

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Sticky Platelet Syndrome

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H&O What is “sticky platelet syndrome”?

JA “Sticky platelet syndrome” is the colloquial term used by Dr. Eberhard Mammen for the platelet aggregation abnormalities he identified in 1984 and reported in the medical literature in 1989 while evaluating families with early episodes of stroke and arterial thrombosis. Affected members of such families exhibited none of the thrombophilic predispositions for which testing was available at the time of their presentation, such as antithrombin 3, protein C, and protein S determinations.

However, subsequent platelet function testing with standard platelet aggregometry in platelet-rich plasma revealed what appeared to be a reproducible autosomal dominant inheritance pattern characterized by increased sensitivity to specific agonists. In the index family, increased aggregation sensitivity—amounting to a lowering of the threshold of activation for epinephrine—was identified. Among three generations of this family, a heritable, consistent pattern of aggregation with concentrations of epinephrine to which normal platelets would not respond was observed.

Dr. Mammen defined three types of sticky platelet syndrome in subsequent family studies: type 1, with a lower activation threshold for both adenosine diphosphate (ADP) and epinephrine; type 2, the most commonly found, with a lower threshold for epinephrine only; and type 3, most infrequently observed, with a lowered threshold for ADP alone. These types were consistent and reproducible over several years among families evaluated for early arterial thrombosis and appeared to be associated with venous thrombosis in some members of the identified families.

The current definition of sticky platelet syndrome is an aggregation amplitude of at least 50%, using concentrations of epinephrine and/or ADP 20-fold or more lower (ie, ≤ 20 nanomolar) than the routine activation thresholds in platelet aggregometry in platelet-rich plasma. Aggregation studies must be performed in a laboratory by technicians skilled in platelet-function testing on at least two occasions at least 2 weeks apart in patients not taking medication that might affect platelet function.

H&O Why is there controversy about whether or not sticky platelet syndrome truly exists?

JA First, the term “sticky platelet syndrome” strikes an odd note in the medical literature, and many clinicians who do not typically examine platelet function as part of their “routine” thrombophilic evaluations have been reluctant to accept this humorous albeit very descriptively named phenomenon as real. Further, clinical reports and commentary in the literature by others following Dr. Mammen’s initial publication have described increasingly complicated definitions of sticky platelet syndrome and have likely exaggerated its prevalence and power as a solitary clinical conditioner of thrombosis. As has been found with many other inherited thrombophilias, not all family members exhibiting the aggregation abnormalities have developed clinical thrombosis, and factors affecting clinical phenotype are not yet fully understood. Finally, firm linkage of this familial aggregation anomaly to one of the several known platelet membrane glycoprotein “gain of function” polymorphisms or signaling pathway abnormalities or demonstration of its unique molecular physiology has not been accomplished, leading many to skepticism about its existence as a unique thrombophilic entity. Platelet aggregometry can be difficult to interpret in the absence of other assays of platelet function and its results subject to variability if performance conditions are not carefully controlled; it thus often lends itself to contradictory findings when performed by unskilled technicians. However, Dr. Mammen’s laboratory studies were meticulously conducted and his findings reproducible by others in these index families and others subsequently studied.

The role of platelet hyperfunction in general as a causative factor in arterial and venous thrombosis has continued to be controversial. Evidence from several laboratories has suggested that it may enhance the likelihood of thrombosis in high-risk situations, but its importance as a primary risk factor has been ill-defined.

H&O Have other platelet hyperfunction studies been conducted?

JA Yes. Several investigators have defined platelet hyperfunction with aggregation studies and related the findings to specific genotypes or molecular mechanisms. Dr. Alan Michelson defined the PIA2 homozygous genotype, an inherited abnormality of the IIIa subcomponent of the membrane IIbIIIa complex that causes aggregometric platelet hyperfunction quite similar phenomenologically to the type I sticky platelet syndrome. First identified among the well-defined Framingham population, this abnormality has been linked to a specific leucine-proline substitution that increases fibrinogen binding to IIbIIIa, membrane expression of P-selectin, and, with low-dose ADP, the surface expression of IIbIIIa. Dr. Paul Bray first reported the increase in fibrinogen stickiness of this altered IIIa that enhanced aggregation among patients thought to be at increased risk for coronary artery disease. Dr. Reiner Zotz evaluated the role of this and another polymorphism, the $\alpha 2\beta 1807TT$ mutation, in a large population of patients with coronary artery disease and found that the polymorphisms were equally prevalent in individuals with and without coronary artery disease, but that the presence of the gain-of-function polymorphisms was associated with significantly earlier closure of diseased coronary vessels. Thus, these mutations, each of which may cause aggregation abnormalities similar to those reported in the sticky platelet syndrome, appear to play a role, not in causing coronary atherosclerosis, but in potentiating myocardial infarction in patients with diseased coronary vessels far earlier than in those with “normal” platelet genotypes.

