Review Article

The “sticky platelet syndrome”: thirty years after its identification in Mexico

Elena Soto-Vega[1,2], Liliana Rivadeneyra-Espinoza[1], Yunam Cuan-Baltazar[1], Samia Gómez-Gómez[1], Oscar Alfonso Reyes-Cisneros[1], Miranda Melgar-de-la-Paz[1,3], Moisés Manuel Gallardo-Pérez[3], Guillermo José Ruiz-Argüelles[3,4]^

[1]Escuela de Medicina, Universidad Anáhuac Puebla, Puebla, México; [2]Consejo de Ciencia y Tecnología del Estado de Puebla, Puebla, México; [3]Centro de Hematología y Medicina Interna, Clínica Ruiz, Puebla, México; [4]Universidad Popular Autónoma del Estado de Puebla, Puebla, México

Contributions: (I) Conception and design: E Soto-Vega, L Rivadeneyra-Espinoza, GJ Ruiz-Argüelles, OA Reyes-Cisneros; (II) Administrative support: E Soto-Vega, L Rivadeneyra-Espinoza, GJ Ruiz-Argüelles; (III) Provision of study materials or patients: GJ Ruiz-Argüelles; (IV) Collection and assembly of data: Y Cuan-Baltazar, S Gómez-Gómez, OA Reyes-Cisneros, M Melgar-de-la-Paz, MM Gallardo-Pérez; (V) Data analysis and interpretation: Y Cuan-Baltazar, S Gómez-Gómez, OA Reyes-Cisneros, M Melgar-de-la-Paz, MM Gallardo-Pérez, GJ Ruiz-Argüelles; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Guillermo José Ruiz-Argüelles, MD, FRCP (Glasg), MACP, DSc (hc), FRCP. Centro de Hematología y Medicina Interna de Puebla, 8B Sur 3710, CP 72530 Puebla, México; Universidad Popular Autónoma del Estado de Puebla, Puebla, México. Email: gruiz1@clinicaruiz.com.

Abstract: Holiday described the sticky platelet syndrome (SPS) and since then, reports from different parts of the world have become available. Initial data on SPS was acquired from studies conducted on Caucasian populations, however, it is imperative to note that further investigations have been undertaken on diverse ethnic groups, such as the Mexican population, which have revealed the existence of certain variations and disparities in the manifestation and characteristics of this syndrome. The Mexican population is defined as “mestizo” and encompasses individuals born in Mexico but with Amerindian and white ancestors. The Mexican Genome Diversity Project (MGDP) showed that the genetic diversity generated by the “mestizaje” is most relevant for some pathologies, including autoimmune disease among others. In Mexico, SPS is the second most common hereditary thrombophilic condition and that most frequently associated with arterial thrombosis, followed by the antiphospholipid syndrome. The preferred therapeutic intervention for patients diagnosed with SPS lies in the administration of antiplatelet medications, as this particular course of action effectively rectifies the phenomenon of platelet hyperaggregability in approximately 75% of afflicted individuals, thus resulting in a notable reduction in the likelihood of rethrombosis to a rate that falls below the 4% threshold. In the last two decades, SPS has become the second most common cause of primary thrombophilia in the Mexican mestizo population, and it is manifested as an autosomal dominant disease, very frequently combined with other coagulopathies. The medical community needs to recognize SPS as a frequent cause of thrombophilia since once identified, its treatment is inexpensive and effective. We herein present data accrued over 32 years, on SPS in Mexico.

Keywords: Platelets; thrombosis; thrombophilia; Mexico; sticky platelet syndrome (SPS)

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^ ORCID: 0000-0002-9335-0653.

