G24 Fatal Pulmonary Thromboembolism and Hereditary Thrombophilias

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The goal of this presentation is to present to the forensic community the role that hereditary thrombophilias may play in deaths due to venous thromboembolism (VTE). Forensic pathologists will understand the availability and usefulness of postmortem DNA testing for hereditary thrombophilias in deaths due to thromboembolic events.

This presentation will impact the forensic community and/or humanity by showing how any and all data generated by increased postmortem testing could bring illuminating information to the medical literature, allowing forensic practice the ability to keep pace with this important and rapidly developing field, and potentially contribute to the reduction of morbidity and mortality and the enhancement of public health.

The autopsy dissection, personal and family medical histories, and ancillary studies pertaining to pulmonary embolism (PE) are important components in the investigation of these deaths. But, the detection of a PE at autopsy and even that of apparent underlying risk factors do not necessarily signify the end of the investigation. Molecular analysis for genetic risk in selected cases might further explain fatal outcomes in persons in whom causality is inadequately explained. Also, on occasion, no apparent predisposing conditions are identified. Hereditary thrombophilias may play a causal role in the development of PE in some of these deaths. With the availability of postmortem molecular testing, their significance in such deaths may be better understood. Most importantly, beyond more accurate death certification, these tests have the potential to reduce morbidity and mortality for surviving family members.

Pulmonary thromboembolism is commonly diagnosed in forensic pathology practice, as it often causes sudden death. It is attributed to a wide variety of predominantly acquired etiologies. Although likely etiologically multifactorial, some commonly diagnosed proximate causes include: surgery, pregnancy, injury or relative inactivity of any cause, cancer, obesity, or serum hyperviscosity. On occasion, no apparent predisposing conditions are identified. In these instances, occult hereditary thrombophilias may play a contributory causal role.

Currently, there are DNA techniques that allow for the postmortem diagnosis of some hereditary thrombophilias. These include Factor V Leiden (FVL), Prothrombin (PT), and Methylenetetrahydofolate reductase (MTHFR) mutations. Less common abnormalities involving antithrombin III, protein C and S, plasminogen, dysfibrinogenemia, hyperhomocysteinemia, and antiphospholipid antibodies were not tested for, as functional and serologic diagnostic assays are ill-suited for postmortem blood.

Resistance to activated protein C, the most potent endogenous anticoagulant, is due to a mutation of the factor V gene (i.e., the Leiden mutation) which results in decreased control of thrombin generation. The G20210A autosomal dominant mutation in the prothrombin gene is associated with an increased amount of prothrombin, which promotes the formation of thrombin. Hyperhomocysteinemia (plasma homocysteine concentration >15 ?mol/L) is a risk factor for venous (and arterial) thrombosis. Increased concentrations of homocysteine are partly determined by enzymes involved in its metabolism. Some mutations in methylenetetrahydrofolate reductase (MTHFR) and cystathione-B-reductase (CBS) are associated with elevated concentrations of homocysteine.

At the Office of Chief Medical Examiner of the City of New York, 124 deaths (of 15,280 undergoing autopsy) were caused by PE between December 2000 and September 2003. Of those, 34 postmortem blood samples from persons having one or more of the selection criteria were analyzed by a molecular fluorescence method (FRET) for FVL, PT, and MTHFR mutations. Characteristics of decedents who were candidates for these tests were based on widely used clinical criteria and included: age < 45 years, pregnancy-related deaths, history of recurrent or unexplained stillbirths, oral contraceptive pill use, hormone replacement therapy, treatment with chemotherapy, weak risk factors (long flights, car rides, or slight obesity), or deep venous thrombosis of undetermined etiology.

Heterozygous mutations involving FVL (1 case), PT (3 cases), and MTHFR (8 cases), as well as a single homozygous mutation for MTHFR, were detected, a total of 35% of those tested. Five deaths were clearly causally related to one or more of these mutations. The possibility of causal relationships in the remaining 29 deaths is discussed.

Venous Thromboembolism, Thrombophilia, Hereditary

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