of platelet physiology: its hemostatic and nonhemostatic role in disease pathogenesis. *Sci World J*. 2014;2014:78185.
6. Holinstat M. Normal platelet function. *Cancer Metastasis Rev*. 2017;36(2):195-198.
7. Estevez B, Du X. New concepts and mechanisms of platelet activation signaling. *Physiology*. 2017;32(2):162-177.
8. Bye A, Unsworth A, Gibbins J. Platelet signaling: a complex interplay between inhibitory and activatory networks. *J Thromb Haemostasis*. 2016;14(5):918-930.
9. Amelirad A, Shamsasenjan K, Akbarzadehlaleh P, Pashoutan Sarvar D. Signaling pathways of receptors involved in platelet activation andShedding of these receptors in stored platelets. *Adv Pharm Bull*. 2019;9(1):38-47.
10. Fountain JH, Lappin SL. *Physiology, Platelet*. En: StatPearls. StatPearls Publishing; 2020.
11. Bennet JSW. The molecular biology of platelets membrane proteins. *Semin Hematol*. 1990;27(2):186-204.
12. Clark EA, Brugge JS. Integrins and signal transduction pathways: the road taken. *Science*. 1995;268(5208):233-239.
13. XieZ TY, Ma L, Lv X, et al. Developments in inhibiting platelet aggregation based on different design strategies. *Future Med Chem*. 2019;11(14):1757-1775.
14. Andrews RK, Berndt MC. Platelet physiology and thrombosis. *Thromb Res*. 2004;114(5–6):447-453.
15. Brenda G-G, Leopoldo R-WF, Juan D-GE. Fisiología plaquetaria, agregometría plaquetaria y su utilidad clínica. *Med. interna Méx. [revista en la Internet]*. 2018 Abr [citado 2021 Abr 14];34(2):244-263.
16. Thomas SG. *The Structure of Resting and Activated Platelets*. En: Platelets. Elsevier; 2019. p. 47-77.
17. Gremmel T, Frelinger AL3rd, Michelson AD. Platelet physiology. *Semin Thromb Hemost*. 2016;42(3):191-204.
18. Koltai K, Kesmarky G, Feher G, Tibold A, Toth K. Platelet aggregometry testing: molecular mechanisms, techniques and clinical implications. *Int J Mol Sci*. 2017;18(8):1803.
19. Nagalla S, Shaw C, King X, et al. Platelet microRNA-mRNA coexpression profiles correlate with platelet reactivity. *Blood*. 2011;117(19):5189-5197.
20. Krammer TL, Mayr M, Hackl M. microRNAs as promising biomarkers of platelet activity in antiplatelet therapy monitoring. *Int J Mol Sci*. 2020;21(10):3477.
21. Lindsay CR, Edelstein LC. MicroRNAs in platelet physiology and function. *Semin Thromb Hemost*. 2016;42(3):215-222.
22. Dahiya N, Sarachana T, Vu L, et al. Platelet MicroRNAs: an overview. *Transfus Med Rev*. 2015;29(4):215-219.
23. Schulte C, Mayr M. MicroRNAs: a new understanding of platelet physiology and pathology. *Thromb Haemost*. 2019;119(2):191.
24. Elgheznawy A, Shi L, Hu J, et al. Dicer cleavage by calpain determines platelet microRNA levels and function in diabetes. *Circ Res*. 2015;117(2):157-165.
25. Stratz C, Nührenberg T, Fiebich BL, et al. Controlled type II diabetes mellitus has no major influence on platelet micro-RNA expression. Results from micro-array profiling in a cohort of 60 patients: results from micro-array profiling in a cohort of 60 patients. *Thromb Haemost*. 2014;111(5):902-911.
26. Edelstein LC, McKenzie SE, Shaw C, Holinstat MA, Kunapuli SP, Bray PF. MicroRNAs in platelet production and activation. *J Thromb Haemost*. 2013;11(Suppl 1):340-350.
27. Kubisz P, Holly P, Stasko J. Sticky platelet syndrome: 35 years of growing evidence. *Semin Thromb Hemost*. 2019;45(1):61-68.
