



Sujatha Krishnan, MD, Naveen Manchanda, MD

Life-threatening Cerebral Sinus Thrombosis from Factor V Leiden Mutation: A Case Report and Review of Factor V Leiden

Key points

1. Discovery of the Factor V Leiden mutation has increased the percentage of patients in whom venous thrombosis could be attributed to a hereditary thrombophilia.
2. Factor V Leiden mutation is the most common inherited clotting disorder.
3. Thrombosis at an unusual site, or a life threatening venous thrombosis, should prompt a workup for a hereditary thrombophilia. Thrombosis in early adulthood is likewise investigated.
4. Anticoagulation with warfarin is recommended for three to six months. Indefinite anticoagulation should be tailored for an individual weighing the risk versus benefit.

Case Report

The subject is a 46-year-old male transferred from a private hospital for neurosurgery consultation regarding a herniated lumbar spine disc. His past medical history was significant for Type 2 diabetes mellitus and dyslipidemia. During the neurosurgery consultation, patient was noted to be confused and not able to follow commands. Initially the patient's confusion was attributed to narcotics he had received for the back pain. Nevertheless he underwent a CT scan of the brain and it showed an acute left temporal hemorrhage. Further evaluation with MRI and MR angiography revealed extensive thromboses of the superior sagittal, transverse and sigmoid sinuses with a left temporal hemorrhagic infarct.

The patient became more obtunded with resultant respiratory failure requiring mechanical ventilation for a week. A hypercoagulable lab panel revealed positive lupus anticoagulant and a positive heterozygous Factor V Leiden mutation. He was carefully anticoagulated with Heparin in view of the concomitant hemorrhagic infarct with a target aPTT twice the baseline (~ 45 seconds).

He went on to have visual disturbances, such as diplopia and blurring. A fundoscopic exam revealed papilledema due to increased intracranial pressure with associated visual field defects. He had a right inferior homonymous hemianopsia and left sixth nerve palsy. He was treated with Diamox. He significantly improved as far as his visual and mental status was concerned after treatment with Heparin and Diamox. He was discharged home in a stable condition after a month of hospitalization, which included three weeks of acute rehabilitation.

Anticoagulation was continued with warfarin sodium aiming at a target international normalized ratio (INR) of 2.0 to 3.0. At one-year follow-up, the patient remained asymptomatic except for minor visual field defects and has resumed work at his prior level.

Introduction

Venous thrombosis is the obstruction of blood flow in the veins by a locally formed blood clot or from a thrombus formed elsewhere. The most common presentations of venous thrombosis are lower extremity deep vein thrombosis (DVT) and pulmonary embolism. They may also occur in uncommon sites like the retina, cerebral veins and sinuses, portal venous system and mesenteric veins. Cerebral vein and dural sinus thrombosis is a rare entity and an infrequent cause of stroke, as witnessed in the patient above. The etiology of thromboses in the cerebral veins and sinuses includes blood disorders, abnormalities in the patterns of blood flow, and infiltrative or inflammatory or hereditary prothrombotic conditions, all of which may promote thrombosis.

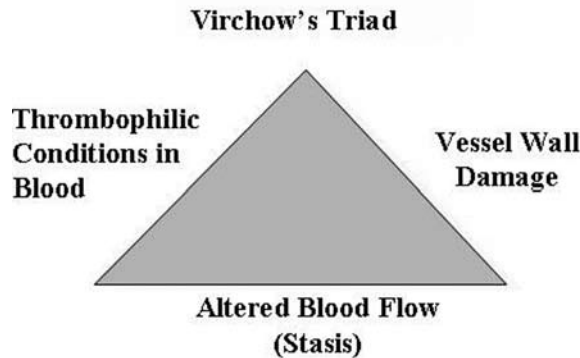
Prothrombotic states stand in the forefront among the causes of cerebral vein thrombosis. Factor V Leiden mutation causing activated protein C (APC) resistance is the most common inherited prothrombotic state found in the United States. Increased awareness, modern neuroimaging modalities

and timely anticoagulation therapy have significantly improved the outcome of life threatening, like cerebral vein, thrombosis.¹⁻⁷