Introduction

Background

Soon after the discovery of platelets in 1882 by Giulio Bizzozero (1), its disorders began to be described. Four decades ago, Holiday *et al.* (2) described a group of patients with arterial or venous thromboembolic disease associated with inherited platelet hyperreactivity and named it as "sticky platelet syndrome" (SPS). SPS is a rare autosomal dominant disease, although not all patients have relatives with the disorder; it is defined as platelet hyperaggregability after stimulation with minimum concentrations of platelet inducers such as adenosine diphosphate (ADP) and/or epinephrine in vitro, in the context of normal platelet response to other aggregation inducers (3,4). According to the platelet aggregation pattern with different ADP and epinephrine concentrations, three forms of SPS have been identified (5) (*Table 1*). SPS does not follow a clear clinical pattern, and its manifestations are very similar to those of other hereditary or secondary thrombophilias; its primary identifying features are:

(I) It is an autosomal dominant hereditary syndrome.
(II) The first thrombotic event typically occurs in adults, between the third and fourth decade of life (individuals with no clinical history of thrombotic disease).
(III) Manifestations are more common in women, they tend to develop during pregnancy and may be related to inadequate vascularization of the placenta, intrauterine fetal growth delays, and in the worst cases, fetal loss. These thrombotic manifestations can be precipitated by the use of anovulatory and replacement hormones.
(IV) Thrombosis occurs in typical sites such as the veins of the lower limbs in the case of venous thromboembolism, and in the coronary and cerebral arteries in cases of arterial thrombosis.
(V) Migraine is a very commonly associated clinical manifestation, and antiplatelet therapy can control the migraine episodes.
(VI) One of its most suggestive manifestations is its lack of response to anticoagulation with either low-molecular-weight heparin or vitamin K antagonists such as warfarin, or in the setting of rethrombosis.

Thromboembolism is one of the main causes of mortality and morbidity worldwide (7). In Mexico, SPS is the second most common hereditary thrombophilic condition and that most frequently associated with arterial thrombosis, followed by the antiphospholipid syndrome. Its incidence is approximately 21% (4).

Table 1 Diagnostic criteria for SPS (6)

SPS type	Diagnosis
I	Hyperaggregation after EPI and ADP
II	Hyperaggregation after EPI alone
III	Hyperaggregation after ADP alone

SPS, sticky platelet syndrome; EPI, epinephrine; ADP, adenosine diphosphate.

The etiology of SPS remains uncertain, but apparently, the glycoprotein (GP) receptors on platelet surface membranes may play a role in causing platelet hyperfunction (3). The most significant advance in the study of hereditary thrombophilia has been the identification of activated protein C resistance (APCr) as a common prothrombotic abnormality (8).

Rationale and knowledge gap

In this review, we analyze a series of studies on primary thrombophilias, including SPS, in the Mexican mestizo population. In 1999, the Ruiz-Argüelles group began to study and treat patients with inherited and/or acquired thrombophilia, and developed a series of prospective studies on primary thrombophilia in Mexican Mestizo individuals. Most of these studies focused on identifying the thrombophilic conditions with a clinical marker suggesting an inherited hypercoagulable state.

The Mexican population is defined as "mestizo" and encompasses individuals born in Mexico but with Amerindian and white ancestors. The Mexican Genome Diversity Project (MGDP) showed that the genetic diversity generated by the "mestizaje" is most relevant for some pathologies, including autoimmune disease among others. The genetic composition of Mexican Mestizos includes 56% of Indian genes, 40% of Caucasian genes, and 4% of Black genes. Ethnic differences in disease must be thoroughly studied since they may translate, as an example, into the greater prevalence of autoimmune disorders in Mexican Mestizos in comparison with Caucasian populations (9,10).

Objective

The objective of this study is to analyze data collected over 32 years on SPS in Mexico.

Historical data on the study of thrombophilia in Mexican mestizos

The first paper on thrombophilic conditions in Mexico was published in 1987 (11). Lobato-Mendizabal *et al.* identified the first Mexican patient with a congenital deficiency of the coagulation protein C (PC) (11). They subsequently published a paper reviewing the activity mechanisms of PC, protein S (PS), and thrombomodulin as natural antithrombotics (12). A group of Mexican mestizo patients with apparent primary thrombophilia was then studied (n=102), and 40 (39%) patients had an APCr phenotype, 4 (3.9%) had a factor V (FV) Leiden mutation, and 5 (5.1%) patients had a functional deficiency of PC, one of whom with associated PC antigenic deficiency. Two percent (2%) of patients had PS deficiency. None of the patients presented abnormalities in antithrombin III (AT-III), plasminogen, tissue-type plasminogen activator (TPA), or plasminogen activator inhibitor (PAI) (6). These results contrast with the data reported at the time in Caucasian populations, in whom the APCr phenotype was found in 20–60% of the study cohort (13), while in Mexican mestizos, only 4% of patients with thrombophilia displayed the APCr phenotype.