28. Bojalian MO, Akingba AG, Andersen JC, et al. Sticky platelet syndrome: an unusual presentation of arterial ischemia. *Ann Vasc Surg*. 2010;24(5):691.e1-6.
29. Ruiz-Argüelles GJ, López-Martínez B, Valdés-Tapia P, Gómez-Rangel JD, Reyes-Núñez V. Garcés-Eisele J. Primary thrombophilia in Mexico. V. A comprehensive prospective study indicates that most cases are multifactorial. *Am J Hematol*. 2005 Jan;78(1):21-26.

30. Campuzano-Maya G, Escobar-Gallo GE. Sticky platelet syndrome. *Medicina & Laboratorio*. 2014;20(11–12):513-528.
31. Kubisz P, Ruiz-Argüelles GJ, Stasko J, Holly P, Ruiz-Delgado GJ. Sticky platelet syndrome: history and future perspectives. *Semin Thromb Hemost*. 2014;40(5):526-534.
32. Coller BS. Historical perspective and future directions in platelet research: platelet history and future directions. *J Thromb Haemost*. 2011;9(Suppl 1):374-395.
33. Born GV. Aggregation of blood platelets by adenosine diphosphate and its reversal. *Nature*. 1962;194(4832):927-929.
34. Platelet aggregation: part II some results from a new method of study. *J Clin Pathol*. 1962;15(5):452-455.
35. Ten Cate JW, Vos J, Oosterhuis H, Prenger D, Jenkins CS. Spontaneous platelet aggregation in cerebrovascular disease. *Thromb Haemost*. 1978;39(1):223-229.
36. Weiss HJ, Vicic WJ, Lages BA, Rogers J. Isolated deficiency of platelet procoagulant activity. *Am J Med*. 1979;67(2):206-213.
37. Holiday PL, Mammen E, Gilroy J. Paper Presented at: The Ninth International Joint Conference on Stroke and Cerebral Circulation. Phoenix, Arizona, USA; 1983 (abstract).
38. Mammen E. Ten Years' experience with the "sticky platelet syndrome". *Clin Appl Thromb Hemost*. 1995;1(1):66-72.
39. Mammen EF. Sticky platelet syndrome. *Semin Thromb Hemost*. 1999;25(4):361-365.
40. Berg-Dammer E, Henkes H, Trobisch H, Kühne D. Sticky platelet syndrome: a cause of neurovascular thrombosis and thrombo-embolism. *Interv Neuroradiol*. 1997;3(2):145-154.
41. Bick RL. Sticky platelet syndrome: a common cause of unexplained arterial and venous thrombosis. *Clin Appl Thromb Hemost*. 1998;4(2):77-81.
42. Andersen JA. Report. Bleeding and thrombosis in women. *Biomed Progress*. 1999;12:40.
43. Chaturvedi S, Dzieczkowski JS. Protein S deficiency, activated protein C resistance and sticky platelet syndrome in a young woman with bilateral strokes. *Cerebrovasc Dis*. 1999;9(2):127-130.
44. Sokol J, Skerenova M, Jedinakova Z, et al. Progress in the understanding of sticky platelet syndrome. *Semin Thromb Hemost*. 2017;43(1):8-13.
45. Fejes Z, Póliska S, Czimmerer Z, et al. Hyperglycaemia suppresses microRNA expression in platelets to increase P2RY12 and SELP levels in type 2 diabetes mellitus. *Thromb Haemostasis*. 2017;117(03):529-542.
46. Yagmur E, Bast E, Mühlfeld AS, et al. High prevalence of sticky platelet syndrome in patients with infertility and pregnancy loss. *J Clin Med*. 2019;8(9):1328.
47. García-Navarrete YI, Vallejo-Villalobos MF, Olivares-Gazca JM, et al. Primary thrombophilia XV: antithrombotic treatment of sticky platelet syndrome worldwide. *Ann Blood*. July 2019;4:15-15.
