

Sticky Platelet Syndrome and the Role of Glycoprotein Receptors: A Review of Literature

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Abstract

Thrombotic events are mainly caused by defects in circulating plasma proteins and platelets. Normally, the formers include hereditary clotting defects [e.g. deficiencies in protein-S (PS), in protein-C (PC), in anti-thrombin (AT) genes, or factor V Leiden, and Prothrombin (PT) G20210A substitution] and autoimmune diseases [(anti-phospholipid-antibodies syndrome (APA)]. Although these conditions are well-described in literature, prothrombotic platelet disorders are less well understood. The sticky platelet syndrome (SPS) is a congenital, autosomal dominant disorder, associated with both arterial and venous thromboembolic events. In pregnant women, complications such as fetal growth retardation and fetal loss have been reported. It is characterized by in vitro platelets hyperaggregability (platelet-rich plasma; PRP) triggered by different agonists responsible for its subclassification: adenosine diphosphate (ADP) plus epinephrine (type I), epinephrine alone (type II, the most frequent), or ADP alone (type III). Clinically, patients may present with acute myocardial infarction (AMI), transient cerebral ischemic attacks (TIA), angina pectoris, stroke, peripheral arterial thrombosis, retinal thrombosis, and venous thrombosis (VT) even during oral anticoagulant therapy. Conversely, low-dose aspirin treatment ameliorates the clinical symptoms and normalizes hyperaggregability. Clinical symptoms, especially arterial, often present following emotional stress. Combinations of SPS with other congenital prothrombotic defects have been described. Currently, a precise and definite etiology of this defect is not recognized, but receptors on the platelet surface are considered strongly involved candidates. Normal levels of platelet factor 4 (PF4) and beta-thromboglobulin (β TG) in plasma suggest that the platelets are not activated at all times; accordingly they appear to become hyperactive upon ADP or adrenaline release. In vivo clumping could temporarily or permanently occlude a vessel, leading to the described clinical manifestations. The syndrome appears to be prominent particularly in patients with unexplained arterial vascular occlusions. Despite studies investigating the role of platelet glycoprotein in SPS have been conducted, the precise defect(s) responsible for the syndrome remains unknown.

This review discusses on the SPS and about the main receptors on the platelet surface, including some polymorphisms that appear to be involved in the pathology.

Keywords: Sticky platelet syndrome; Membrane glycoproteins (GPs); SNPs; Thromboses

Introduction

Platelets are essential for primary haemostasis but they also play a key role in atherogenesis and thrombus formation [1].

Thrombosis, especially arterial, develops by mediation of platelets, adhering to collagen fibers at areas of endothelial cell damage. At this phase, platelet activation leads them to secrete factors [ADP, Fibrinogen, von Willebrand Factor (vWF), Fibronectin, Factor XIII] capable of promoting cell aggregation/adhesion and coagulation, inducing vasoconstriction (thromboxane A₂) and acting as mitogens [Platelet-Derived Growth Factor (PDGF)]. Together with Tissue Factor, they activate the coagulation system that starts secondary haemostasis, and potentially, the temporary or permanent vascular occlusion [2,3].

Coagulation defects raising thrombotic risk are already well known, from the less frequent deficiencies of anti-coagulant factors (PC, PS, AT) to the more frequent factor V Leiden and PT G20210A gene variation to the APA syndrome. As far as platelet defects are concerned, wide knowledge is available on the hemorrhagic side [4], conversely less data are present in the scientific literature on their role to predispose arterial or venous thrombosis [5,6].

The role of the demonstrated platelet hyperaggregability as a possible risk factor for venous thromboembolism is not well defined [1-3,7,8]. Some authors described an enhanced maximal platelet aggregation by platelet aggregometry as a contributing factor for arterial and venous thrombosis; naming this observation "Sticky-Platelet Syndrome" (SPS) [5,6,9-12].

