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Casos clínicos

Sticky platelet syndrome in a patient with transitory ischemic attack and the family. A case report

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RESUMEN

Antecedentes: el síndrome de las plaquetas pegajosas es una trombofilia hereditaria frecuente, autosómica dominante y caracterizada por hiperagregación de las plaquetas después de concentraciones bajas de inductores de plaquetas (difosfato de adenosina (ADP) o epinefrina). El síndrome se manifiesta con angina de pecho, infarto agudo de miocardio, accidentes isquémicos transitorios, accidentes cerebrovasculares, trombosis retiniana, pérdida recurrente del embarazo, trombosis de arterias periféricas y trombosis venosas, frecuentemente recurrente bajo tratamiento con anticoagulantes orales.
Caso clínico: se comunica el caso de un paciente que tuvo un episodio de isquemia cerebral transitoria en quien se demostró síndrome de las plaquetas pegajosas tipo I, por lo que se indicó profilaxis a largo plazo con la aspirina a dosis bajas (100 mg). Su madre había tenido un ictus y dos veces isquemia cerebral transitoria y la hermana mayor tuvo un aborto espontáneo. Tanto en la madre como en la hermana se demostró síndrome de las plaquetas pegajosas tipo I. Además, en los dos hijos del paciente y en otra hermana se encontró síndrome de las plaquetas pegajosas, sin manifestaciones clínicas. En dos hijos de la hermana mayor de la paciente se encontró síndrome de las plaquetas pegajosas tipo II. En los miembros de esta familia con síndrome de las plaquetas pegajosas se ha empleado aspirina a dosis bajas, con lo que se ha normalizado la hiperagregabilidad plaquetaria. En la hija se necesitó una combinación de aspirina y ticlopidina para abatir la hiperagregabilidad.
Conclusión: los hallazgos son compatibles con la idea de que el síndrome de las plaquetas pegajosas es hereditario y es claro que se necesitan estudios adicionales para definir su causa.
Palabras clave: síndrome de las plaquetas pegajosas, agregometría, adenosin trifosfato, epinefrina, aspirina.

ABSTRACT

Background: SPS is most likely a hereditary, autosomal dominant thrombophilia characterized by platelet hyperaggregation after low concentrations of platelet inducers - adenosine diphosphate (ADP) and/or epinephrine (EPI). It manifests with angina pectoris, acute myocardial infarction (MI), transient cerebral ischemic attacks (TIA), stroke, retinal thrombosis, early pregnancy loss syndrome, peripheral arterial thrombosis, and venous thrombosis, sometimes recurrent under oral anticoagulant therapy.
Case report: We report a case of a patient, who has undergone TIA, was diagnosed SPS type I and uses long-term prophylaxis with low-dose aspirin (100 mg). Her mother had once stroke and twice TIA and her older sister had a spontaneous abortion and both were diagnosed SPS type I. Patient's both children and her oldest sister had only laboratory diagnosis of SPS type I without clinical manifestation. Two kids of patient's oldest sister had SPS type II. In our patient and her relatives low dose aspirin prophylaxis appeared to be sufficient based on control aggregometry examination. The only exception was patient's daughter, where combined therapy with ASA+ticlopidin was required.
Conclusion: There is still a lot of concern about SPS. We believe that this case report and many others support its existence, although it is still a long way out to discover its exact cause.
Key words: Sticky Platelet Syndrome, Aggregometry, Adenosine Diphosphate, Epinephrine, Kindreds, Aspirin.

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Sticky platelet syndrome (SPS) was first described by Holliday at the Ninth Conference on stroke and cerebral circulation in Arizona in 1983.[1] It is most likely a hereditary, autosomal dominant thrombophilia characterized by platelet hyperaggregation after low concentrations of platelet inducers - adenosine diphosphate (ADP) and/or epinephrine (EPI).[2] Clinically, patients may present with angina pectoris, acute myocardial infarction (MI), transient cerebral ischemic attacks, stroke, retinal thrombosis, early pregnancy loss syndrome, peripheral arterial thrombosis and venous thrombosis, sometimes

recurrent under oral anticoagulant therapy.[3] Clinical symptoms, especially arterial thrombosis, often present following emotional stress.[4]

