Health Experts Meet to Discuss Genetic Testing for Factor V Leiden

The incidence of venous thrombosis in the United States is estimated to be 1.2 cases per 1000 persons per year, with cases occurring more frequently with increasing age. Thrombosis increases morbidity and contributes to an estimated 60,000 deaths each year. Furthermore, approximately 5% of the population may have inherited thrombophilia (a genetic defect that predisposes them to thrombosis), with the Factor V (FV) Leiden mutation being one of the more prevalent mutations.

Last April the Centers for Disease Control and Prevention (CDC) convened a meeting of experts to discuss current information about FV Leiden. Conference participants included experts in bleeding and clotting disorders from CDC, clinical practice, research institutions, and laboratories. Because only limited outcome data on FV Leiden are available, the meeting was not designed to develop recommendations. Rather, it provided a forum for researchers and clinical experts to discuss which types of information are needed for FV Leiden screening to become an effective public health/diagnostic tool and which issues require further research.

Although the primary focus of the meeting was to discuss FV Leiden testing, it became clear that this issue could not be addressed without considering the broader issues surrounding genetic testing. Presentations were made on the relationship of genetics and public health; genetic testing; genetic risk factors for thrombotic disease; the relationship between FV Leiden and thrombotic risks associated with hormone replacement therapy (HRT), oral contraceptive (OC) use, and pregnancy; and laboratory issues involved in genetic testing. The following are brief synopses of these issues.

Genetics and public health

Although the role of genetics in public health is receiving increasing recognition, there are not practice guidelines for genetic testing, thus patients are not identified consistently. Effective public health leadership is needed to translate genetic discoveries into action plans to improve health and prevent disease. Specifically, the objectives of collecting genetic information should be to increase understanding about the nature and scope of hereditary conditions and to provide useful information for individuals at risk.

Genetic testing

Usually genetic testing is conducted to diagnose conditions, determine carrier status, or determine susceptibility. Evidence-based testing begins with a well-defined clinical problem and a genetic test that is thought to contribute to either the work-up or management of the problem. Then, data must be gathered to confirm or disprove the hypothesis. This scenario holds true for FV Leiden. Because the potential health benefits from FV Leiden testing are significant, a systematic study to define the clinical utility of FV Leiden testing is needed. Before such a study can begin, however, efforts are needed to determine the selection and size of the study population, the intervention to be used, the study design, and the clinical endpoints to be examined.

Genetic risk factors for thrombotic disease

Genetic hypercoagulability was first described in 1965, with the identification of antithrombin III deficiency (AT-III) as a risk factor for thrombosis. Since that time, several other hereditary risk factors have been identified. These include protein C and protein S deficiencies, resistance to

activated protein C (APCR), FV Leiden, and, most recently, prothrombin G20210A gene mutation. The most common combined defect is dual heterozygosity for the FV Leiden and prothrombin G20210A mutations. Studies indicate that the risk ratio for the development of thrombosis among persons with any of these genetic variations is highest for persons homozygous for FV Leiden, followed by those with AT-III and persons heterozygous for FV Leiden. Environmental and other risk factors can interact with genetic risk factors (e.g., age, a history of recurrence, and OC and HRT use by women with a family history of thrombosis) to further increase the risk for thrombosis.

Relationship between FV Leiden and HRT, OC use, and pregnancy

Some studies have found a higher risk of venous thromboembolism among HRT users with APCR, low antithrombin III, and high factor IX levels. However, some protective effects against arterial thrombosis from HRT has also been found, although not among women with FV Leiden.

Studies of the effect of OC use on thrombotic risks have found conflicting results, likely because of biases such as age differences in the study populations and preferential prescribing of the newer, low-dose-estrogen OCs. While FV Leiden screening may be potentially useful in some populations of OC users, the cost-prevention and other effects of such screening should be heavily considered. As an example, several thousand women would have to forego the use of OCs to prevent one death.

Thromboembolism is the leading cause of maternal mortality. Other pregnancy complications relating to hypercoagulability include a) preeclampsia, b) recurrent fetal loss, c) intrauterine

growth restriction, and d) abnormal placental vasculature. The main heritable causes of thrombophilia–protein C, protein S, and AT-III deficiencies–account for only a small proportion of pregnancy-related thromboses. Depending on the prevalence of FV Leiden among pregnant women who develop thrombosis, screening could be done as part of general prenatal screening or on a limited basis for women who have had a previous thrombotic event or who have a strong family history of thrombosis.

Laboratory issues involved in genetic testing

Before routine testing for thrombophilia is implemented, it is important to determine whether test results will help prevent episodes of thrombosis. Currently, there are problems with results from laboratory testing for genetic thrombotic disorders, including misclassification, inaccuracy, and the confounding effects of other conditions such as pregnancy and anticoagulation therapy. Most laboratories cannot determine the analytic validity of genetic testing, and more data are needed to refine estimates. These data could be collected as part of routine practice or could be method- or laboratory-specific. Also, studies of laboratory testing for FV Leiden, protein C activity, and antithrombin activity have shown wide discrepancies in results. Additional studies are needed to determine whether these errors are occurring (i.e., are they concentrated in poorly performing laboratories) and whether the technical errors are correctable (or even detectable) by the laboratory.

Conclusions

Following the presentations, the participants and presenters broke into groups to discuss four key areas (reproductive issues, family testing issues, testing for individuals, and research priorities) related to FV Leiden testing. The participants concluded that much more research was needed

before any recommendations could be made to routinely screen for genetic clotting defects. However, they identified the following areas as research priorities:

- Studies of the safety/benefit of HRT for post-menopausal women who have FV Leiden or a family history of thrombosis
- Studies on the risk for thrombosis among pregnant women
- Studies on the risks for thrombosis among young women using OCs

  Studies in minority populations who have low FV Leiden prevalence but a high prevalence of thrombosis