Overview of Venous Thrombosis

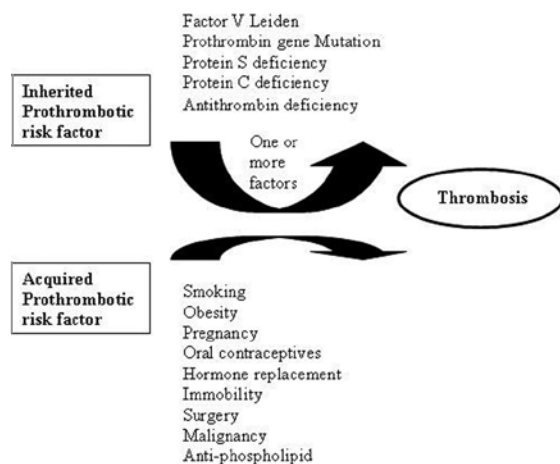
One of the important concepts in pathology, “Virchow’s Triad” (Figure 1) describes the three elements causing thrombosis.

Figure 1.



The prothrombotic etiology could be hereditary or acquired. In most cases more than one prothrombotic factors are frequently found. An acquired risk factor like smoking, surgery, pregnancy, or oral contraceptive pills is seen in combination with the inherited etiology most of the time. A causative factor could be found in almost 80% of the patients. Figure 2 shows the most common causes of thrombosis.^{8,9}

Figure 2.



One or more inherited prothrombotic factors along with an acquired risk factor are the usual etiology behind thrombosis.

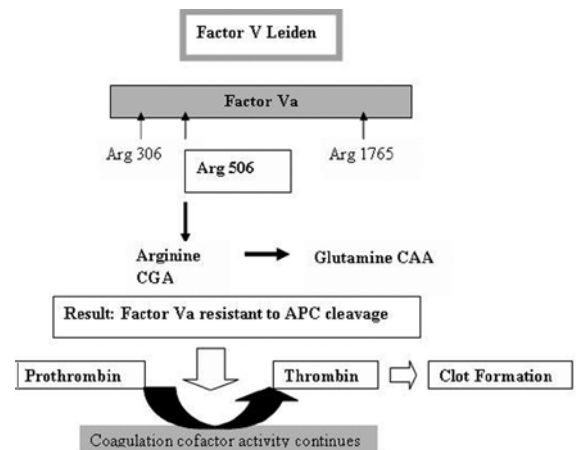
Activated protein C resistance and Factor V Leiden

Inability to cleave Factor V defines APC resistance. With the discovery in 1994 that APC resistance could be attributed to Factor V Leiden mutation, it is now thought that this mutation accounts for about 50% of cases of DVT and is the most common inherited clotting disorder in the United States. It is present in 3 to 5% of the population and is correctly called a polymorphism. The most common cause of APC resistance is a mutation of Factor V in the clotting cascade. The study by Rosendall et al in 1995 showed a relative risk for a deep venous thrombosis to be seven-fold for heterozygotes and eighty-fold for homozygotes of the Factor V Leiden mutation.¹⁰

Physiology

Factor V is an inactive cofactor in plasma. It is activated by thrombin to Factor Va, which acts as a cofactor in the conversion of prothrombin to thrombin. Factor Va is inactivated by APC, thus making Factor V as a negative control point in the coagulation cascade. Bertina et al identified a mutation in the gene coding for coagulation Factor V leading to APC resistance.¹¹ The gene product is mostly from a single DNA base pair mutation in the Factor V gene, where guanine (G) is replaced by adenine (A). This change leads to a substitution of glutamine for arginine at position 506 (Figure 3), and the altered Factor V is called “Factor V Leiden” named after the town in the Netherlands where it was discovered. The mutated Factor V has a different three-dimensional conformation of the cleavage site, where APC normally binds to inactivate it.¹² Factor Va becomes not susceptible to cleavage by APC and this leads to a hypercoagulable state, as more Factor Va is available within the prothrombinase complex, thereby increasing the generation of thrombin.