Case report

We report a case of 29-years old female patient, presented with backache and pain in her neck with progressive weakness in the left side of her body while she was playing tennis. She was immediately admitted to the Department of Neurology with the preliminary diagnosis of suspect stroke. Neurological treatment was successful and she was discharged from hospital without any neurological defect. Because of this neurological event she was referred by the neurologist to the examination of thrombophilic states to our center. History taking revealed positive family history of stroke. Her mother suffered a stroke when she was 40 years old and then she suffered also transient ischemic attacks twice during her life. Her grandmother suffered a stroke too and her great-grand mother died from stroke when she was 28 years of age. In her personal history there were neither chronic diseases, nor any thromboembolic events prior to the known neurological event. She had recurrent gynaecological operations and 2 pregnancies without any thromboembolic complications. She denied using contraceptive pills. At physical examination and also in basic laboratory tests such as blood count and basic coagulation tests there were no pathological findings. We investigated the whole board of tests of thrombophilia including: ProC global test, factor VIII activity, activity of natural coagulation inhibitors (antithrombin III, protein C, protein S), screening tests for antiphospholipid syndrome, DNA analysis of gene polymorphisms – factor V Leiden, factor II 20210A, glycoprotein III and aggregometry after stimulation with EPI and/or ADP in 3 concentrations (according to the method by Mammen). Results showed platelet hyperaggregability after stimulation with both, EPI and ADP in each concentration and therefore the diagnosis of sticky platelet syndrome type I was established and lifelong antiplatelet therapy was recommended to the patient. Other thrombophilic state was not found. She was taking low-dose aspirin (100 mg) once a day, which efficiency was verified by control aggregometry after one month from the commencement of this therapy. After 4 months the aspirin therapy was switched to clopidogrel, because of stomach ache and dyspepsia. Results of control aggregometry demonstrated poor efficiency of this therapy and therefore she was switched back to low dose aspirin, but the enterosolvent form was selected. The patient has tolerated this treatment better and until today she has been without any thromboembolic events.

Description of the kindred

The investigation of the patient´s consanguineous relatives was indicated because of hereditary nature of SPS (Figure 1).

Children: Our patient has got two children and in both of them the same diagnosis as in their mother was established by the aggregometry after stimulation with EPI and ADP in 3 concentrations (according to the method by Mammen). The older girl was born in 1994, she was 11-years old at the time of examination and she has not had any thrombosis yet. The antiplatelet therapy by aspirin in dose 30 mg thrice a week was recommended to her, but it was not effective. Results of control aggregometry showed remaining platelet hyperaggregability after both platelet inducers. The therapy was switched to ticlopidin in dose 120 mg twice a day for this reason. Following control aggregometry after one month verified sufficient decrease of platelet aggregability after stimulation by ADP, but hyperaggregability after stimulation by EPI still remained (Table 1). Therefore combination of antiplatelet agents was indicated. The patient has tolerated such treatment without bleeding complications and until today she has been without any thromboembolic event.

The younger boy was born in 1997, he was 8-years old at the time of examination and he has not had any thrombosis yet. The antiplatelet therapy by aspirin in dose 30 mg thrice a week was recommended to him, but it was not effective as well. Despite the escalation of the dose to 50 mg and then to 75 mg once a day, results of next control aggregometry showed insufficient inhibition of platelet aggregability after 3 concentrations of ADP and 2 concentrations of EPI. Dose 100 mg once a day was laboratory verified as effective in this patient.

Mother: Her mother was born in 1948 and she was 57-years old at the time of examination. She has been treated for arterial hypertension, hyperlipidemia and vertebroalgic syndrome. She had suffered a stroke once and transient ischemic attack twice, without any triggering factor. She has not had any venous thrombosis yet and she denied also any pregnancy complications. Results of