A comparison of allele mutations linked to the risk of venous thrombosis in Caucasians and Mexicans was conducted. In Caucasian patients, factor V1691 was detected in 21%, the methylenetetrahydrofolate reductase (*MTHFR*) gene in 10%, and the prothrombin 20210 variant in 6% of the patients (14-18). In the Mexican mestizo population, factor V1691 was found in 10.8% of patients, the *MTHFR* gene in 61%, and prothrombin 20210 in 6%. The frequency of the *MTHFR* 677 mutation in Mexican mestizos was significantly higher in patients (61%) but was also detected in healthy individuals (78%), so it does not appear to play a major role in thrombogenesis among Mexicans (8).

A group of 10 patients with clinical markers associated with a primary hypercoagulable state was studied to determine if they harbored SPS, following the Mammen method; the results revealed that in Mexican mestizo thrombophilic patients, SPS was associated with other thrombosis-prone conditions, so the authors now refer to this platelet abnormality as "multifactorial thrombophilia" (19).

Other mutations were slowly being associated with thrombophilic states, and were also investigated in the Mexican mestizo population; these include:

(I) FV Leiden mutation, named for the city in which it was identified (Arg506Gln) (20).

(II) FV HR2, characterized by a constellation of six polymorphisms in FV and marginally low FV levels, and associated with a slightly decreased APC response (20,21).

(III) FV Cambridge, described in an English patient with thrombosis (Arg306Thr mutation in the FV gene) (22).

(IV) FV Hong Kong, found in Chinese patients with thrombosis (Arg306Gly mutation in the FV gene) (23).

(V) FV Liverpool, found in two siblings with the APCr phenotype (Ile359Thr) (24).

None of the patients studied by the Mexican group presented the Cambridge nor the Liverpool mutations, so these polymorphisms of the FV gene were not major contributors to the thrombophilic state observed in Mexican mestizos. Ten percent (10%) of patients were heterozygous for the FV Leiden mutation, 28% had the HR2 haplotype, and only 1 patient (2%) presented the Hong Kong mutation (25).

Mutation typification continued in Mexico, and a group of 46 patients with a primary hypercoagulable state were studied: 48% of the patients had SPS, whereby 80.4% of them developed two or more coagulation abnormalities previously associated with SPS. Twenty-four percent (24%) presented the APCr phenotype, 11% had a FV Leiden mutation, 15% a prothrombin gene mutation, 63% showed the *MTHFR* gene mutation, 24% had the FV HR2 haplotype, 24% had antiphospholipid antibodies, 9% displayed PS deficiency, 13% PC deficiency, one patient had the FV Hong Kong mutation, and one patient had AT-III deficiency. These results led to the conclusion that most cases of thrombophilia in Mexico were multifactorial (26).

In a cohort of 100 Mexican mestizo patients, 63% manifested the SPS, and 81% were found to have 2 to 5 coexisting abnormalities; however, the only significant association was between the FV Leiden gene mutation and the APCr phenotype ($r=0.495$, $P<0.001$). The study also established that the *MTHFR* 677 mutation was present as a heterozygous or homozygous gene and that it does not determine the presence or absence of thrombophilia unless associated with other pro-thrombotic conditions (27). In addition, the results supported the model proposed by Schafer *et al.* (28), suggesting that patients with venous thromboembolism are genetically predisposed to one or more inherited thrombophilic conditions that determine individual hypercoagulability, the so-called "thrombosis threshold".

