Primary Thrombophilia XIV: Worldwide Identification of Sticky Platelet Syndrome

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Sticky platelet syndrome (SPS) is a prothrombotic platelet disorder characterized by increased in vitro platelet aggregation after activation with low concentrations of adenosine diphosphate and/or epinephrine.[1–67] Recently, Favaloro and Lippi[66] provided a commentary on the increasing number of papers published on SPS along the historical timeline, since its initial description in 1988,[3] and in response an update review was also published in this journal.[67] As noted in both reports,[66,67] the condition is not recognized by all workers involved in the study for treatment of thrombophilic conditions. One reason to explain the fact that some researchers recognize SPS as a genuine thrombophilic condition whilst other do not is that not everybody employs the same criteria to define the condition. We and others,[11,53] attempting to standardize its investigation, employ the criteria originally described by Mammen et al[3] to define SPS, and accordingly, our group has been able to show that around 15% of Mexican mestizo persons within the general normal population meet the criteria to identify them as bearers of SPS and that this figure goes up to 60% in Mexican mestizo patients with a clinical marker of inherited thrombophilia. Accordingly, we have been able to gather prospectively a group of 165 Mexican mestizo patients with SPS, 121 of whom (66.7%) display another thrombophilic condition in addition to SPS. Employing the database PubMed, we similarly looked for all entries using the term "sticky platelet," either in the title and/or in the body of the abstract. The salient features of each publication were then further analyzed. The initial search identified a total of 108 papers. Forty-one of them included the combination of words but did not actually describe SPS and were accordingly discarded; 24 papers comprised reviews about SPS and 43 papers described either cases or series of patients; these latter 43 papers were further analyzed. The first paper describing patients with SPS was identified to be published in 1988, and was authored by Mammen et al.[3] Since then and until February 2019, as noted above, 67 papers were identified.[1–67] ►**Fig. 1** depicts the number of papers published as a cumulative timeline, whereas ►**Fig. 2** depicts the countries in which these papers were published. It is interesting to note that the country with the largest number of papers published on SPS is the United States with a total of 14, followed by Slovakia with 12, Germany with 8, and México with 6, whereas Hungary, Turkey, Russia, and New Zealand had only 1 publication each. What is also interesting is the absence of reports from most other geographies (►**Fig. 2**).

A total of 1,783 patients with SPS have been described and published in these 30 years (1988–2019) of reports. The rate of description of these cases has increased in the last 10 years (►**Fig. 1**). The most number of cases have been identified and published in Slovakia ($n = 845$), followed by the United States ($n = 451$), México ($n = 322$), Germany ($n = 88$), and Russia ($n = 70$). The thromboses identified in these patients were both venous and arterial; in some patients SPS was identified together with another thrombophilic condition, either inherited or acquired. ►**Table 1** gathers the salient information from all these publications. Most patients (72%) were treated with aspirin and/or other antiplatelet drugs, whereas 27% were given oral anticoagulants or heparin.

According to several publications, SPS is thought, at least by several investigators, to be the most common inherited

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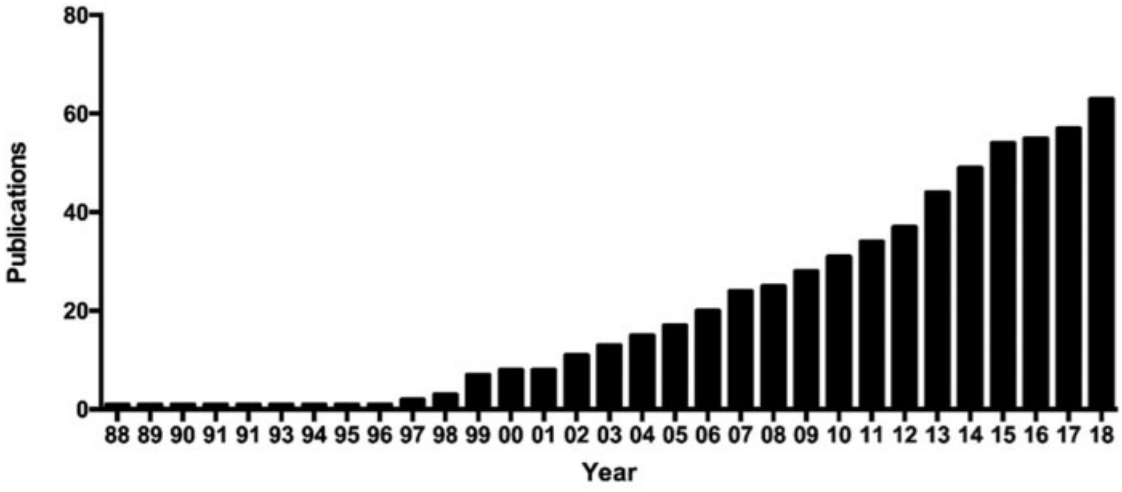