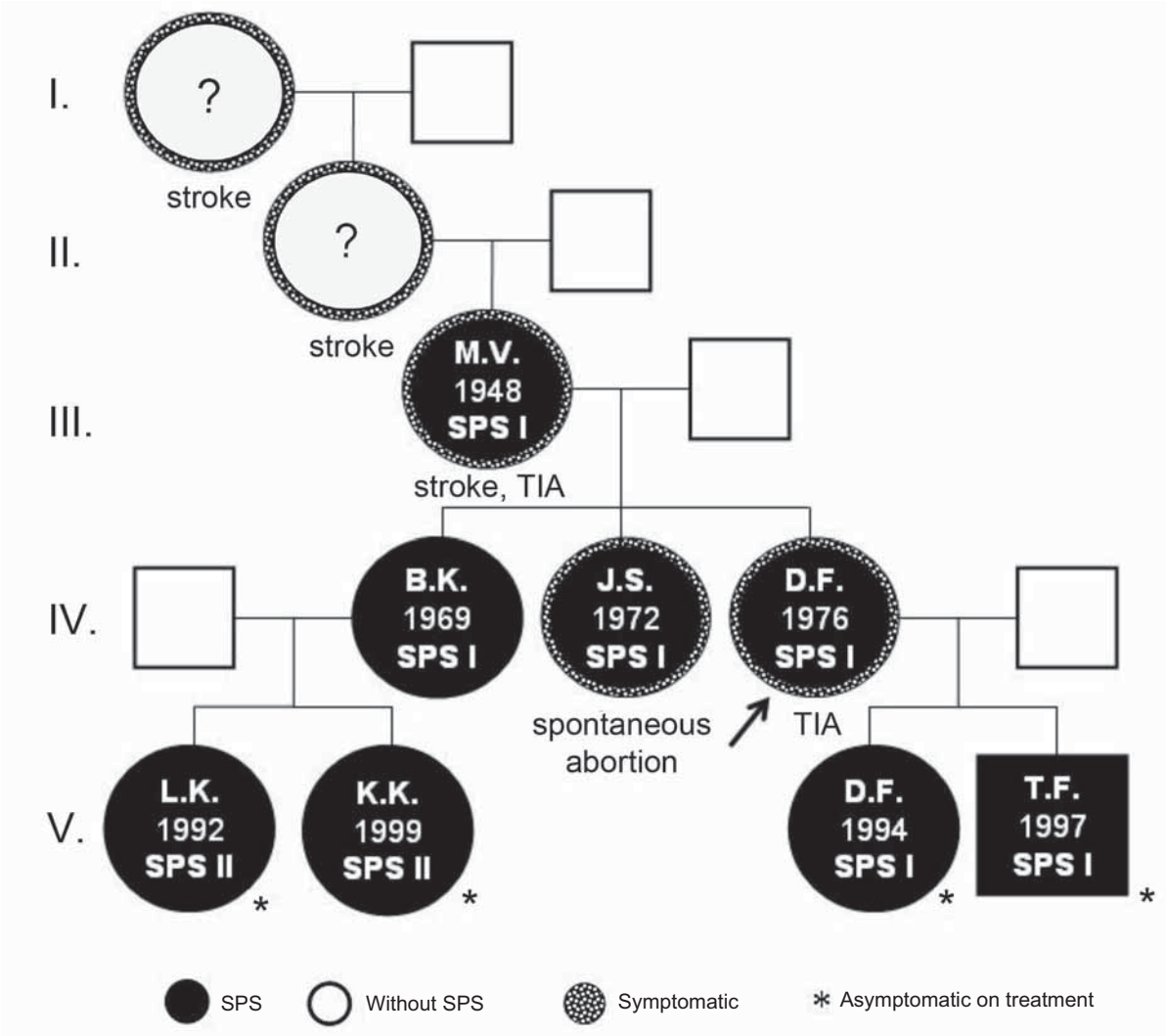

Figure 1. Incidence of SPS phenotype in family tree of the patient

Table 1. Comparison of control platelet aggregometry results in patient´s daughter.

Inducers	*Before antiplatelet therapy*	*ASA*	*Ticlopidin*	*ASA+Ticlopidin*
Platelet aggregation after stimulation by ADP				
ADP 2,3 µmol/l	88 %	82 %	4 %	9 %
ADP 1,2 µmol/l	89 %	83 %	3 %	4 %
ADP 0,6 µmol/l	89 %	3 %	2 %	1 %
Platelet aggregation after stimulation by EPI				
EPI 11 µmol/l	87 %	86 %	87 %	25 %
EPI 1,1 µmol/l	87 %	86 %	90 %	10 %
EPI 0,6 µmol/l	85 %	87 %	89 %	3 %

aggregometry suggested the diagnosis of sticky platelet syndrome type I, the same type as in her daughter. No other thrombophilic state was found. The antiplatelet therapy with low dose aspirin (100 mg) once a day was laboratory and also clinically effective.

Sisters: The oldest sister was born in 1969 and she was 36-years old at the time of examination. She had to undergo a knee surgery twice (because of posttraumatic damages of joint and ligaments) without any thromboembolic complications. She denied using contraceptive pills or hormonal therapy and she has not had any pregnancy-related complications. Results of aggregometry showed hyperagregability after both platelet inducers and the

diagnosis of sticky platelet syndrome type I, the same as in her sister, was established, thus she was indicated for using lifelong antiplatelet therapy. Efficiency of the low dose aspirin treatment (100 mg) once a day was verified one month later. Until now she has been without any thromboembolic events. Investigations of thrombophilic state SPS was provided also in her children. Results of aggregometry suggested the diagnosis of sticky platelet syndrome type II in both children. Because of the different SPS type in the children as compared to their mother, we also examined their father, but no thrombophilic state was detected.

