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Commentary

Severe Thrombophilia in Idiopathic Fatal Pulmonary Embolism

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Pulmonary embolism is caused by blockage of an artery in the lung due to a clot that travels from elsewhere in the body. The main causes are stasis, surgery and cancer, but older age, use of oral contraceptives, and prior unprovoked venous thromboembolism in non-anticoagulated patients are also clear risk factors for pulmonary embolism (Kline and Kabrhel, 2015). When pulmonary embolism causes sudden death and common risk factors are not identified in young decedents, thrombophilia tests are requested, but only factor V Leiden and prothrombin G20210A are sequenced. However, they play little role in fatal pulmonary embolism (Tang et al., 2011). Thrombophilia is an abnormality of blood coagulation that increases the risk of thrombosis (Heit, 2007). It may be congenital or acquired. Congenital thrombophilia may be caused by an excess activity of coagulation factors or by the inefficient inhibition of certain coagulation factors by natural anticoagulants. The main causes of congenital thrombophilia are Factor V Leiden and Prothrombin G20210A, although they provoke mild risk of thrombosis (Rosendaal and Reitsma, 2009). However, deficiencies of natural anticoagulants (antithrombin, Protein C, and Protein S) significantly increase the risk of thrombosis with an estimated risk of thrombosis of up to 50-fold for the antithrombin deficiency (Lijfering et al., 2009).

The work of Halvorsen and coworkers argues the requirement of a thrombophilia study that includes the assay of anticoagulants antithrombin, protein C, and protein S in those decedents beyond idiopathic fatal pulmonary embolism. They also study other genes related to thrombophilia in these samples, but they only find association with mutations in natural anticoagulants (Halvorsen et al., 2017). This thrombophilia study is justified since the anti-coagulant deficiencies are hereditary disorders. Knowledge of the anticoagulant-deficiency justifies the thrombophilia study of the family members and may help physicians in the management of certain situations with high risk of thrombosis such as pregnancy, birth control, or any surgery. The anticoagulant function of antithrombin, protein C, and protein S may be easily evaluated by functional tests. Unfortunately, biochemical-based blood testing for natural anticoagulants is not feasible in postmortem samples and the only tool available is the gene testing. After well-defined selection criteria, the cohort in which Halvorsen and coworkers perform whole exome sequencing (WES) with collapsing analysis for cases *versus* controls is small, but allows the identification of 13.2% cases with severe thrombophilia due to natural anticoagulant deficiency. This result completely supports the sequencing of *SERPINC1*, *PROC* and *PROS1* genes in cases of idiopathic fatal pulmonary embolism.

One of the questions that arise from the study is: What is the underlying cause for the rest of cases? As authors address in the paper, WES may not detect those variants in non-coding regions neither deletions nor gene rearrangements. Indeed, next-generation sequencing techniques using densely placed probes throughout the entire genes including non-coding regions or multiplex ligation-dependent probe amplification (MLPA) would be required to detect gross deletion and duplication variants. Those mutations in genes responsible for transcriptional and translational regulation are also not detected. For instance, variations in long non-coding RNAs and miRNAs could be responsible for the abnormal transcription of the mRNA or the aberrant translation of the protein (Salloum-Asfar et al., 2016). Antithrombin, protein C, and protein S are glycoproteins. WES cannot detect variants that affect the final glycosylation of the protein. In fact, it has been recently described that congenital disorders of glycosylation may influence the glycosylation of antithrombin and, therefore, its final secretion in antithrombin-deficient patients in which *SERPINC1* has no mutations (de la Morena-Barrio et al., 2016). Glycosylation may have great relevance to the function as has been reported for antithrombin and protein C (Martínez-Martínez et al., 2012; Gleeson et al., 2015). As a consequence, all those alterations in the glycosylation of natural anticoagulants may result in a functional deficiency. Additionally, Halvorsen and coworkers detect new variants in *SERPINC1* and *PROC* genes that should be studied and characterized to understand the effect of the mutation and to determine the frequency in the population or in selected cohorts. Among the mutations identified in *SERPINC1*, antithrombin Cambridge II variant was not detected, even though it is considered the most common mutation among antithrombin deficiencies. This is explained by the fact that this mutation is an ethnic-specific variant, rare in Africans and Asians. In addition, the analysis pipeline removes any variants with allele frequency higher than 0.1%. There are other

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variants detected in *SERPINC1*, *PROC*, and *PROS1* whose effect is described by other studies in which the same residue is affected although the change is not the same (Halvorsen et al., 2017). All these mutants should also be further characterized to better know the effect or the mechanism by which they provoke the deficiency.

Further studies are needed to evaluate the role of severe thrombophilia in larger cohorts in additional fatal pulmonary embolism cases beyond idiopathic pulmonary embolism. However, the result obtained in this phenotypically well-defined population clearly justifies the evaluation of severe thrombophilia in out-of-hospital fatal pulmonary embolism.

Conflict of interest

The author has no conflicts of interest.

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