Fig. 1 Cumulative frequency distribution curve along time of papers published on the sticky platelet syndrome between 1988 and 2018 inclusive.

Fig. 2 Countries in which the sticky platelet syndrome has been described between 1988 and 2018 inclusive.

prothrombotic platelet defect and thus likely to be of the greatest clinical importance.[49] The recognition of SPS as a genuine entity has prompted the development of both promoters and opponents to the concept.[66,67] Up to now, the lack of a definite molecular basis for the condition has been a major obstacle for its acceptance by many as a distinct entity and several skeptical scientists remain reluctant to consider this disease as a true distinct clinicopathological entity.[49,66,67] On the other hand, unlike plasma-based hemostasis research work, the study of SPS requires fresh patient material and highly meticulous sample collection and handling; as a consequence, the patients under investigation require blood collection at the time of investigation, and then platelet function testing needs to be performed immediately afterwards by experienced personnel. Some hemostasis experts still consider the aberrant platelet aggregation responses seen in this condition as laboratory artifacts[49]; however, SPS seems to be building up an increasing belief base, if we accept that the increasing publication rate on the topic (66; ►**Fig. 1**), coupled with the additional information presented here, represents increasing acceptance of SPS as a prothrombotic condition. Taking into account the number of inhabitants in each of the countries which have reported cases of the SPS, it is clear that the countries which have made the most contributions on SPS per number of inhabitants are Slovakia and México; this finding reflects mainly the interest in the condition of groups of scientists living in these two countries, headed by

Table 1 Salient features of the patients with the sticky platelet syndrome who have been described in different countries between 1988 and 2018 inclusive