In patients with chronic myeloproliferative disorders, essential thrombocythemia and polycythemia vera (PV), a mutation in the *JAK2* gene has been described and found to foster thrombophilia; in Mexican patients (n=77), the specific V617F mutation of the *JAK2* gene could not be identified; Garcés-Eisele *et al.* concluded that the *V617F JAK2* gene mutation is an unlikely cause of primary thrombophilia in Mexican mestizos, and the study of those genes should be limited to specific patients (29).

To determine the role of genetics in SPS expression and its inheritance pattern, five kindreds with several family members presenting the SPS phenotype were analyzed. Three of 5 of the studied kindred had a co-existing SPS phenotype and the *MTHFR* 677 gene mutation, one presented clinical SPS and the thalassemia phenotype, and another only had the SPS phenotype with no associated prothrombotic conditions. This family study suggests that, most likely, the SPS phenotype has a genetic origin, and is apparently inherited as an autosomal dominant trait. Also, as suggested in previous studies, in most cases SPS is manifested in the context of co-existing prothrombotic conditions and markers. The *MTHFR* gene mutation is the most frequently associated with this genetic demographic context. However, it is possible to find SPS as the only thrombophilia marker. This platelet abnormality further underscores the multifactorial thrombophilia concept (30).

Núñez-Martínez *et al.* conducted a cross-sectional study of 967 patients with thrombosis, between 2003 and 2008. They identified 25 patients fulfilling the SPS criteria (31). Some results obtained in this series do not agree with those reported by Azamar-Solis *et al.*, interestingly, the incidence of venous thrombosis reported by Núñez-Martínez was 40%, while Azamar-Solis found it was 70%. Another discordance was detected in the male-female ratio, whereby the Núñez-Martínez series reported 11 males and 14 females, while the Azamar-Solis series found that 83% of their patients were females. Both authors agreed that type I was the most frequent (31,32).

Weiss *et al.* reported that there is a strong association between the PlA2 polymorphism of the glycoprotein IIIa gene and acute coronary thrombosis, specially in patients who had had coronary events before the age of 60 years (33). However, Kubisz *et al.* investigated if the glycoprotein IIIa PlA1/A2 polymorphism is a defect responsible for the sticky platelet syndrome and their study reported that they are not related. Nevertheless, they had a limited number of patients investigated and for this reason, the patient group must be extended in order to give a more reliable answer to their hypothesis (34).

SPS treatment is based on the decrease of excessive platelet activity with medications such as acetylsalicylic acid (ASA). Velázquez-Sánchez-de-Cima *et al.* conducted a study in which patients were monitored before and after treatment with a daily dose of 100 mg ASA. They found that 75% of the patients responded to ASA treatment, while the remaining 25% warranted an alternative antiplatelet medication such as clopidogrel. Three-point six percent (3.6%) of patients developed a vaso-occlusive episode after treatment at 52 and 129 months respectively, after initiating therapy, and both were cases of rethrombosis of the central retinal artery (35).

Statistically, the rate of freedom from rethrombosis in these patients was found to be 96.4% at 129 months. According to the study, the platelet aggregation response to ADP and epinephrine in patients with the SPS phenotype was reverted after the administration of antiplatelet drugs. This strongly suggests that therapy with ASA or other antiplatelet agents is efficient, not only in the treatment of thrombotic events in patients with SPS but also in the prevention of these phenomena (36-38). Kubisz *et al.* proposed that this treatment was only pertinent when SPS was the only identified abnormality and did not coexist with other prothrombotic conditions. On the other hand, combined abnormality cases may require different therapeutic measures (39).

The correlation between the primary thrombophilic condition and APCr was evaluated in a prospective study (n=96 Mexican mestizos), and an abnormal APCr phenotype was identified in 19% of individuals; 44% had a FV Leiden mutation, 22% had an increased level of factor VIII, 16% antiphospholipid antibodies, and 6% a lupus anticoagulant. By odds ratio means, some results were significantly associated:

- APCr phenotype and FV Leiden mutation (odds ratio: 97.8; P=0.0022).
- APCr phenotype and the use of direct oral anticoagulants (DOA) (odds ratio: 4.7; P=0.0065).
- Antiphospholipid antibodies and lupus anticoagulant (odds ratio: 29.8; P=0.0001).

