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Factor V Leiden

Impact on Infusion Nursing Practice

ABSTRACT

As one whose family has been affected by factor V Leiden since 1980, the author knows firsthand the impact of this disease process on patients, outcomes, and practice. In today's healthcare environment, genetic screening for the factor V mutation is routine among pregnant women. Preoperative testing is often done on those "at risk." This article addresses the genetics, the occurrence, the treatment, and practice implications.

INCIDENCE

The factor V mutation (factor V Leiden) is the most common genetic cause of venous thrombosis. It is involved in 20% to 40% of cases and is present in 3% of the general population. The mutation causes resistance to activated protein C (APC), and this induces a defect in the natural anticoagulation system. The other major genetic causes of venous thrombosis (deficiencies of protein C, protein S, and antithrombin III) combined account for only 5% to 10% of cases. The presence of the factor V mutation increases the risk for venous thrombosis 7-fold in heterozygotes and 80-fold in homozygotes. This risk is increased still further in situations such as pregnancy, oral contraceptive use, estrogen therapy, malignancy, diabetes mellitus, immobilization, or surgery. Ten percent of heterozygotes and almost all homozygotes experience venous thrombosis in their lifetime.[1] Table 1 addresses the incidence.[1]

DISCOVERY PROCESS

In 1980, the author's husband was hospitalized with polymyositis and treated with high-dose cortisone therapy. After several weeks of treatment, he developed deep vein thrombosis (DVT) and was subsequently treated with low-dose heparin. The synergistic effect of the residual cortisone with heparin led to a retroperitoneal bleed and emergency interventions to save his life. Fast-forward 15 years, the author's daughter was diagnosed with DVT following extensive air travel. She was treated with Lovenox® and tested for factor V Leiden. She tested positive for factor V Leiden, and the physician team suggested that all family members be tested. First on the list was the author's husband, who tested positive. A cadre of family members surfaced with positive results and a history of clotting episodes. Thus began this author's journey to discover more about factor V Leiden and what it might mean to infusion patient care.

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THROMBOPHILIA

The term *thrombophilia* includes a number of genetic conditions that increase the tendency of the blood to clot, leading to sometimes serious or life-threatening complications depending on the location of the clot. Severity of complications varies depending upon the location and size of the clot; thus, we see superficial thrombophlebitis or DVT, both painful conditions. Clots in the veins of major organs, such as the brain, the liver, and the lungs, can be acutely life threatening, and arterial clots can lead to cerebral vascular accident or infarction.

INDICATIONS FOR TESTING

A plethora of patients presenting with a multitude of diagnoses are candidates for further testing. Indications include venous thrombosis or pulmonary embolism, transient ischemic attacks or premature stroke, peripheral vascular disease, particularly lower-extremity occlusive disease, history of a thrombotic event, family history of thrombosis, or known factor V mutation in a relative. Other risk factors include major surgery, pregnancy, postpartum, oral contraceptive use, or estrogen

TABLE 1

Factor V Leiden Complications

Factor V Leiden can be associated with the following complications:
Venous thrombosis blood clots in veins, such as
Deep vein thrombosis, veins in arms and legs
Superficial thrombophlebitis
Sinus vein thrombosis, veins around the brain
Mesenteric vein thrombosis, intestinal veins
Budd-Chiari syndrome, liver veins
Pulmonary embolism, blood clots in the lungs
Arterial clots (stroke, myocardial infarction) in selected patients (some smokers)
Possibly with stillbirth or recurrent unexplained miscarriage
Preeclampsia and eclampsia (toxemia while pregnant)

therapy. A personal or family history of thrombosis and previous findings of APC resistance by laboratory analysis, DVT, and pulmonary embolism also predispose one to risk.[2]

Venous thrombosis and pulmonary embolism pose a serious health problem. In this country, a half-million people are hospitalized each year, and 50,000 to 100,000 deaths occur because of venous thrombosis, which is also a leading cause of maternal death. The incidence of symptomatic venous thrombosis cases is approximately 1 in 1000 people per year.[1]

Venous thrombosis is a multifactorial condition caused by a combination of genetic, acquired, or environmental influences. Natural anticoagulant systems (the protein C system and antithrombin III) are in place to keep coagulation in check. Excess clotting occurs when there is a disturbance in one of the coagulation inhibitor mechanisms or in natural lysis of clots. Known genetic causes explain about 50% of venous thrombosis cases. Most inherited thrombosis disorders involve a defect in one of the natural anticoagulant mechanisms.[2]

DIAGNOSTIC WORKUP

The diagnostic workup of all thrombotic patients should include the factor V mutation test along with an "inherited hypercoagulability" panel. Diagnosis of an inherited thrombotic disorder can be made in approximately 50% of all venous thrombosis cases. The factor V mutation test is accurate regardless of the clinical condition or medication of the patient.[2]

If the mutation is identified, it establishes an etiology for an individual's thrombosis, identifies individuals and families at increased risk for future thrombosis, and may contribute toward prevention of thrombosis by influencing patient management (eg, avoidance of oral contraceptives for individuals with the factor V mutation and aggressive anticoagulant therapy after major surgery).