The older sister was born in 1972 and she was 33-years old at the time of examination. She has undergone 2 surgeries with no thrombotic complications in the postoperative period, had no significant comorbidities and no history of thrombosis. She did not use any regular medication prior to the examination, including oral contraceptives. Importantly, she had one spontaneous abortion and one physiological delivery. Aggregometry revealed the diagnosis of sticky platelet syndrome type I. She started using the antiplatelet therapy with low dose aspirin (100 mg) once daily rendering good effect and tolerance.

DISCUSSION

Platelets are intimately involved in the pathogenesis of thromboembolic disorders, especially arterial forms of thrombosis. Although most arterial thromboses develop on the basis of endothelial injury, some do not. In these instances "hyperactive" platelets could be the cause. Hyperaggregable platelets have been described in association with a number of acquired disease entities whereby the cause-and-effect relationship is unclear. In contrast, the sticky platelet syndrome is a congenital disorder.[5] However, the cause of SPS still remains to be discovered, initially it was suggested that glycoprotein receptors on the platelet surface membrane may be involved and thus their abnormality leads to platelet hyperfunction in SPS patients. Abnormalities of GPIIb/IIIa (CD41/61), a receptor for fibrinogen have a crucial role in platelet aggregation and GPIa/IIa (CD29/49b) that serves as a receptor for collagen and mediates platelet adhesion on collagen type I were studied by flow cytometry or molecular and genetic methods as well.[6,7] Some authors suggested that abnormal GAS-6 protein may be engaged in etiopathogenesis of SPS and its polymorphism GAS-6 c.834 + 7G > A was studied, but our own work did not verify this hypothesis.[8,9,10]

One way or another, SPS is probably the third most common hereditary thrombophilia, after resistance to activated protein C (APC-R), as well as it is the second most common thrombophilia (after antiphospholipid syndrome) that causes recurrent spontaneous abortions or fetal loss syndrome[11] and the most common thrombophilia associated with arterial thrombosis with the incidence of approximately 21%.[6,12,13] This syndrome is defined as a platelet hyperaggregability after stimulation by low concentrations of platelet inducers – after ADP and EPI, whilst platelet response to other inducers is normal.[13] By the results of aggregometry in platelet-rich plasma (PRP) SPS is classified as type I (hyperaggregation after both ADP and EPI), as type II (hyperaggregation after EPI alone) and as type III (hyperaggregation after ADP alone). SPS type II seems to be the most common.[12,13] Our patient met the diagnostic criteria for SPS type I and manifested with transient ischemic attack (TIA). Her mother had once stroke and twice TIA and her older sister had a spontaneous abortion and both were diagnosed SPS type I. Patient's both children and her oldest sister had only laboratory diagnosis of SPS type I without clinical manifestation. Above mentioned facts indicate possible autosomal dominant heredity of this thrombophilic disorder. Since the exact cause of SPS remains undisclosed, it is difficult to discuss why the two kids of patient's oldest sister had SPS type II. As a matter of interest, we assessed polymorphisms P2Y12 (H1/H2 haplotype) i742T/C, P2Y12 32C/T, GPVI 13254T/C, PAR-1 (IVSn-14A/T), COX-1 -842A/G, COX-1 50C/T, GPIa 807C/T and GPIIIa (PlA1/PlA2). We found that patient´s siblings and children with SPS type I were carriers of heterozygous genotype GPIa 807C/T. The two daughters of patient´s oldest sister who had the diagnosis of SPS type II were homozygotes for GPIa 807T/T genotype (see figure 2). Thus the GPIa C807T polymorphism might be associated with the SPS type II phenotype, however larger studies are needed to confirm this hypothesis.