Nowadays SPS, in which hyperaggregable platelets can lead to transient or permanent vascular occlusions, has been established as a factor with a definite role in AMI, TIA and strokes, ischemic optic neuropathy and VT [5,6,13]. Muhlfed et al. [14] and El -Amm et al. [15] ascribed to the syndrome a possible role for thrombotic complications and impaired functions of the graft in kidney transplantation respectively. Also, two recent family studies providing evidence for the familiar occurrence and the possible genetic background of the syndrome were reported [16,17]. During past years, several studies focused on etiology and pathogenesis of the SPS, but they failed to fully reveal the genetic basis underlying this syndrome [18-24].

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Sticky platelet syndrome

Firstly described in 1983 by Holiday et al. at The Ninth International Joint Conference on Stroke and Cerebral Circulation in Arizona [25], it has been for a long time primarily just a theoretical concept with little practical basis. Although the overall clinical picture of SPS, with its transient or permanent vascular occlusions, is well known, the pathophysiological mechanism of the syndrome remains unclear [10,11,26]. It was regarded as a frequent disease and the clinical symptoms, especially arterial thrombosis, often present following an emotional stress [5,6,11]. According to Mammen [26], SPS was considered the second most frequent hereditary thrombophilia. It has been also suggested that it is connected with other hereditary thrombophilic states, and is a common feature in selected groups of patients with vascular thrombosis [27]. In a study involving 153 patients with unexplained deep venous thrombosis (DVT) or arterial thrombosis, it has been reported that 14.1% of those with DVT and 22% of those with arterial thrombosis were found to have SPS [27]. Furthermore, two additional reports discussed on a causal relation between SPS and recurrent miscarriages (64 SPS diagnosis among 351 women with miscarriages; 20%) [28]. As well as between SPS and recurrent vascular access site thrombosis in hemodialysis patients (11 of 27 patients; 41%) [29]. Recently, it was also found that SPS is a very frequent condition in patients with AIDS receiving antiretroviral therapy for at least 6 months and suffering from unexplained cardiovascular events [30].

Despite the reported high prevalence of the disease in selected patient groups, it seems likely that not all carriers of the syndrome experience clinical symptoms, considering a possible autosomal dominant mode of inheritance [26]. So far, the prevalence of SPS in the general population is not known and can be even considered an infrequent or even rare thrombophilic defect in Whites [11].

According to the available literature, patients with SPS are usually young, children included (aged 5-50 years), and are not affected by other hyper-coagulation disorders although hyper-coagulation states can occur in combination. Often they do not have identifiable risk factors for vascular thrombosis [26,31-33].

Recurrent thromboembolic events can emerge despite optimal oral anticoagulation whilst adequate antiaggregant treatment with acetylsalicylic acid effectively reduces platelet hyper-reactivity and ameliorates clinical symptoms [15,34].

The etiology of SPS is still uncertain, but from the limited epidemiological data available and from familial/case reports, it emerges that the glycoprotein (GP) receptors on platelet surface membrane and/or the intracellular signals of the platelet activation pathways could be considered strong candidate factors.

Classification and diagnosis of sticky platelet syndrome

SPS is defined by clinical and laboratory features and not by genetic testing, although it is generally regarded as an inherited disorder. At present, the diagnostic criteria proposed by Mammen [26] and Bick [27] are usually accepted and they were used in all published studies. According to these criteria, SPS is a thrombophilic thrombocytopathy with familiar occurrence, showing autosomal dominant trait and affecting both genders, characterized by increased *in vitro* platelet aggregation after low concentrations of ADP and /or Epinephrine (EPI). Aggregation in response to other agonists (collagen, arachidonic acid, ristocetin, and thrombin) remains normal [11].

Depending on the results of aggregometry, three types of SPS are defined: type I-an increased aggregation induced by both inducers; type

II-an increased aggregation induced only by epinephrine, and type III-an increased aggregation induced by ADP [27] (Table 1).