The use of DOA was reported in 61% of the APCr patients, of which 39% of cases were associated with an additional cause of an abnormal APCr phenotype, and in the remaining cases, it was the only possible explanation of the abnormal phenotype (40).

Pregnancy predisposes to thrombosis as a result of low blood pressure and a turbulent flow circulation pattern in the

placenta, in association with its characteristic hypercoagulable state (41). In Mexico, the rate of miscarriage in the general population is 12% (42). SPS is the second most common thrombophilic condition that causes recurrent miscarriage or fetal loss syndrome (43-45). A prospective study conducted between 1989 and 2016 that included 108 thrombophilic female patients, revealed that 37% had a history of miscarriage, and 86% of them had SPS (46). In a subset of 73 patients with SPS who had experienced pregnancy at least once, 32% referred to a miscarriage. A comparison of the percentage of miscarriages in the general population and in SPS patients revealed that the risk of miscarriage is 2.66 times greater in patients with SPS (47).

At that time, studies by Škereňová *et al.* (47) in women with recurrent fetal loss and diagnosed with SPS established a strong association with 4 single-nucleotide polymorphisms (SNPs) in the *GP6* gene (rs1613662, rs654416, rs304167, and rs671152) in allelic equilibrium and the creation of minor haplotypes at the protein level with PENA protein residues.We hypothesized that the abnormal phosphorylation due to the previously mentioned disequilibrium could lead to platelet hyperaggregability in SPS patients.

A retrospective, descriptive study evaluating 30 years of work with Mexican patients with primary thrombophilia and a history of thrombosis, was undertaken to determine the main localization of the thrombotic events. The cohort included 86 patients with SPS as the single thrombophilic condition and at least one clinical marker of thrombophilia. Thirty percent of episodes were arterial, including pulmonary embolism (50%), central nervous system (CNS) involvement (38%), placental infarction (9%), and 1 case of myocardial infarction. The venous thrombotic events were most frequent (70%) in the lower limbs (59%), CNS (13%), upper limbs (8%), mesenteric veins (7%), and retinal veins (5%). According to the SPS type classification, the results showed that type I was the cause of 65% of cases, type II accounted for 10%, and type III for 25% of the cases. There was no association between SPS type and the location of the vaso-occlusive episode, nor between gender and localization, or gender and SPS subtype (48).

There is controversy among different authors on the existence or not of the SPS. One reason for this discrepancy could hinge on the diagnostic criteria used to identify patients; or perhaps, it depends on the sample since the laboratory requires fresh blood samples. In a literature review (49), García-Navarrete *et al.* identified 67 papers published since 1988 when SPS was first described by Mammen *et al.* to 2019; these studies included a total of 1,783 patients studied in the United States (14 papers), Slovakia (12 papers), Germany (8 papers), Mexico (6 papers), Hungary, Turkey, Russia, and New Zealand (1 paper).

The main hindrance to the definitive recognition of the syndrome is the lack of reliable molecular markers in the general population that could be associated with SPS throughout the world (49).

García-Navarrete *et al.* analyzed different treatments used worldwide. A total of 16 papers that studied 332 patients with SPS were found, and the main treatment modality was aspirin alone (303 patients), and some cases warranted its combination with heparin or coumadin (29 patients) (49). In most of the analyzed studies, platelet aggregation studies were not repeated once treatment had begun, and despite this lack of control, the rate of rethrombosis was very low (1.5%). This data proves that physicians worldwide are aware that the best treatment for people with SPS is the use of antiplatelet drugs to minimize the rate of rethrombosis (50,51).

Findings to date, have allowed us to define, identify, characterize, classify, and describe both the syndrome and its treatment. In Mexico, SPS is the most frequent cause of venous and arterial thrombophilia. SPS is a hereditary condition whose phenotype is well-established, but not its genotype. The untimely diagnosis of SPS appears to depend on the mismanagement of the necessary laboratory studies such as the use of non-fresh blood samples or the lack of adequate platelet aggregometry equipment.