Figure 3.



A mutation occurs in the Factor V gene at position 506, where guanine (G) is replaced by adenine (A). The product, Factor V Leiden is resistant to cleavage by APC, thereby promoting thrombosis.

Prevalence

APC resistance of the heterozygous Factor V Leiden variety accounts for 90 to 95% of mutations. Homozygosity for the mutation accounts for less than 5%.

The prevalence of heterozygosity for the Factor V Leiden mutation in Caucasians ranges from 1 to 8.5%. The mutation is extremely rare in black Africans, Japanese and Chinese people. In a survey of 4047 American men and women participating in the Physicians' Health Study and the Women's Health Study by Ridker et al in 1997, carrier frequency of Factor V Leiden was 5.27% in Caucasians, 2.21% in Hispanic Americans, 1.23% in African Americans, 0.45% in Asian Americans, and 1.25% in Native Americans.^{13,14}

There are various studies supporting increased incidence of APC resistance in patients with other thrombophilic states and acquired factors like advanced age, pregnancy and oral contraceptives.

Pseudohomozygous Factor V Leiden is a very rare condition. Patients with these mutations have decreased normal Factor V levels as well as heterozygous mutation of Factor V Leiden protein. Their risk levels are similar to that of an individual with a homozygous Factor V Leiden mutation.

Clinical Presentation

Factor V Leiden is the most common hereditary prothrombotic state. Its most common presentation is a deep vein thrombosis or pulmonary embolism.¹⁵⁻¹⁹ The risk for thromboses in uncommon sites like cerebral veins and sinuses, uterine vessels, and retina is increased with APC resistance. In a case-control study by Zuber et al in 1996, Factor V Leiden mutation is a risk factor for cerebral venous thrombosis and may be the most common inherited coagulation defect associated with this condition.⁶ It has been frequently noted that the relative risk of venous thrombosis greatly increase with coexistence of another inherited or acquired prothrombotic state (Figure 4).

Various obstetric complications like intrauterine growth retardation, abruptio placentae, preeclampsia and inadequate placental perfusion have also been linked with Factor V Leiden mutation. Multiple studies have evaluated the risk of Factor V Leiden mutation in arterial thrombosis like myocardial infarction

and stroke.²⁰ Increased incidence for an arterial thrombosis has not been well established from these studies.

Figure 4.
Leiden Thrombophilia Study Group Data

Risk and Incidence of First Episode of Venous Thrombosis in Adult Subjects

	Relative risk for venous thrombosis	Incidence, percent per year
Normal	x 1	0.008
Factor V Leiden heterozygote	x 7	0.06
Factor V Leiden homozygote	x 80	0.5-1.0
Oral contraceptives/ HRT	x 4	0.03
Oral contraceptives		
+		
Factor V Leiden	x 35	0.29

Diagnosis

The screening test for APC resistance is activated partial thromboplastin (aPTT) time based assays. The first generation APC resistance assays used a patient's plasma aPTT measured in the presence and absence of a standardized amount of APC. The two clotting times are calculated as a ratio and compared with the normal range or normalizing it to the APC resistance ratio from a normal pool of plasma. The results were influenced by various factors like the level of APC, the aPTT reagent, subjects with an already existing abnormal aPTT from another coagulation defect, acute thrombotic state and pregnancy.

Second generation coagulation assays use the patient's plasma diluted in a Factor V deficient plasma and then performing an aPTT-based assay. This is more sensitive and specific.²¹ Positive second generation APC resistance assays can also be subjected to genomic DNA analysis in peripheral blood mononuclear cells by a polymerase chain reaction to confirm a Factor V Leiden mutation as the cause of APC resistance.