Factor V Leiden is suspected in individuals with a history of venous thromboembolism (VTE) manifest as DVT or pulmonary embolism, especially in women with a history of VTE during pregnancy or in association with oral contraceptive use and in individuals with a personal or family history of recurrent thrombosis. The diagnosis of factor V Leiden is made either using a coagulation screening test or by DNA analysis of the *F5* gene, which encodes the factor V protein. The term *factor V Leiden* refers to the specific G-to-A substitution at nucleotide 1691 in the gene for factor V that predicts a single amino acid replacement (R506Q) at 1 of 3 APC cleavage sites in the factor Va molecule.

Activated protein C resistance and deficiencies of protein C, protein S, and antithrombin III are the most common causes.[3] In those affected, the first thrombotic event usually occurs in adulthood except for homozygous protein C deficiency, which can cause severe thrombosis in the newborn. Studies have shown that up to one-third of families affected with inherited thrombosis have 2 genetic defects,[3] one of which is the factor V mutation. The factor V mutation has been discovered in numerous families with deficiencies in protein C, protein S, or antithrombin III. This combination of 2 genetic risk factors (or 1 genetic defect for homozygosity) increases penetrance, dramatically, resulting in very high risk of thrombosis.[4]

Acquired or environmental conditions can precipitate a thrombotic event, including, but not limited to, pregnancy, oral contraceptive use, estrogen therapy, obesity, malignancy, diabetes mellitus, venous stasis from immobility, trauma, surgical interventions, and lupus.

THE FACTOR V MUTATION AND APC RESISTANCE

Activated protein C is a component of the anticoagulant system that functions by inactivating, through cleavage, factors V and VIII in the coagulation cascade. Activated protein C resistance occurs when there is a poor anticoagulant response to APC. The factor V mutation (Leiden) is the cause of more than 95% of APC resistance cases. This mutation is a single G-to-A base change that results in the replacement of an arginine with a glutamine in the protein, destroying a cleavage site and thereby limiting factor V degradation by APC.

THE FACTOR V MUTATION TEST

Factor V Leiden increases the risk of venous thrombosis 3- to 8-fold for *heterozygous* (1 compromised gene inherited) and substantially more, 30- to 140-fold, for *homozygous* (2 compromised genes inherited) individuals.[4]

Testing for the factor V mutation involves polymerase chain reaction amplification followed by detection of the single base change through restriction enzyme digestion and gel electrophoresis. The test determines the presence or absence of the mutation and distinguishes between the heterozygous genotype and the homozygous genotype. Accuracy is more than 99%. The test can be performed rapidly, with results available in 1 to 2 days.[4]

Within the general population, the mutation is common; 2% to 7% of whites are heterozygotes and about 0.1% are homozygotes. Almost all factor V mutation homozygotes and about 10% of heterozygotes experience at least 1 thrombotic event during their lifetime. Thrombosis incidence is increased 7-fold in heterozygotes and 80-fold in homozygotes compared with incidence in people without the mutation. The risk is still higher when clinical or environmental risk conditions are also present. The risk of recurrent thrombotic events is also significantly higher in carriers of the factor V mutation than in patients without this abnormality.[5]

THE FACTOR V MUTATION IN WOMEN'S HEALTH

As clinicians, we are aware of the risks associated with pregnancy, oral contraceptive use, and estrogen replacement therapy. Imagine the complexity when coupled with a genetic hypercoagulability defect. Research indicates that there may be an association between the factor V mutation and second-trimester pregnancy loss. It has recently been shown that 60% of women who develop thrombosis during pregnancy or the postpartum period have the factor V mutation.[5] It is standard practice for women with a history of thrombosis to receive thromboprophylaxis during pregnancy.

Factor V mutation testing should be performed before prescription of oral contraceptives if there is a personal or family history of thrombosis. Heterozygotes should receive counseling about their increased risk when taking oral contraceptives (35-fold greater than nonusers of oral contraceptives who do not have the mutation), and all homozygotes should discontinue oral contraceptive use.[5]

MOLECULAR GENETIC TESTING

Molecular genetic tests are reliable in individuals taking warfarin or heparin anticoagulation and independent of thrombotic episodes. DNA extracted from peripheral blood leukocytes should be interpreted with caution in the setting of liver transplantation or hematopoietic stem cell transplantation.[1] Diagnosis of factor V Leiden in hematopoietic stem cell transplant recipients requires molecular analysis of nonhematopoietic tissue.[5]

DISEASE CHARACTERISTICS

Factor V Leiden thrombophilia is characterized by a poor anticoagulant response to APC and an increased risk of VTE. Deep venous thrombosis is the most common VTE, with the legs being the most common site. Thrombosis in unusual locations is less common. Evidence suggests that a heterozygous factor V Leiden mutation has at most a modest effect on the risk of recurrence after initial treatment of a first VTE. Consider those with central venous catheters candidates for thrombosis.