Platelet aggregation is evaluated by methods commonly used: optical or impedance aggregometry. PRP, obtained from freshly drawn blood mixed with the fitting anticoagulation reagent (usually 3.2% sodium citrate), is used for the testing. Three concentrations of each reagent are repeatedly tested, as a standard. Optical aggregometry was used in the first reports and remained an ideal option in most studies.

Sticky Platelet Syndrome (SPS) and Single-Nucleotide Polymorphisms (SNPs)

Whilst SPS phenotype, including familiar occurrence, is clearly defined, the exact genetic cause is still not sufficiently explained [17,35].

Since the role of platelets in blood clot formation involves membrane glycoprotein (GPs), changes in related genes could impair platelet aggregation. In this context, abnormalities in the membrane GPs receptors, assessed by flow cytometry and molecular methods (GP IIb/IIIa, GP Ia/IIa), leading to platelet hyperfunction, have been speculated as being associate with SPS, but their relevance remains still obscure [18].

Moreover, research had focused also on GPVI and Gas6 proteins [36-40]. These GPs were particularly interesting because certain mutations in their genes were shown to modulate the risk of thromboembolism in humans.

A combined influence of gene polymorphisms on platelet function is supported by the observation that several studies show only a limited impact of the sole polymorphism of GPs on the platelet function, although, as suggested by the testing of siblings and twins, an overall genetic influence seems to be rather high (estimated to be about 50%) [41-44].

In general, all studies failed to prove that a single genetic defect is responsible for SPS, neither a consistent relation to SPS and its types has clearly emerged (Table 2).

Divergences in genetic studies as well as laboratory heterogeneity of SPS (three distinct types) might suggest a multifactorial genetic pattern, as it is already known in some other haemostatic disorders, such as some types on von Willebrand disease, where different mutations of the same or even other genetic loci can result in the similar phenotype [11].

SPS and GPIIIa PLA1/A2

Glycoprotein IIb/IIIa (GPIIb/IIIa), a heterodimeric platelet surface receptor consisting of the α IIb (CD41) and the β 3 (CD61) subunits,

| Studies considered | SPS patients (n) | Population (n) | | Prevalence of Sticky Platelet Syndrome Type | | |
|---------------------------------------|------------------|----------------|----|---|--------|--------|
| | | M | F | | | |
| Kubisz et al (2006) | 9 | 4 | 5 | 22.2% | 66.6% | 11.1% |
| Ruiz-Argu elle set al (2012) | 95 | 43 | 52 | 64.2% | 6.31% | 29.47% |
| Kubisz et al (2010) | 128 | 42 | 86 | 27.34 | 71.1% | 1.56% |
| Kotulicova et al (2012) | 77 | - | - | 28.57% | 70.13% | 1.03% |
| Sokol et al (2012) | 27 | - | 27 | 25.93% | 74.07% | - |
| Kubisz et al (2012) | 71 | 24 | 47 | 23.94% | 73.24% | 2.81% |
| Kubisz et al (2013, unpublished data) | 23 | | 23 | - | 100% | - |

M: Male; F: Female

Table 1: Prevalence of Sticky Platelet Syndrome types in selected studies of the last 10 years.