SPS rarely triggers a thrombotic event, but if combined with other thrombophilic conditions, thrombotic events can develop, particularly as a result of estrogen administration. The treatment of choice for SPS is the use of antiplatelet drugs, since it reverses platelet hyperaggregability in 75% of patients, thus decreasing the risk of rethrombosis to less than 4%. In conclusion, physicians should be aware of SPS in order to establish a timely diagnosis and initiate the required simple and low-cost treatment (52).

Discussion

Since studies on SPS are scant, the prevalence of SPS is unclear. As of 2019, only 43 papers from 8 different countries had been published. Mexico has played a role in expanding our understanding of SPS (*Table 2*). Notably, in the Mexican mestizo population, SPS is the second most common inherited thrombotic condition, with an estimated

Table 2 Studies conducted in Mexico on SPS, markers used in each study, results, and main conclusion

Author	Year	Study design	Markers associated with thrombophilia	Results	Conclusion
Lobato-Mendizabal *et al.* (11)	1987	Case report	PC	First case of inherited PC deficiency in Mexico	Type II deficiency
Ruiz-Argüelles *et al.* (6)	1999	Prospective cross-sectional, 36-month period (n=102)	APCr phenotype, factor V Leiden mutation, PC, PS, AT-III, TPA, PAI, APLA, lupus anticoagulants	4% patients factor V Leiden mutation, 39.2% APCr phenotype	Most of the cases were acquired or unrelated to the factor V mutation; this result could be associated with the composition of the Mexican mestizo group analyzed
Ruiz-Argüelles *et al.* (8)	2001	Prospective case-control study, 37 thrombophilic Mexican patients *vs.* 50 healthy controls	APCr phenotype, coagulation PC activity and antigen, PS, AT-III, plasminogen, TPA, PAI, IgG and IgM antiphospholipid isotypes, factor V Leiden mutation, 677 C to T mutation in the 5, 10-MTHFR, G20210A polymorphism in the 3'-untranslated region of the prothrombin gene	Frequency of *MTHFR* 677 gene mutation was significantly higher (59%), the prothrombin was presented in 16%, and factor V Leiden (13.5%)	In Mexican Mestizo thrombophilic patients, the prevalence of factor V Leiden gene mutation is significantly lower when compared with the results found in Caucasians, while the *MTHFR* 677 and the prothrombin 20210 gene mutation is significantly more frequent
Ruiz-Argüelles *et al.* (19)	2002	Prospective cross-sectional study (n=10)	APCr phenotype, coagulation PC activity and antigen, PS, AT-III, plasminogen, TPA, PAI, IgG and IgM antiphospholipid isotypes, factor V Leiden mutation, 677 C to T mutation in the 5, 10-MTHFR, G20210A polymorphism in the 3'-untranslated region of the prothrombin gene	6/10 patients presented SPS. Five of the six patients were heterozygous for *MTHFR* 677	SPS is a relatively frequent finding in Mexican mestizo thrombophilic individuals SPS is, in most cases, associated with other pro-thrombotic conditions, the most representative one being the *MTHFR* 677 gene mutation
Ruiz-Argüelles *et al.* (25)	2004	Prospective cross-sectional study (n=39)	Factor V Leiden, factor V HR2, factor V Cambridge, factor V Hong Kong, factor V Liverpool	10% of patients, heterozygous for the FV Leiden mutation 28% HR2 haplotype 1 patient, Hong Kong mutation	There are differences in the genetic background of thrombophilia across ethnicities The studied polymorphisms are not relevantly implicated in thrombophilia in Mexican Mestizos
