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α1-antitrypsin and the maintenance of hemostatic balance

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doi:10.3324/haematol.2009.006882

Serine protease inhibitors, known as serpins, belong to a superfamily of proteins that are the quintessential regulators of extracellular peptidase pathways.[1] Serpins prevent the deleterious effects of excessive peptide bond hydrolysis. The principal determinant of serpin specificity appears to be the P1 residue localized within the substrate recognition sequence of the reactive center loop.[2] A serine protease and its specific serpin form a tight inactive complex after cleavage of a scissile bond between P1 and P1' residues. Antithrombin is the principal serpin involved in the regulation of blood clotting proteinases but it differs from other serpins in having several multiple target proteinases such as thrombin, factor Xa, factor IXa, factor XIa and factor XIIa. Its importance as a major regulator of thrombin generation is well demonstrated since the initial publication of antithrombin deficiency.[3] Alpha1-antitrypsin has major homology with antithrombin, but its major substrate is the leucocyte elastase, with accessory inhibitory activity toward trypsin, chymotrypsin and activated protein C. P1-P1' residues in antithrombin are constituted of the Arg 393-Ser 394 residues when this bound is Met 358-Ser 359 in α1-antitrypsin.

In 1978, Lewis *et al.* described the first report of α1-antitrypsin Pittsburgh (Met 358 to Arg mutation) as a variant causing severe hemorrhagic disease in a young boy born in 1966 who died at the age of 14 of a huge hematoma of his leg and abdomen in 1981, after more than 50 severe bleeding episodes during his short life.[4,5] We described, in 1992, a second case of α1-antitrypsin Pittsburgh in a 15 year-old boy during a routine preoperative laboratory investigation before an operation.[6,7] We have been following this case since 1990 and he is now 35 years-old. He has had an uneventful life except for one bleeding episode of the right buttock after a minor trauma that required surgery due to compression of the sciatic nerve.[7] Since then he has never experienced new bleeding episodes. In this issue of the journal, Hua

et al.[8] describe 2 new cases of α1-antitrypsin Pittsburgh and the first history of family transmission of the mutation from one father to his daughter.[8] The father presented several bleeding episodes after mild triggering factors and his daughter had pelvic hematoma following surgery for ovarian hematoma due to rupture of an ovarian corpus luteum. Both patients presented with mild bleeding tendency in agreement with the clinical features depicted by the second patient we reported.

What could explain the discrepancy between the first case of α1-antitrypsin Pittsburgh who died of severe bleeding compared to now 3 other cases who have experienced only mild bleeding tendency after triggering events? We can speculate that the first case had maybe another bleeding disease associated with α1-antitrypsin Pittsburg mutation, as the initial description reported an abnormal bleeding time. On the other hand, and as reported in this issue, patients with α1-antitrypsin had normal platelet aggregation except when thrombin was used as an agonist. That was probably due to inhibition of the low dose of thrombin used and it would have been of interest to demonstrate that higher doses of this platelet agonist overcome this inhibition. The second explanation is the inhibition of protein C associated with the variant form of α1-antitrypsin.[9,10] In a detailed evaluation of the second case we analyzed the mechanism of protein C inhibition: in the presence of α1-antitrypsin Pittsburgh protein C can be activated but is abnormally rapidly cleared by this variant.[7] The very low levels of protein C observed in the second reported case, as well as in these 2 new reports, could partially explain the discrepancy observed. In a plasma sample kept frozen for more than ten years from the original case, protein C level was only slightly decreased (62%), but α1-antitrypsin/protein C complexes were still detected.[7] We can now reconsider the consequences of α1-antitrypsin Pittsburgh and affirm with more certainty that it is associated with a mild bleeding tendency, bleeding episodes occurring after triggering events such as mild trauma, surgery or follicle rupture. It also raises questions on prophylactic treatment in this young woman who experienced ovarian hematoma after ovulation, and on treatment procedure in case of pregnancy, a problem that is absent in classical forms of hemophilia. The autosomic transmission of the disease could also lead to ethical considerations concerning genetic screening of the variant in case of pregnancy in women expecting a daughter. In order to overcome these difficult issues we will have to update information among clinicians in charge of patients who are carriers of this orphan disease.

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