Treatment

Anticoagulation by unfractionated Heparin or low molecular weight Heparin is the treatment of choice for acute venous thromboembolism. It is followed by an oral anticoagulant like warfarin with a target INR of 2.0 to 3.0. The duration of oral anticoagulation therapy is controversial.²²⁻²⁶ A minimum of three to six months is suggested by most studies. The duration

of anticoagulation after that depends on the number of recurrences, number of thrombophilic states and nature (homozygous vs. heterozygous), life threatening thrombosis and patient preferences. There is data from several studies arguing against the indefinite use of warfarin after the first episode of venous thrombosis from a Factor V Leiden mutation. The unpredictable pharmacokinetics of warfarin, and the potential bleeding complications associated with its use, is the main reason for failure of long-term prophylaxis. Novel therapies with synthetic pentasaccharides fondaparinux and oral direct thrombin inhibitor ximelagatran are under investigation for a better predictable anticoagulation and long-term secondary prophylaxis with lesser bleeding risks.

Currently, indications for indefinite anticoagulation as a long-term prophylaxis is justified in high risk patients with inherited thrombophilia, unprovoked thrombosis in an unusual site, unprovoked life threatening thrombotic event, thrombosis caused by two or more inherited thrombophilias and two or more episodes of venous thrombosis from any cause.²⁷

Conclusion

Factor V Leiden mutation causing APC resistance is the most common inherited prothrombotic state. In combination with other prothrombotic factors it can cause venous thrombosis of uncommon sites like cerebral veins, retinal and mesenteric veins. Prompt recognition of this condition and adequate anticoagulation can be life saving.

Dr. Sujatha Krishnan completed her Internal Medicine Residency at the University of Illinois at Urbana-Champaign College of Medicine, Internal Medicine Residency Program in June of 2006. Dr. Krishnan is currently Chief Resident at Provena Covenant Medical Center for the University of Illinois Internal Medicine Residency Program.

Naveen Manchada, MD, is a hematologist in the Division of Oncology/Hematology at the Carle Clinic Association, Urbana, Illinois.

References

1. Stam J. Thrombosis of the cerebral veins and sinuses. *N Engl J Med* 2005;352(17):1791-1798.
2. Enevoldson TP, Russell RW. Cerebral venous thrombosis: new causes for an old syndrome? *Q J Med* 1990;77(284):1255-1275.
3. Ludemann P, Nabavi DG, Junker R, Wolff E, Papke K, Buchner H, et al. Factor V Leiden mutation is a risk factor for cerebral venous thrombosis: a case-control study of 55 patients. *Stroke* 1998;29(12):2507-2511.
4. de Bruijn SF, Stam J, Koopman MM, Vandenbroucke JP. Case control study of risk of cerebral sinus thrombosis in oral contraceptive users who are carriers of hereditary prothrombotic conditions. *BMJ* 1998;316(7131):589-592. Erratum in: *BMJ* 1998;316(7134):822.
5. Martinelli I, Sacchi E, Landi G, Taioli E, Duca F, Mannucci PM. High risk of cerebral-vein thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives. *N Engl J Med* 1998;338(25):1793-1797.
6. Zuber, M, Toulon, P, Marnet, L, Mas, JL. Factor V Leiden mutation in cerebral venous thrombosis. *Stroke* 1996;27(10):1721-1723.
7. Deschiens, MA, Conard, J, Horellou, MH, Ameri A, Preter M, Chedru F, et al. Coagulation studies, factor V Leiden, and anticardiolipin antibodies in 40 cases of cerebral venous thrombosis. *Stroke* 1996;27(10):1724-1730.
8. Lopez J, A. Kearon C, Lee AY. Deep venous thrombosis. *Hematology (Am Soc Hematol Educ Prog)*2004: 439-456.
9. Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet* 1999;353(9159):1167-1173.
10. Rosendaal, FR, Koster, T, Vandenbroucke, JP, Reitsma PH. High-risk of thrombosis in patients homozygous for factor V Leiden (acquired protein C-resistance). *Blood* 1995;85(6):1504-1508.
11. Bertina RM, Koeleman BPC, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature* 1994;369(8935):1453-1457.
12. Thorelli E, Kaufman RJ, Dahlback B. Cleavage of factor V at Arg 506 by activated protein C and the expression of anticoagulant activity of factor V. *Blood* 1999;93(8):2552-2558.

