Factor V Leiden Mutation Causing Thrombophilia

Synonyms: 'activated protein C resistance: Leiden type' and 'factor V:G1691A mutation'

Genetics

Factor V Leiden (FVL) mutation (named after the Dutch university where it was discovered) is a point mutation in the gene for clotting factor V.

- It has autosomal dominant inheritance and is the most common cause of inherited thrombophilia.
- FVL is the most prevalent thrombotic risk factor known in the Caucasian population (around 5%).[1]
- Heterozygotes have a three to five times increased risk of thrombosis. Homozygotes are much less common but have a much higher thrombotic risk, around eight times increased risk.
- It leads to a hypercoagulable state. Heterozygous FVL mutation and the G20210A mutation in the prothrombin gene are the most frequent clotting abnormalities associated with venous thromboembolism (VTE). The two mutations may co-exist.
- An individual may be heterozygote or homozygote for the FVL mutation. It is difficult to estimate the increased risk of thrombosis in individual women, particularly heterozygotes, due to the variable penetrance of the thrombotic tendency (interaction with rest of genotype) and variation in other risk factors. Heterozygous carriers have a 4- to 8-fold increased risk of VTE and homozygotes have an 80-fold increased risk.[1]
- The risk of VTE of a FVL mutation is considerably lower than a deficiency of protein C, protein S, or antithrombin III.[2]

NB: FVL mutation should be distinguished from factor V deficiency, also known as Owren's disease (or parahaemophilia), which is a rare, inherited coagulopathy.[3]

Pathophysiology

Factor V is one of the essential clotting factors in the coagulation cascade. Its active form, factor Va, acts as a cofactor allowing factor X to stimulate the conversion of prothrombin to thrombin. Thrombin is then able to cleave fibrinogen to fibrin and a fibrin clot is formed.

Activated protein C is a natural anticoagulant. It limits the extent of clotting by destroying factor V and reducing further thrombin formation. FVL mutation causes activated protein C resistance, hence leading to the hypercoagulable state.

Epidemiology

- FVL is present in around 5% of Caucasians.[4]
- It is rare or absent in people of black African, Far East Asian, native Australian and native American origin.

Presentation

The condition is usually diagnosed following thrombophilia screening due to VTE in the patient or a close relative. It may also be detected after investigation for recurrent miscarriage.

Carriers of FVL mutation have actually been reported to have various advantageous phenotypes related to haemostasis, inflammation and fertility. These include less menstrual blood loss, decreased risk of intracranial haemorrhage, higher survival in and lower susceptibility to severe sepsis, higher survival in acute respiratory distress syndrome and less severe diabetic nephropathy.[4]

Investigations

- Screening tests for hereditary thrombophilia should only be carried out by physicians with a specialist knowledge who can explain the relevance of the findings to the patient and give any necessary therapy. Screening for thrombophilic disorders should not be undertaken routinely. [5]
- Genetic testing can be performed. The polymerase chain reaction for the presence of the FVL mutation is 99% accurate. See separate article Thrombophilia, which describes general investigations for thrombophilia.

Management

General

There is no evidence that the risk of VTE is high enough to warrant long-term anticoagulation in carriers of the gene, even in the homozygous state. Guidelines published by the British Society of Haematology state that:[5]

- Initiation and intensity of anticoagulant therapy following a diagnosis of acute venous thrombosis should be the same in patients with and without heritable thrombophilia.
FVL mutation and the combined oral contraceptive pill (COCP)/hormone replacement therapy (HRT)