| Authors | Mutation (polymorphisms) tested | Population | Results |
|--|--|---|---|
| Kubisz et al. [18] | GPIIIa PIAA ¹ /A ² | 9 patients with SPS (4M/5F; 2TI/6TII/1TIII); whites | No clear relation between SPS and SNP |
| Kubisz et al. [19] | Gas6 c.834 +7G > A | 128 patients with SPS (42M/86F; 35TI/91TII/2TIII); 137 controls; whites | No significant differences between SPS and control group; G allele more prevalent in SPS Type II |
| Ruis-Argüelles et al. [21] | GPIIIa PIAA1/A2 | 95 patients with SPS (43M/52F; 61TI/6TII/28TIII); 127 controls; Mexican mestizo | No significant differences between SPS and control group |
| Kubisz et al. [22] | 6 GP6 SNPs (rs1654410, rs1671153, rs1654419, rs11669150, rs12610286 and rs1654431) | 71 patients with SPS (stroke; 24M/47F; 17TI/52TII/2TIII) 77 controls; whites | No significant differences between SPS and control group; SNP rs12610286, haplotype TTGTGA significant more frequent in SPS Type I compared with controls |
| Sokol et al. [23] | | 27 patients with SPS (fetal loss; 27F; 7TI/20TII); 42 controls; whites | 3 SNPs significantly more frequent (rs1671153, rs1654419, rs1613662) in SPS group; significant higher occurrence of 2 haplotypes (CTGAG, CGATAG) |
| Kotuličová et al. [24] | | 77 patients with SPS (VTE; 22TI/54TII); 77 controls; whites | 2 SNPs (rs1613662, rs1654419) significant more frequent in SPS group; 2 SNPs (rs1671153, rs1654419) significantly more frequent in Type II compared with controls |
| Kubisz et al. (Peter Kubisz, MD, DSc, Unpublished data March 2013) | 4 Gas6 SNPs (rs7400002, rs1803628, rs8191974, rs9550270), 2 PEAR1 SNPs (rs12041331, rs12566888), 2 MRV1 SNPs (rs7940646, rs187445) | 23 patients with SPS (fetal loss 23, W; 23, TIII); 42 controls; whites | 1 GAS6 SNP (rs7400002) and 1 PEAR1 SNP (rs12566888) significantly more frequent in SPS group |

GP: Glycoprotein; M: Men; SNP: Single Nucleotide Polymorphism; SPS: Sticky Platelet Syndrome; T: Type; VTE: Venous Thromboembolism; W: Women; TI: Hyperaggregability to ADP and EPI; TII: Hyperaggregability to EPI alone

Table 2: Summary of limited genetic studies related to the prevalence of the defects in SPS patients.

serves as fibrinogen receptor, thus having an important role in platelet aggregation. The protein chain gene GPIIIa is localized on chromosome 17 (17q21.32). The GPIIb/IIIa receptor gene is highly polymorphic [41]. One of the polymorphism, the GPIIIa PLA1/A2 (rs5918; L33P substitution in the GPIIIa β3 subunit), affects the postoccupancy signaling by the platelet fibrinogen receptor IIB/IIIa and it was deeply studied for several years in the pathogenesis of thromboembolism [18]. Despite its relation to thrombotic events remains controversial, and no correlation between venous thrombosis and the GPIIIa PLA1/A2 polymorphism was found, it is reported that PLA2 allele is associated with increased risk for arterial thrombosis, particularly for myocardial infarction and restenosis after revascularization procedures [42-45]. Furthermore, Feng et al. [46] found that in vitro platelet aggregation can be induced with lower concentrations of ADP and EPI in PLA2 carriers than in PLA1 carriers.

Similar observations were made by Michelson et al. [41]. By measuring increased granule release, GPIIb/IIIa activation and fibrinogen binding, they found increased reactivity to low-dose ADP in PLA2 positive platelets.

In the population of Northern European ancestry, the prevalence of the PLA2 allele is approximately 25% and the frequency of the PLA2/A2 homozygotes about 2% [41]. Feng et al. [46] analyzed 1,422 patients from the Framingham Offspring Study and established the prevalence of the PLA1/A1 homozygotes, PLA1/A2 heterozygotes, and PLA2/A2 homozygotes to be 71.5%, 26.1%, and 2.5%, respectively. PLA2 allele rather high prevalence and its association with arterial thrombosis and increased platelet aggregation arose the question of whether the GPIIIa PLA1/A2 polymorphism could be one of the suggested glycoprotein modifications involved in the pathogenesis of SPS, particularly in the formation of arterial thrombus in this syndrome. Although the relation between the GPIIIa PLA1/A2 polymorphism and venous thromboembolism is not well defined and most studies failed to establish the PLA2 allele as a clear risk factor for venous thrombosis [46,47], the fact that PLA2 carriers in the Kubisz study suffered from both arterial and venous thrombotic events must be taken into account [18]. However, even these partial results suggest that the GPIIIa PLA1/A2 polymorphism cannot fully explain the pathogenesis

