

Is Factor V Leiden An Important Risk Factor For Thrombosis?

A balance exists between procoagulant forces as represented by activated clotting factors and naturally occurring anticoagulants, especially protein C. This balance can be disrupted by inheritance of certain pro-thrombotic genetic risk factors, or by circumstantial clinical factors like cancer, immobilization, age, surgery, pregnancy and postpartum, estrogenic hormones and oral contraceptives, certain drugs used in cancer therapy, and inflammatory diseases^{1,4,5}.

By 1993 it was known that activated protein C was a crucial natural anticoagulant, which functions by inhibiting activated procoagulant factors VIII and V. A serendipitous laboratory observation that year led to the discovery of an inherited mutation of factor V which was resistant to the anticoagulant effect of protein C, a phenomenon coined "APC resistance". For complex reasons, impairment of the degradation of factor VIIIa also occurred in these patients. The slower than normal degradation of mutant factor V leads to increased thrombin production and hypercoagulability. This mutation subsequently was named Factor V Leiden (FVL) after the Dutch city where it was first reported¹.

Prevalence

FVL is the most common inherited thrombophilia. Several European and American case series of venous thromboembolism (VTE) found APC resistance in 20-60% of cases studied. In certain areas of Northern Europe, Greece, and the Middle East FVL has been found in 10-15% of healthy asymptomatic individuals, while in Italy and Spain prevalence was 2-3%. In Caucasian Americans the average incidence was 5.2%; however, it is rare or absent in the Far East Asian, black African, and indigenous populations of America and Australia. This pattern suggests that the mutation occurred after the "out of Africa exodus" and the subsequent separation of the human races about 21,000 years ago. Thus, it seems that the absolute numbers of individuals with this thrombophilic trait worldwide are exceedingly high¹.

Natural History of Heterozygotic FV Leiden

Studies of patients with a first VTE episode revealed FVL in 15-20% of cases³. In series of patients with recurrent VTE, FVL was found in 50%. On the other hand, the lifetime risk for VTE in asymptomatic patients is only 10%, which indicates that this is a mild thrombophilic state. Although the FVL mutation produces lifelong hypercoagulability with about a 4-5 fold increase in VTE risk, the vast majority of carriers never have a thrombotic event. From a different perspective, a population of FVL may expect 1-2 VTE events/1000 persons per year⁵. When these occur, most are deep venous thromboses (DVT); pulmonary embolism as a presentation is not common¹. More importantly, the majority (50-75%) of events are provoked by a circumstantial clinical risk factor as described above, which triggers the event². An example is that heterozygotic women with FVL using oral contraceptives have a 30 fold increased risk of VTE, and with pregnancy they have increased maternal and fetal complications¹.

The FVL heterozygotic state has not had a significant negative impact on survival¹. But as individuals with FVL age, they are very likely to encounter medical situations associated with hypercoagulability such as orthopedic and abdominal surgery, immobilization, and cancer. Any one of these factors may change the risk of VTE from low to high and raise the necessity of careful prophylaxis to prevent thromboembolism.

Furthermore, in societies where FV Leiden and other thrombophilic factors are common, many individuals may be expected to carry more than one genetic risk factor. The two most prevalent thrombophilic factors occurring in Caucasians of European ancestry are FV Leiden (5-10%) and the prothrombin G20210A mutation (1-3%). A combination of these two mutations in the same person would be expected to occur at a frequency of 1-2 per 1000¹. Double heterozygotes are at far greater risk for thrombotic events, with a 20 fold increase in venous thromboses^{5,8}.

Homozygous FV Leiden

The incidence of homozygosity is about 0.06 to 0.25% in population

groups derived from Northern Europeans, or about 1:5000. This type of thrombophilia is much more serious than heterozygotic FVL with a relative risk for thrombosis about 50-80 fold higher than normal. Most cases present at a much younger age and are often women taking oral contraceptives (> 100 fold increase in thrombotic risk). Virtually all homozygotes experience one thrombosis during their lifetimes, and most experience multiple events^{2,7}.

Therapy

Most experts believe that all patients should receive antithrombotic prophylaxis when exposed to clinically important acquired risk factors whether or not they have thrombophilia. Prophylaxis regimens are the same for normal and thrombophilic patients. Treatment of an acute thromboembolic event likewise is not different. Standard anticoagulant regimens apply, but the duration of therapy usually is individualized depending on the clinical presentation. Assessment of a first thrombotic event includes a number of important clinical issues, such as whether the VTE is superficial or deep, proximal or distal, provoked or unprovoked, associated with a PE or not, and if a PE was life-threatening. Guidelines for treatment duration exist for each of these clinical circumstances and vary from 6 weeks to indefinite, but the standard for an uncomplicated DVT/PE provoked by a reversible risk factor is at least 3 months⁶.

The duration of anticoagulant therapy for FV Leiden patients after a first VTE is somewhat controversial. The purpose of extended anticoagulation ("secondary prophylaxis") is to prevent a recurrent thrombosis. This may be a complex decision in FV Leiden patients as it depends on an estimate of the risk of a subsequent thrombosis versus the risk of major bleeding. Some experts recommend at least 6-12 months for a first VTE for thrombophilic patients. Others argue that since the risk of recurrence has proved to be only slightly higher than normal in FVL, in the absence of persisting hypercoagulable factors it is not worth the increased bleeding risk to subject FVL to anticoagulation beyond the usual 3 months^{3,5}.

However, long term or sometimes indefinite anticoagulation after a VTE is considered when there have been recurrences, in the presence of additional clinical or inherited thrombophilic risk factors, if the patient is homozygous, and if the initial or subsequent events were spontaneous and unprovoked⁶. A decision to treat long-term also is relevant if the initial event is a major symptomatic PE, because recurrences generally also are PEs with unusually high mortality rates (34%). Since the risk of a recurrence is greatest within the first 6 to 12 months and declines with time while the risk of major bleeding increases with time, the decision to use long term or indefinite anticoagulation needs to be constantly re-evaluated and never should be considered final⁶.

Testing Family Members

Patients who have a family history of FVL and subsequently develop VTE should be tested for the mutation². Other indications for testing are clinical situations suspicious for thrombophilia, such as DVTs or PEs that are unprovoked (idiopathic) or recurrent, occur at a young age, or during pregnancy or hormone exposure, and venous thrombi in unusual anatomical sites. On the other hand, testing asymptomatic family members of patients with FVL is controversial. Although the identification of this mutation usually stimulates beneficial counseling on how to avoid risk factors, it may also lead to unwarranted anxiety, withholding hormone therapy, and insurance and employment bias². Testing asymptomatic individuals is a decision that should be individualized.

References

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