Thrombotic complications in thalassemic patients: Contribution of red blood cells and platelets

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Thalassemia is the most common form of congenital hemolytic anemia caused by partial or complete deficiency in one of the major α or β proteins of hemoglobin A (1). Improvement of the standard care of homozygous patients, with almost doubling of their life expectancy, unveiled a higher incidence of additional complications which have not been previously recognized. In particular, profound haemostatic changes have been observed, manifesting biochemical evidence of hypercoagulable state, with an increased risk of developing venous and arterial thrombosis, mainly in splenectomized patients with β-thalassemia intermedia. These patients have increased number of circulating pathological red blood cells (RBC) and platelets (2).

Extra- and intra-cellular forms of iron, non-transferrin-bound iron (NTBI) and labile plasma iron (LPI), respectively, have been found in thalassemia and other haemolytic anemias. These iron species are known to catalyze the formation of free oxygen radicals inducing oxidative stress (3). It has been shown that secondary to continuous oxidative stress, thalassemic RBC membrane expresses abnormally high levels of negatively charged phospholipids, particularly phosphatidylyserine. The negatively charged lipid membrane surface assembles the prothrombinase complex, resulting in increased thrombin generation, which in turn promotes fibrin clot formation. In addition, oxidative stress contributes to activation of platelets (4) as shown by increased circulating platelet aggregates, shortening of platelet survival, caused by increased consumption, elevation in urinary metabolites of thrombexane A2 and prostacyclin, and last but not least increased fraction of activated platelets measured by flow cytometry of CD62P (P selectin) and CD63 (5).

In the report of Goldschmidt et al. (6), platelet adhesion under flow conditions, the primary event in thrombus formation, was studied in thalassemia using the cone and platelet analyzer which evaluates whole blood platelet adhesion on a thrombogenic surface under flow conditions (7). The results demonstrated that platelet adhesion under flow was increased in thalassemic patients compared to controls. The effect was more prominent in patients who experienced arterial and venous thromboembolic events. Additional increase in platelet adhesion was found in splenectomized patients with a higher platelet count.

Moreover, the role of thalassemic RBC in conferring a hyper-adhesive phenotype to the platelets was confirmed by an increase in normal platelets surface coverage and average size when reconstituted with thalassemic RBC. However, despite the cumulative laboratory data and clinical evidence of thromboembolic events in certain groups of thalassemic patients (1, 2), the potential benefit of antithrombotic therapy has not yet been established. The application of the cone and platelet analysis, in addition to other diagnostic criteria, might help to identify thalassemic patients at a high risk for developing thromboembolic events, which might benefit from preventive therapy with anticoagulants and/or platelet aggregation inhibitors and may also be used to monitor their effects. To verify these assumptions prospective clinical trials are warranted.

References

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