Ruiz-Argüelles *et al.* (26)	2005	Prospective cross-sectional study, 36-month period (n=46)	APCr phenotype, coagulation PC activity and antigen, PS, AT-III, plasminogen, TPA, PAI, IgG and IgM antiphospholipid antibodies, factor V mutation, 677 C to T mutation in the 5, 10-MTHFR, G20210A polymorphism in the 3'-untranslated region of the prothrombin gene	22 (48%) presented SPS with APCr phenotype 5 (11%) with factor V Leiden mutation 7 (15%) with prothrombin gene mutation 32 (69%) with the *MTHFR* 677 gene mutation	Abnormalities found in the normal anticoagulant system are not always the explanation to the manifested thrombosis. Most cases are multifactorial
Ruiz-Argüelles *et al.* (27)	2007	Prospective cross-sectional study (n=100)	APCr, factor V Leiden, factor V HR2, factor V Cambridge, factor V Hong Kong, factor V Liverpool, 677 C to T mutation in the 5, 10-MTHFR, G20210A polymorphism in the 3'-untranslated region of the prothrombin gene	57 patients were found with SPS 36 (63%) of them presented type I, 7 (12%) type 2, and 14 (25%) type 3 81% presented 2 to 5 co-existing abnormalities The only significant association between factor V Leiden gene mutation and APCr phenotype (r=0.495, P<0.001)	Thrombophilia in Mexican mestizos is a multifactorial disease Most abnormalities detected are not associated with one another The *MTHFR* 677 either presented as a heterozygous or homozygous gene mutation, does not determine the presence or absence of thrombophilia unless associated with other pro-thrombotic conditions
Garcés-Eisele *et al.* (29)	2008	Prospective cross-sectional study (n=77)	*JAK2* V617F mutation	None of the individuals studied presented the mutation	According to these results, it was concluded that the V617F *JAK2* gene mutation is an unlikely cause of primary thrombophilia in Mexican Mestizos
Ruiz-Argüelles *et al.* (30)	2011	Cross-sectional study (5 kindred)	APCr, factor V Leiden, factor V HR2, factor V Cambridge, factor V Hong Kong, factor V Liverpool, 677 C to T mutation in the 5, 10-MTHFR, G20210A polymorphism in the 3'-untranslated region of the prothrombin gene, *JAK2* V617F mutation	3 out of 5 of the studied kindred had co-existing SPS phenotype and *MTHFR* 677 gene mutation 1 presented SPS and thalassemia phenotype 1 presented only SPS phenotype, with no other prothrombotic conditions.	This family study suggests that the SPS phenotype most likely has a genetic origin and is apparently inherited as an autosomal dominant trait The *MTHFR* gene mutation is the most frequent It is possible to find SPS as the only thrombophilia marker. This suggests that this platelet abnormality contributes to the concept of multifactorial thrombophilia
Núñez-Martínez *et al.* (31)	2011	Cross-sectional study	factor V Leiden, prothrombin mutation G20210A, functional and antigenic protein C tests, and functional and antigenic protein S test, antithrombin were analyzed but all reported as normal	Venous thromboses are more common than arterial thromboses. Slightly more frequent in women than men. Group I was the most frequent among these patients	These results coincide with other descriptive studies worldwide, with some differences in other bibliographies in the Mexican series
Ruiz-Argüelles *et al.* (36)	2013	Cross-sectional study (n=160)	GPIIIa, PLA1/A2 (HPA-1a/b) gene polymorphism	11 of the healthy patients and 16 of the patients with SPS, the A2 allele for GP IIb/IIIA was found. Statistically, the association between the two, was found to be weak and not significant (OR 2.14, 95% CI: 0.94–4.85)	In the Mexican mestizo patients, the platelet GP IIIa PLA1/A2 gene polymorphism does not lead to the SPS phenotype

Table 2 (*continued*)

Table 2 (*continued*)