Thus, there is a great deal of evidence suggesting that there are heritable platelet disorders participating in clinical thrombosis that are associated with platelet hyperfunction detectable by platelet aggregometry. However, no cross-correlation study has been conducted specifically evaluating the patients originally studied by Dr. Mammen and no molecular mechanism has been defined for the sticky platelet syndrome he originally reported.

H&O Are potential mechanisms being investigated?

JA Yes. It appears that one family does exhibit the PIA2 homozygosity abnormality described by Dr. Michaelson,

but other mechanisms are likely operative in other families. One candidate is a protein called Gas6, a product of growth arrest-specific gene 6.

Gas6 is a vitamin K-dependent α -granule protein with considerable homology to protein S that interacts with Axl/Sky/Mer tyrosine kinases and has been reported in mouse models to enhance aggregation by affecting the function of both the α -2 adrenergic and ADP receptor. Knockout of Gas6 in mouse models decreases platelet secretion and aggregation, especially at low agonist concentrations. The mechanism of this protein in platelet hyperfunction has not been clear, and recent studies have suggested that its action is relatively late, enhancing platelet function following activation by primary agonist. A recent study by Chen and coauthors suggests that one of the Gas6 receptor tyrosine kinases, Mer, is present in human platelets, and that its knockout impairs platelet aggregation as well. Currently, there is controversy regarding whether this mechanism is operative in human platelets and plasma or whether the phenomenon exists among animals only. Abnormalities in Gas6-Mer interaction might explain to some extent the variability of patterns of activation observed among the families studied by Dr. Mammen. The vitamin K-dependent activity of the protein also hints at a potential therapeutic benefit from warfarin in platelet hyperfunction mediated by this pathway, a possibility that is not considered in the classic anticoagulation lexicon. A well-crafted editorial by the late Lawrence Brass places the Gas6-Axl/Rse/Mer pathway in the complex context of platelet membrane receptor-signaling mechanisms and subsequent thrombus promotion.

H&O Why is it important to know whether or not this syndrome exists?

JA One of the reasons for continuing to study and define sticky platelet syndrome is that it may be the cause of certain currently unexplained clinical phenomena. For example, when examining the various issues associated with the currently defined thrombophilias, there remains a population of patients who experience “idiopathic” thrombosis. This absence of identifiable molecular mechanisms is particularly apparent in patients presenting with arterial thrombosis who do not have the typical diabetic atherosclerotic hypercholesterolemic phenotype, or whose presentation is at an unusually early age.

Many interesting issues are being studied with regard to the cellular contributors to thrombosis, such as inherited inflammatory response genotypes and haplotypes, such as interleukin-1 haplotypes that may affect the expression of procoagulant inflammatory proteins and may create competition for anticoagulant proteins such as protein S.

However, the platelet component of hypercoagulability has been more difficult to define in research thus far. Part of the challenge is in finding out how to test for these components. Clinically, premature arterial thrombosis and sometimes venous thrombosis appear idiopathic because the patients in whom they present do not express the classic thrombophilia genes. The inherited thrombophilias that have been well defined are infrequent among African American and Asian populations, leaving a large group of people experiencing conditions such as retinal vein thrombosis, early stroke unrelated to hypertension, and diabetes, with no clear etiology and no specific recommendations for prevention strategies.

The original white family in which sticky platelet syndrome was first described exhibited clinical thrombosis in the absence of these other conditions (the family has been fully evaluated for the majority of identified heritable and acquired thrombophilias), making this syndrome an interesting candidate in terms of possible underlying causes for otherwise unexplained early stroke and other thrombosis. This family experienced early myocardial infarction and stroke in a pattern that appeared to be one of autosomal dominant inheritance. Arterial thrombosis and to some extent venous thrombosis, particularly retinal vein, among these individuals appeared to be associated only with consistent platelet hyperfunction with specific agonists.

It has been difficult to define nonclassical risk factors for coronary artery disease and heart disease in general. Large studies have come to different conclusions regarding whether or not the *PLA2* genotype or 807TT polymorphism are involved. These abnormalities appear to be risk factors in some populations but not in others for reasons that are not well explained.

H&O How does the method of testing platelet function affect this area of research?

JA There is no gold standard for testing platelet function. Most of the systems are artificial, *ex vivo*, and involve

manipulating cells from single blood specimens at one point in time. All are vulnerable to conditions of sampling, including, importantly, patient medication. It may be that the originally described sticky platelet syndrome is actually a collection of syndromes with a variety of mechanisms. The various ways in which platelet function testing is done—platelet function analyzers, aggregometry with and without specific quantitative secretion studies, flow cytometry, and others—are cumbersome, time-consuming and expensive. Many hospitals are not able to perform or interpret them. However, for patients in whom there is no clear explanation for an arterial event, it would certainly be appropriate and important to try to test platelet function. If laboratories and investigators across the country—and the world—could work together in gathering these data and reanalyzing data from previously studied patients and stored DNA, the questions of whether or not sticky platelet syndrome exists and what its true association is with these clinical phenomena and other identified molecular mechanisms of platelet hyperfunction could be settled once and for all.

Suggested Reading

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