Author	Country	Year	Cases	Location of thrombosis	Treatment
Mammen et al[3]	United States	1988	?	MI	Aspirin
Berg-Dammer et al[4]	Germany	1997	2	Superior sagittal sinus/middle cerebral artery/left subclavian/ left vertebral artery	Heparin/aspirin/catheter/ thrombolysis
Baker and Bick[6]	United States	1999	153	DVT/stroke/MI/retinal vein	Aspirin
Chaturvedi and Dzieczkowski[8]	United States	1999	1	Acute stroke	Heparin/warfarin
Bick[10]	United States	2000	21	Recurrent miscarriage	Aspirin
Weber et al[12]	Germany	2002	34	DVT/retinal vein thrombosis/ portal vein thrombosis/ pulmonary embolism	Heparin/aspirin
Frenkel and Mammen[15]	United States	2003	200	Acute stroke, DVT	Aspirin 81 mg/d
Lewerenz et al[17]	Germany	2004	1	Acute stroke/MI	Aspirin
Kahles et al[21]	Germany	2006	1	Acute myocardial infarction/ pulmonary embolism	Abciximab/stent/antiplatelet therapy/t-PA/heparin
Kubisz et al[20]	Slovakia	2006	128	Acute stroke/MI/DVT/ recurrent miscarriage	–
Fodor et al[23]	Hungary	2007	1	Left internal carotid artery	Aspirin 300 mg/d
Mühlfeld et al[25]	United States	2007	3	Renal allograft rejection/ colonic microinfarctions/ pulmonary embolism/DVT	Heparin/aspirin
Randhawa and Van Stavern[26]	New Zealand	2007	1	Ischemic optic neuropathy	Aspirin 81 mg/d
Ruiz-Argüelles et al[24]	Mexico	2007	46	Thrombosis at younger than 40/recurrent thrombosis/ thrombosis in unusual sites	Aspirin
El-Amm et al[27]	United States	2008	3	Renal allograft rejection	Aspirin
Mears and Van Stavern[29]	United States	2009	1	Ischemic optic neuropathy	Aspirin 81 mg/d
Sand et al[28]	Germany	2009	1	Cutaneous microembolism on fingers	Heparin/aspirin
Bojalian et al[3]	United States	2010	1	Popliteal artery/renal and splenic infarction/left axillar artery/left subclavian artery/ left internal jugular vein	Heparin/embolectomy/aspirin
Loeffelbein et al[32]	Germany	2010	1	Venous and arterial flap thrombosis	Aspirin
Alexandra et al[34]	United States	2011	1	Retinal vein	Aspirin
Gehoff et al[36]	Germany	2011	1	Acute stroke	Aspirin
Rac et al[35]	United States	2011	1	Recurrent miscarriage	Aspirin 325 mg/d
Kotuličová et al[40]	Slovakia	2012	77	Pulmonary embolism/DVT/MI/ acute stroke	–
Kubisz et al[38]	Slovakia	2012	9	2 DVT/4 arterial (acute stroke, MI, arterial thrombosis)/3 both	–
Sokol et al[39]	Slovakia	2012	27	Recurrent miscarriage	Aspirin
Darulová et al[44]	United States	2013	1	Pulmonary embolism	Alteplase/heparin
Ruiz-Argüelles et al[47]	Mexico	2013	100	Thrombosis at younger than 40/recurrent thrombosis/ thrombosis in unusual sites	Aspirin
Šimonová et al[46]	Slovakia	2013	9	Cerebral venous thrombosis/ DVT/pulmonary embolism/ acute stroke/MI	Heparin/aspirin
Tekgündüz et al[42]	Turkey	2013	6	History of thrombosis	Aspirin 100 mg/d
Vasil'ev et al[41]	Russia	2013	70	Thrombosis	Heparin/aspirin

(*Continued*)

Table 1 (*Continued*)

Author	Country	Year	Cases	Location of thrombosis	Treatment
Castillo-Martínez et al[52]	Mexico	2014	1	Cutaneous limb veins	Aspirin 81 mg/d
Hayes et al[51]	United States	2014	64	Acute stroke/DVT/MI	Aspirin
Kubisz[48]	Slovakia	2014	71	Acute stroke	–
Ruiz-Arguelles[50]	Mexico	2014	95	Thrombosis at younger than 40/recurrent thrombosis/ thrombosis in unusual sites	Aspirin
Alsheekh et al[55]	United States	2015	1	Carotid artery	Abciximab/thrombectomy
Sokol et al[53]	Slovakia	2015	23	Recurrent miscarriage	Aspirin
Sokol et al[56]	Slovakia	2015	20	Recurrent miscarriage	Aspirin
Yagmur et al[54]	Germany	2015	48	TIA/ DVT/pulmonary embolism/renal infarction	Heparin/aspirin
Ruiz-Delgado et al[60]	Mexico	2017	77	Recurrent miscarriage	Aspirin
Škereňová et al[63]	Slovakia	2018	37	Recurrent miscarriage	Aspirin
Sokol et al[65]	Slovakia	2018	84	DVT	Aspirin
Sokol et al[62]	Slovakia	2018	360	DVT/pulmonary embolism/MI/ miscarriage/migraine	Aspirin 325 mg/d
Solis-Jimenez et al[61]	Mexico	2018	1	Renal allograft rejection (renal infarction)	Nephrectomy/aspirin

Abbreviations: DVT, deep vein thrombosis; MI, myocardial infarction; t-PA, tissue plasminogen activator.

professors Peter Kubisz in Slovakia and Guillermo Ruiz-Argüelles in México.[49] We hope that the presentation of this information will result in the development of additional interest in other investigators who could eventually contribute to the better understanding and acceptance of the syndrome, its pathophysiology and treatment, with the goal of helping patients afflicted by thrombophilia, which is currently one of the leading causes of death in developed societies.

Conflicts of Interest

The authors disclose no conflicts of interest.

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