Author	Year	Study design	Markers associated with thrombophilia	Results	Conclusion
Velázquez-Sánchez-de-Cima *et al.* (35)	2015	Cross-sectional, prospective study		2 (3.6%) out of 55 patients developed another vaso-occlusive episode after treatment. The rethrombosis rate of the cohort was 96.4% at 129 months	Using aspirin or clopidogrel as treatment for SPS patients, results in a substantial decrease in the rethrombosis rate
Vallejo-Villalobos *et al.* (40)	2017	Prospective study, 276-month period (n=96)	APCr and FV Leiden	APCr/FV Leiden: OR 97.8, P=0.0022 APCr/DOACs: OR 4.7, P=0.0065 Antiphospholipid antibodies and lupus anticoagulant: OR 29.8, P=0.0001	61% of the 18 individuals referred recent use of direct oral anticoagulants, 39% of cases were associated with an additional cause of abnormal APCr phenotype, and in the rest of the cases it was the only possible explanation for the abnormal phenotype
Azamar-Solis *et al.* (32)	2019	Retrospective descriptive study, 30 years		Cohort of 86 patients describing: SPS I in 65% SPS II in 10% SPS III in 25%	The predominant subtype of SPS in the cohort was type II (commonly seen in Mexican mestizos). Venous thrombotic events were more common than arterial events. There was no association between SPS type and vaso-occlusive episode location nor between gender and localization or gender and subtype of SPS
Ruiz-Delgado *et al.* (46)	2017	Retrospective study, 27-year period (n=268)		In a subset of 73/108 patients with a history of pregnancy, 23 (32%) had a miscarriage. In general, in the Mexican pregnant population, only 12–13% of all pregnancies end in miscarriage	The relative risk of miscarriage is 2.66 times greater in female patients with SPS in comparison with the general population (P=0.001)

SPS, sticky platelet syndrome; PC, protein C; APCr, activated protein C resistance; PS, protein S; AT-III, antithrombin III; TPA, tissue-type plasminogen activator; PAI, plasminogen activator inhibitor; APLA, antiphospholipid antibodies; FV, factor V; HPA, human platelet antigen; GP, glycoprotein; OR, odds ratio; DOAC, direct oral anticoagulant.

prevalence of 44%, notably different from that reported among Caucasians. As previously noted by Kubisz *et al.* the epidemiological data of SPS remains limited since most population-based studies have been conducted in Caucasians in whom the prevalence of SPS is 15–20% in patients with unexplained thromboembolism, and in women with recurrent miscarriages (53).

As a result of years of study of SPS in Mexico, it has become clear that there are differences determined by the studied populations' ethnic composition; for example, the FV Leiden mutation is unusual while APCr is the most frequent condition in Mexican mestizos (6), but other thrombophilic conditions such as PC and PS deficiency have been identified in similar proportions to those described in Caucasians. In Mexican mestizos, the SPS phenotype is the second most frequent thrombophilic condition identified in individuals with a clinical marker of thrombophilia, only surpassed by the 677 C->T mutation in the *MTHFR* gene, which alone, may not be a fully recognized thrombophilic condition as it is usually associated with other thrombosis-prone states (30,31).

In the first study conducted in Mexico on inherited thrombophilic conditions, the markers used at the time precluded the Ruiz-Argüelles group from detecting primary thrombophilic conditions in 54% of patients (6); but five years later, with the availability of the necessary markers, patients without an identifiable cause of thrombophilia decreased to 8%. The search for new molecular markers such as miRNAs (miRNA-26b, miRNA-233, and miRNA-126) is imperative, since they can mediate intracellular communication, and have been proposed as novel biomarkers of diseases associated with platelet function.

Finally, once a patient is diagnosed with SPS, treatment begins with antiplatelet drugs to decrease abnormal platelet activity. One such drug is ASA, a cost-effective option with excellent results.

Conclusions

In Mexico, according to the data presented in the summarized studies, and thirty years after its initial identification in the country, the following generalities on SPS can be ascertained:

(I) SPS is associated with arterial and venous thrombosis.
(II) SPS is a hereditary condition that follows an autosomal inheritance pattern.
(III) SPS is one of the most frequent causes of hereditary thrombophilia in Mexico.
(IV) SPS is a frequent cause of miscarriage and obstetric complications.
(V) SPS is usually associated with another thrombophilic condition to be fully expressed as a thrombotic episode.
(VI) SPS reverts with the use of antiplatelet drugs, and the re-thrombosis rate is very low.

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Footnote

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