13. Ridker PM, Miletich JP, Hennekens CH, Buring JE. Ethnic distribution of factor V Leiden in 4047 men and women. Implications for venous thromboembolism screening. *JAMA* 1997;277(16):1305-1307.
14. Rees DC, Cox M, Clegg JB. World distribution of factor V Leiden. *Lancet* 1995;346(8983):1133-1134.
15. Middeldorp S, Meinhart JR, Koopman M, van Pompus EC, Hamulyak R, van Der Merr J, et al. A prospective study of asymptomatic carriers of the factor V Leiden mutation to determine the incidence of venous thromboembolism. *Ann Intern Med* 2001;135(5):322-327.
16. Emmerich J, Rosendaal FR, Cattaneo M, Margalione M, De Stefano V, Cumming T, et al. Combined effect of factor V Leiden and prothrombin 20210A on the risk of venous thromboembolism--pooled analysis of 8 case-control studies including 2310 cases and 3204 controls. Study group for pooled-analysis in venous thromboembolism. *Thromb Haemost* 2001;86(3):809-816. Erratum in: *Thromb Haemost* 2001;86(6):1598.
17. Koeleman, BPC, Reitsma, PH, Allaart, CF, Bertina RM. Activated protein C resistance as an additional risk factor for thrombosis in protein C-deficient families. *Blood* 1994;84(4):1031-1035.
18. Koeleman, BPC, van Rumpft, D, Hamulyak, K, Reitsma PH, Bertina RM. Factor V Leiden An additional risk factor for thrombosis in protein S deficient families? *Thromb Haemost* 1995;74(2):580-583.
19. Price, DT, Ridker, PM. Factor V Leiden mutation and the risks for thromboembolic disease: A clinical perspective. *Ann Intern Med* 1997;127(10):895-903.
20. Ridker PM, Hennekens CH, Lindpaintner K, Stampfer MJ, Eisenberg PR, Miletich JP. Mutation in the gene coding for coagulation factor V and the risk of myocardial infarction, stroke, and venous thrombosis in apparently healthy men. *N Engl J Med* 1995;332(14):912-917.
21. Zehnder JL, Benson RC. Sensitivity and specificity of the APC resistance assay in detection of individuals with factor V Leiden. *Am J Clin Pathol* 1996;106(1):107-111.
22. Bauer, KA. The thrombophilias: well-defined risk factors with uncertain therapeutic implications. *Ann Intern Med* 2001;135(5):561-568.
23. Schulman S, Rhedin A-S, Lindmarker P, Carlsson A, Lafars G, Nicol P, et al. A comparison of six weeks with six months of oral anticoagulation therapy after a first episode of venous thromboembolism. *N Engl J Med* 1995;332(25):1661-1665.
24. Schulman S, Granqvist S, Holmström M, Carlsson A, Lindmarker P, Nicol P, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. *N Eng J Med* 1997;336(6):393-398.
25. Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, Anderson DB, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med* 1999;340:901-907. Erratum in: *N Engl J Med* 1999;22;341(4):298.
26. Agnelli G, Prandoni P, Santamaria MG, Bagatella P, Iorio A, Buzzam M, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. *N Engl J Med* 2001;345(3):165-169.
27. Huisman MV, Bounameaux H. Treating patients with venous thromboembolism: initial strategies and long-term secondary prevention. *Semin Vasc Med* 2005;5(3):276-84.

CME Questions 6a-d

Please select the correct answer for the following questions:

- 6a. In a rare venous thrombosis like cerebral vein thrombosis, the etiology is usually single.
 - a. True
 - b. False

- 6b. Factor V Leiden mutation accounts for > 50% of deep vein thromboses and is the most common inherited thrombotic state in the United States.
 - a. True
 - b. False

- 6c. APC resistance from Factor V Leiden is commonly found in Hispanic, African-American and Asian populations.
 - a. True
 - b. False

- 6d. Anticoagulation by unfractionated Heparin / LMW Heparin is the treatment of choice for acute venous thromboembolism caused by Factor V Leiden.
 - a. True
 - b. False