of SPS. Therefore it seems likely that other glycoprotein defects or pathophysiological mechanisms should be considered to explain platelet hyperaggregability in SPS [48].

SPS and glycoprotein VI SNPs

Glycoprotein VI (GPVI), a member of the immunoglobulin superfamily, is a platelet transmembrane glycoprotein consisting of 319 amino acids, located in the platelet membrane in noncovalent complex with FcRγ subunit [36]. GPVI is a product of the GP6 gene, which is localized on chromosome 19 (19q13.4) [49]. Since the identification and analysis of the GP6 gene in the 1990s, its numerous SNPs have been identified [50]. However, the clinical importance for haemostasis, if any, as it happens of the majority of polymorphisms, is not yet clear.

Vessel wall damage exposes the subendothelial component collagen to platelets in the blood flow. Interaction of platelets with collagen via the GPVI receptor results in platelet activation and adhesion, processes that are essential for thrombus formation [23].

GPVI was shown, by several *in vitro* and *in vivo* studies, to be essential for activation of integrin for stable adhesion and subsequent signal transduction (via activation of phosphatidylinositol-3-kinase and phospholipase Cγ2) that leads to granule release, activation of GPIIb/IIIa via inside-out signaling, and platelet aggregation [49].

Considering the critical role of GPVI in collagen-initiated signal transduction and platelet procoagulant activity, the observed variations in GPVI content may influence the risk for thromboembolic disorders [51].

The GPVI is a crucial platelet membrane glycoprotein for adequate platelet activation, adhesion, and aggregation. In the past few years, the question of the impact of genetic changes within the GP6 gene on platelet function has emerged, with the identification of numerous polymorphisms in the GP6 gene. In this context, Kotulicova et al. [24] recently reported the prevalence of selected GP6 gene polymorphisms (SNPs rs1613662, rs1671153 and rs1654419) as independent risk factor for deep vein thrombosis in patients with platelet hyperaggregability. Sokol et al. [23] found that the global variability of the GP6 gene may be associated with platelet hyperaggregability in patients with SPS and fetal loss as well. In this context, SPS is regarded as the second most

common thrombophilia (after APA syndrome) that causes recurrent spontaneous abortions or fetal loss syndrome [52-54]. Thus, although these polymorphisms are not the underlying disorders, they could have a modulating effect on the clinical presentation of the syndrome.

The importance of variability in the GP6 gene and in other membrane receptor genes for platelet hyperaggregation was stressed by a recent genome-wide meta-analysis by Johnson et al. [55]. The analysis focused on the evaluation of the genetic influence on platelet functions and identified seven loci associated with platelet aggregation to physiologic agonists (ADP, collagen, and EPI). One of the loci is strongly associated ($P = 4.6 \times 10^{-13}$) with increased aggregation to collagen within the region of the GP6 gene [55]. Though a large number of SNPs have been identified in the GP6 gene to date, their exact relation to platelet function remains unknown, with few exceptions [50].

SPS and Gas6 gene

Growth arrest-specific gene 6 (Gas6) was originally identified as a gene whose expression in fibroblasts was increased by serum starvation and contact inhibition, and was therefore implicated in reversible growth arrest [56]. Gas6, present in α -granules, belongs to the family of plasma vitamin K-dependent proteins, which comprises proteins with phospholipid binding properties conferred by the N-terminal Gla-module. The function of these proteins is essential in haemostasis. Gas6 is localized on chromosome 13 (13q34). It has a high structural homology with the natural anticoagulant PS, having 40% sequence identity, and interacts with Axl/Sky/Mer tyrosine kinases [37,38,57,58].