- There is no evidence that routine screening for the FVL mutation should be carried out in women starting the COCP. [7]
- The relative risk of VTE is significantly increased but the absolute incidence of thromboembolic events is low and fatal pulmonary embolism is rare.
- The absolute risk of VTE increases in women with FVL mutation during COCP use. However, this risk is still lower than the absolute risk during the pregnancy postpartum period.
- Asymptomatic women with a family history of venous thrombosis should be tested if a thromboembolic event in a first-degree relative was unprovoked, or provoked by pregnancy, COCP exposure or a minor risk factor. The result will be more informative if the first-degree relative has a known thrombophilia. [5]
- Most women with a previous unprovoked venous thrombosis or pregnancy or COCP-related thrombosis will qualify for thromboprophylaxis on clinical risk alone and so testing for heritable thrombophilia is not required.
- COCPs are usually discouraged in women with any thrombophilic defects. [8]
- It is important that women are educated regarding contraceptive options and also the risks of both VTE and unintended pregnancy, to enable these women to make an informed choice regarding contraception. [6]
- The use of thrombophilia screening for women considering COCP use, who have a family history of VTE, is unclear. Women with a family history of VTE in a first-degree relative <45 years of age may indicate an increased likelihood of a hereditary thrombophilia. Screening should be considered in women with a history of previous VTE or a strong family history of VTE who wish to take the COCP. [7]
- If a first-degree relative with venous thrombosis has not been tested for FVL then those women should consider an alternative contraceptive or transdermal HRT. Testing for heritable thrombophilia will provide an uncertain estimate of risk and is not recommended. [5]
- If a first-degree relative with venous thrombosis has been tested and the result is positive then that woman should also consider an alternative contraceptive or transdermal HRT before being considered for testing, as a negative test result does not exclude an increased risk of venous thrombosis. Testing for heritable thrombophilia may assist counselling of selected women particularly if a high-risk thrombophilia has been identified in the symptomatic relative. [5]

FVL mutation and pregnancy

VTE

- Inherited thrombophilia is present in 30-50% of women with pregnancy-associated VTE, with FVL being the most frequently identified thrombophilia in the white population. [9]
- Whether the administration of low-molecular-weight heparin (LMWH) during pregnancy is effective in preventing obstetric complications and pregnancy-related VTE in women who are carriers of FVL is controversial. [10]
- Current opinion is often based on consensus and clinical judgement of the benefits and risks of antithrombotic therapy in individual cases. Joint opinion of haematologist, obstetrician and patient should decide the issue in non-straightforward cases.
- Therapeutic decisions should be based on clinical circumstances and not on the results of thrombophilia testing. For example, in the case of the older woman (eg, aged >35 years) with a poor obstetric history a decision to treat with low-dose heparin should not be determined by the results of testing for heritable thrombophilia. [5] Antithrombotic therapy should not be given to pregnant women based on tests for heritable thrombophilia. Randomised controlled trials with a no treatment or placebo arm in women with a history of pregnancy complications are in progress. [5] LMWH prophylaxis has been shown to reduce the risk of obstetric complications in carriers of FVL, particularly in those with previous obstetric events. In addition, LMWH prophylaxis reduces the risk of pregnancy-related VTE. [10]
- The use of LMWH during pregnancy has been shown to be safe and effective in preventing VTE in susceptible patients with FVL. [11]
- Heterozygotes are not routinely anticoagulated but a personal or family history of VTE or other risk factors (eg, obesity) may make them candidates for haepranisation. [12]
- Once a woman is in labour or thinks she is in labour, she should discontinue her heparin and be reassessed, on admission to hospital, by medical staff. Local guidelines should be followed. [12]
- Those considered to be in need of anticoagulation should usually receive warfarin or heparin for at least six weeks postpartum, when the risk of VTE is high. It is safe to breast-feed whilst taking warfarin.

Pregnancy loss

- Carriers of FVL have double the risk of experiencing recurrent miscarriage compared with women without this thrombophilic mutation. [13]
- One study clearly demonstrated a positive correlation between recurrent pregnancy loss and FVL gene mutations. [14]
- Current recommendations are that women with second-trimester miscarriage should be screened for inherited thrombophilias including FVL. [13]
However, one recent study has shown that the frequency of FVL mutation was not significantly different between patients with recurrent miscarriage and healthy women.\(^{[15]}\)

**Further reading & references**

5. Clinical guidelines for testing for heritable thrombophilia; British Committee for Standards in Haematology (January 2010)
7. First Prescription of Combined Oral Contraception; Faculty of Family Planning and Reproductive Health Care (2007); now known as the Faculty of Sexual and Reproductive Healthcare
12. Reducing the Risk of Thrombosis and Embolism during Pregnancy and the Puerperium; Royal College of Obstetricians and Gynaecologists (November 2009)
13. Recurrent Miscarriage, Investigation and Treatment of Couples; Royal College of Obstetricians and Gynaecologists (May 2011)

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