CLINICAL MANAGEMENT OF FACTOR V HETEROZYGOTES AND HOMOZYGOTES

Homozygotes, with or without a history of thrombosis, receive preventive therapy during at-risk situations and extended anticoagulant therapy after a thrombotic event. Heterozygotes with a history of thrombosis are treated like patients with a history of thrombosis because of deficiencies of protein C, protein S, or antithrombin III. In addition, heterozygotes without personal or family history of thrombosis receive prophylactic anticoagulant therapy in situations known to provoke thrombosis. Those with a factor V mutation should be counseled about secondary risk situations, and relatives should be offered testing.

The first acute thrombosis is treated according to standard guidelines, including intravenous unfractionated heparin or low-molecular-weight (LMW) heparin and concurrent oral administration of warfarin (except during pregnancy). The duration of oral anticoagulation therapy is debated. Long-term oral anticoagulation is considered in those with recurrent VTE, multiple thrombophilic disorders, or coexistent circumstantial risk factors and in factor V Leiden homozygotes.

Prevention of Primary Manifestations

In the absence of a history of thrombosis, long-term prophylactic anticoagulation is not routinely recommended for asymptomatic factor V Leiden heterozygotes. A short course of prophylactic anticoagulation when circumstantial risk factors are present may prevent initial thrombosis in factor V Leiden heterozygotes.[6,7]

Prevention of Secondary Complications

Enoxaparin prophylaxis in women heterozygous for factor V Leiden who have a history of recurrent pregnancy loss may minimize the risk of an unfavorable pregnancy outcome. Patients are monitored and reevaluated at regular intervals. Molecular genetic testing can establish the genetic status of asymptomatic at-risk family members; however, the indications for family testing are unresolved. Clarification of factor V Leiden allele status may be useful in at-risk relatives considering hormonal contraception or pregnancy or in families with a strong history of recurrent venous thrombosis at a young age. Asymptomatic factor V Leiden heterozygotes and homozygotes should be aware of the signs and symptoms of VTE that require immediate medical attention and the potential need for prophylactic anticoagulation in high-risk circumstances.

ANGIOGENESIS

Angiogenesis is the formation of new blood vessels. Angiogenesis is a process controlled by certain chemicals produced in the body. Some of these chemicals stimulate cells to repair damaged blood vessels or form new ones. Other chemicals, called angiogenesis inhibitors, signal the process to stop. Angiogenesis plays an important role in the growth and spread of cancer. Collateral vessels "feed" the cancer cells with oxygen and nutrients, allowing these cells to grow, invade nearby tissue, spread to other parts of the body, and form new colonies of cancer cells.[8]

THE EVIDENCE BASE

The evidence suggests an important role for the infusion nurse related to venous access placement and/or exchange. Clinicians and educators must fully integrate critical thinking skills related to inquiry and understand the importance of evidence-based nursing practice. The knowledge, experience, and competencies gleaned from evidence-based nursing practice enhance professional growth and development through continuous learning and facilitate the understanding of clinical research.

The evidence suggests that all patients with proximal DVT require some form of heparin therapy until the dose of sodium warfarin is therapeutic.[6,9] This has traditionally been with intravenous unfractionated heparin, and this is still the standard of care. The use of LMW heparin, however, may allow certain patients to avoid hospitalization. The LMW form of heparin is depolymerized from unfractionated heparin and has a more predictable anticoagulant effect, thus avoiding the need to assess prothrombin times.[8,9] It also promotes less antibody formation and is associated with a lower risk of heparin-associated thrombocytopenia. Hemorrhagic adverse effects appear to be similar to those with standard heparin. At least 2 studies have shown that patients treated at home with LMW heparin plus warfarin compare favorably with those treated in the hospital with intravenous heparin plus warfarin. The incidence of the recurrence of thromboembolism was 6.9% versus 8.6% in one study[10] and 5.3% versus 6.7% in the other. The incidence of major bleeding was similar (0.5% vs 2% and 2% vs 1%). A recent Cochrane Library review concluded that LMW heparin was at least as effective as unfractionated heparin and that its use was associated with a lower incidence of major hemorrhage and decreased overall mortality.[11,12]

Candidates for home infusion therapy must be able to learn how to self-administer and to understand when to call their physicians for adverse events, especially those related to site maintenance and dosing. The infusion nurse contributes greatly to this process, offering oversight, troubleshooting, and follow-up. With a team approach to care, outpatient treatment of DVT is feasible, equally efficacious, and probably cost-effective.[12,13] In all of these patients, warfarin therapy should be initiated on day 1. The heparin (intravenous or LMW) can be discontinued after at least 4 to 5 days and when the international normalized ratio is greater than 2.0 for 2 consecutive days.

SUMMARY

The discovery[14] of the factor V mutation in 1994 has revolutionized the diagnostic workup of patients with hypercoagulability, and the ability to detect this mutation in asymptomatic relatives offers the opportunity to prevent venous thrombosis through special management of those at risk. For infusion nurses, the clinical path is clear. Know your patient, your laboratory test results, and understand the risks associated with venous access. Be a resource for the patient and the family and offer information as needed concerning procedures and access. The credentialed infusion nursing specialist plays a significant role in patient assessment and outcomes and contributing to the evidence base for safe practice.[15]

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