The low-dose treatment (100 mg per day) by acetylsalicylic acid (ASA) normalizes platelet hyperaggregability in most of SPS patients and thus protects them against recurrent thromboembolic events. Only in rare cases the higher dose of ASA is needed, no more than 325 mg per day. If the platelet hyperaggregability still remains, other

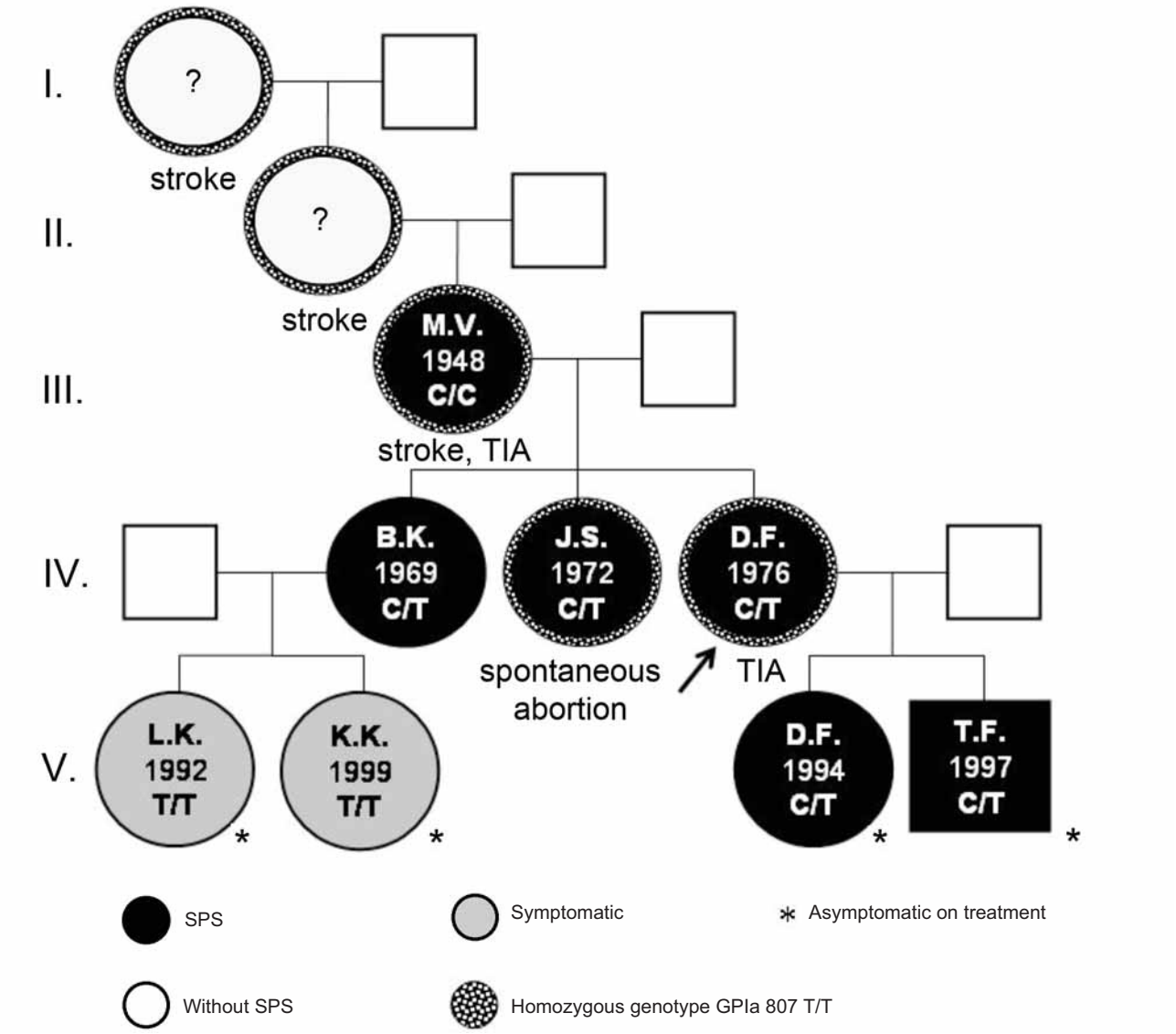

Figure 2. GPIa C807T genotypes in family tree of the patient

antiplatelet agents are indicated, especially ADP inhibitors (ticlopidin, clopidogrel, prasugrel).[7,13] In our patient and her relatives low dose ASA prophylaxis appeared to be sufficient, based on control aggregometry examination. The only exception was patient's daughter, where combined therapy with ASA+ticlopidin was required. Patient´s kindreds have been asymptomatic after the assessment of diagnosis SPS until today thanks to adequate antiplatelet therapy.

CONCLUSION

There is still a lot of concern about SPS. We believe that this case report and many others[14-25] support its existence, although it is still a long way out to discover its exact cause.

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