48. Vallejo-Villalobos MF, Gomez-Cruz GB, Cantero-Fortiz Y, et al. Primary thrombophilia XIV: worldwide identification of sticky platelet syndrome. *Semin Thromb Hemost*. 2019;45(4):423-428.
49. Vadelova L, Skerenova M, Ivankova J, et al. MicroRNA and hyperaggregability of platelets in women with sticky platelet syndrome and pregnancy complications. *Bratislava Med J*. 2020;121(10):700-704.
50. Kubisz P, Stanciakova L, Stasko J, et al. Sticky platelet syndrome: an important cause of life-threatening thrombotic complications. *Expert Rev Hematol*. 2016;9(1):21-35.
51. Ruiz-Argüelles GJ, Garcés-Eisele J, Camacho-Alarcón C, et al. Primary thrombophilia in Mexico IX: the glycoprotein IIIa PLA1/A2 polymorphism is not associated with the sticky platelet syndrome phenotype. *Clin Appl Thromb Hemost*. 2013;19(6):689-692.
52. Maus G C. Myths and reality of the sticky platelet syndrome. *Rev Hematol Mex*. 2011;12(2):55-56.
53. Parra OI, Martínez AM, López MB. Diagnosis and characteristics of sticky platelet syndrome. *Rev Mex Patol Clin Med Lab*. 2016;63(2):60-66.
54. Kubisz P, Stasko J, Holly P. Sticky platelet syndrome. *Semin Thromb Hemost*. 2013;39(6):674-683.
55. Velázquez-Sánchez-de-Cima S, Zamora-Ortiz G, Hernández-Reyes J, et al. Primary thrombophilia in México X: a prospective study of the treatment of the sticky platelet syndrome. *Clin Appl Thromb Hemost*. 2015;21(1):91-95.
56. Malacards. org. [citado el 6 de mayo de 2021]. Disponible en: https://www.malacards.org/card/sticky_platelet_syndrome Accessed May 6,2021.
57. Stanciakova L, Skerenova M, Holly P, et al. Genetic origin of the sticky platelet syndrome. *Rev Hematol Mex*. 2016 abril;17(2):139-143.
58. Kotuličová D, Chudý P, Škereňová M, Ivanková J, Dobrotová M, Kubisz P. Variability of GP6 gene in patients with sticky platelet syndrome and deep venous thrombosis and/or pulmonary embolism. *Blood Coagul Fibrinolysis*. 2012;23(6):543-547.
59. Kubisz P, Ivanková J, Škereňová M, Staško J, Hollý P. The prevalence of the platelet glycoprotein VI polymorphisms in patients with sticky platelet syndrome and ischemic stroke. *Hematology*. 2012;17(6):355-362.
60. Sokol J, Skerenova M, Ivankova J, Simurda T, Stasko J. Association of genetic variability in selected genes in patients With deep vein thrombosis and platelet hyperaggregability. *Clin Appl Thromb Hemost*. 2018;24(7):1027-1032.
61. Sokol J, Biringer K, Skerenova M, et al. Platelet aggregation abnormalities in patients with fetal losses: the GP6 gene polymorphism. *Fertil Steril*. 2012;98(5):1170-1174.
62. Carrizzo A, Izzo C, Oliveti M, et al. The main determinants of diabetes mellitus vascular complications: endothelial dysfunction and platelet hyperaggregation. *Int J Mol Sci*. 2018;19(10):2968.
63. Vojtková J, Motyková K, Bánovčin P. Possible association between haemostasis dysfunction and early onset of microvascular complications in patients with type 1 diabetes. *Pediatr Endocrinol Diabetes Metab*. 2020;26(2):89-96.
64. Peng X, Wang X, Fan M, Zhao J, Lin L, Liu J. Plasma levels of von willebrand factor in type 2 diabetes patients with and without cardiovascular diseases: a meta-analysis. *Diabetes Metab Res Rev*. 2020;36(1):e3193.
65. Ruiz-Delgado G, Cantero-Fortiz Y, Mendez-Huerta M, et al. Primary thrombophilia in México XII: miscarriages are more frequent in people with the sticky platelet syndrome. *Turk J Hematol*. 2017;34(3):239–243.