The thrombomodulin resistance in prothrombin Belgrade mutation carriers

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Introduction: The prothrombin Belgrade (FIIc.1787G>A) mutation leads to Arg596Gln substitution, which impairs binding of antithrombin to thrombin and results in antithrombin resistance in mutation carriers. Besides antithrombin resistance, increased endogenous thrombin potential and decreased prothrombin clotting activity with normal prothrombin antigen was reported in carriers1,2. However, the thrombin/thrombomodulin interactions in Belgrade mutation carriers have not been elucidated so far.

Aim: We aimed to analyze the effects of the prothrombin Belgrade mutation on thrombin/thrombomodulin interactions in a large Serbian family with this mutation.

Methods: Plasma samples from 19 family members (10 mutation carriers and 9 non-carriers) were tested. Six out of 10 carriers developed thromboembolic events, while 4 were asymptomatic (Table 1). Not one subject without mutation suffered thrombotic episode. We tested thrombin/thrombomodulin interactions using previously described method based on fibrinogen clotting assay3. The Oxyuranus scutellatus venom with phospholipid and CaCl2 was used for prothrombin activation. The activity was determined by fibrinogen clotting assay performed with 20μg/mL recombinant soluble thrombomodulin (+TM) or without (-TM) (Figure 1). The results were normalized with standard human plasma (100%) and residual activity ratio was calculated (+TM/-TM).

Results: The residual activity ratio was significantly increased (p<0.001) in mutation carriers (18.94 ± 2.30) in comparison to non-carriers (14.5 ± 2.91), indicating the presence of thrombomodulin resistance in prothrombin Belgrade carriers (Figure 2). The increased residual activity ratio was associated with prothrombin Belgrade mutation, regardless carriers’ age and gender.

Conclusion: Our results indicate that both antithrombin and thrombomodulin resistance are involved in complex mechanism by which prothrombin Belgrade mutation influences haemostatic balance and leads to thrombophilia.