The mechanism by which Gas6 protein modulates platelet aggregation has not been clearly determined yet, but some authors suggest that it acts relatively late, contributing more in platelet stabilization rather than in the initial platelets aggregate formation, thus enhancing platelet action following their activation by primary inducers (ADP, EPI, collagen) [19,38,59].

Its role in thrombosis was confirmed by several studies in mouse models where Gas6 protein inhibition, by antibodies or Gas6 protein receptors (Mer, Axl, Sky) blocking, leads to a decreased risk of EPI-, collagen-, or stasis-induced thrombosis. Gas6-deficient animals were protected against fatal thrombosis, the development of thrombus was not so rapid, and the clot was significantly smaller than in Gas6-positive individuals. Munoz described the association of Gas6 polymorphism (Gas6 c. 834+7G>A; rs8191974) with stroke and defined the A-allele as less common in patients with stroke [37,60]. The Kubisz study [19] was performed to assess the prevalence of Gas6 polymorphism in patients with SPS and healthy controls in Slovak population. The results of this research are discordant to those of Munoz who found the A-allele to be more prevalent in healthy individuals and very rare in patients with thrombosis. According to Kubisz's findings, the G-allele is equal present in the majority of SPS patients and healthy controls, and there are no significant differences between these two groups in the prevalence of Gas6 genotypes. It is possible that there is no relation between Gas6 polymorphism and SPS indeed. Thus, there is a question whether we may consider Gas6 polymorphism as a causative factor of SPS at all.

However, if the G-allele is supposed to be associated with thrombosis and it is equally common in both the investigated groups, can we say that Slovak population is predisposed to thrombophilia in general? Certainly, the Kubisz study has no evidence for this hypothesis. Probably other genetic mechanisms than Gas6 polymorphism can be involved in the etiology of SPS. In the same patients with SPS,

the authors identified another polymorphism strongly associated ($P = 3.4 \times 10^{-12}$) with fetal loss, the PEAR1 (rs12566888) [55], that is responsible for signaling on the formation of platelet-platelet contacts secondary to platelet aggregation.

However, according to the authors, further studies including more patients and healthy controls are needed to verify the relation of Gas6 and PEAR1 polymorphisms and SPS [11], though their initial findings provide new functional insights into platelet aggregation pathways and may suggest novel anti-platelet therapeutic targets [55].

Conclusion

In initial reports, SPS was seen as an isolated defect in haemostasis. With the increase of the number of diagnosed patients, combinations with other inherited or acquired thrombotic events were reported [61,62].

SPS is associated with both venous and arterial thrombosis and can cause pregnancy-related complications, but the exact incidence in general population is yet to be determined. Although efforts in investigating several platelet GPs as potential causes for hyperaggregation and inherent platelets' activation, the precise defect responsible for the syndrome and the exact pathogenesis of SPS remain not sufficiently explained.

Clinically, this syndrome is quite heterogeneous. In fact it can be silent, or it can be presented by stroke, transient cerebral ischemic attacks, acute coronary syndrome, and arterial or venous thrombosis [63].

In routine hematological screening of hereditary thrombophilia, examination aimed to detect SPS is not included. SPS testing is well known and easy to perform, but, maybe for lacking of practical experience with this kind of thrombophilia, it is not part of the routine thrombophilic screening. Despite this scarce clinical experience, SPS should be seen as a serious risk factor for patient's health. So benefit of SPS testing included in standard screening deserves consideration.

Since cases in which the SPS coexisting with other thrombotic conditions have already been described [9], it is possible that this platelet abnormality may contribute to the so called "multifactorial thrombophilia" in some patients [9,35]. More clinical data will be useful for better understanding this syndrome, especially on the genetic side.

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