Review Article

Genetics of Cerebral Venous Thrombosis

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Abstract

Cerebral venous thrombosis (CVT) is rare compared to arterial causes of stroke. It is often encountered in young patients and may occur in children and neonates. Predisposition to CVT also has a genetic basis and inherited thrombophilias are known to cause 22.4% of the CVT cases. Inherited thrombophilias should be suspected if a patient has recurrent CVT, is less than 45 years age, has a family history of venous thrombosis or has no apparent acquired risk factor. Factor V Leiden (FVL) is the most common genetic risk factor, followed by the prothrombin gene mutation G20210A. Other less common inherited venous thrombophilias include deficiencies of Protein S, Protein C and antithrombin III. FVL, the G20210A prothrombin gene mutation and a deficiency of protein S and C, cause a reduction in the control of thrombin generation. Deficiency of antithrombin causes a decreased neutralization of thrombin. Both these mechanisms are responsible for venous thrombosis. Inherited thrombophilias with concomitant acquired risk factors like surgery, trauma, prolonged immobilization, pregnancy and puerperium, oral contraceptives, antiphospholipid antibodies and hyperhomocysteinemia may increase the risk of CVT manifold. Similarly the co-inheritance of two or more known mutations also increases the risk markedly. FVL, prothrombin G20210A mutation, increased factor VIIIc, protein C & S deficiency and antithrombin III deficiency have all been reported to cause neonatal stroke due to CVT. Maternal and foetal testing is suggested when CVT occurs in neonates.

Introduction

Advancements in genetics over the last decade have led to the identification of a genetic basis of a number of neurological diseases. Although rare, predisposition to cerebral venous thrombosis (CVT) also has a genetic basis and inherited thrombophilias constitute 22.4 % of the CVT cases.[1] Inherited thrombophilias should be suspected if a patient has CVT, recurrent venous thrombosis, is less than 45 years age, has a family history of venous thrombosis or has no apparent acquired risk factor. In this article we will discuss the genetic predisposition to CVT.

Background

Antithrombin 111 deficiency and dysfibrogenemia as causes of inherited venous sinus thrombosis were first reported in 1965,[2,3] while protein C and protein S deficiency as a cause of venous thrombo-embolism were first described in 1981[4] and 1984.[5] Few advances were made in the next ten years, until 1993, when resistance to activated protein C (APC-R) was discovered.[6] This was found to be due to a substitution in the factor V gene (G1691A) that causes arginine in residue 506 of factor V protein to be replaced by glutamine (Arg 506Glu), giving rise to the protein called factor V Leiden (FVL).[7] FVL reduces the rate of inactivation of factor Va, which leads to increased generation of thrombin. In addition FVL has diminished cofactor activity in the inactivation of factor VIIIa by activated protein C (APC) - causing APC-R. This results in the failure of APC to prolong the activated partial-thromboplastin time (APTT). Another recently identified is a mutation in the prothrombin gene(factor II), called the G20210A mutation[8], causes an elevated level of prothrombin and an increases risk for venous thrombosis by promoting thrombin generation. Thus Factor V Leiden, the G20210A prothrombin gene mutation and a deficiency of protein S and C, cause a reduction in the control of thrombin generation. Deficiency of antithrombin causes a decreased neutralization of thrombin. Both these mechanisms are responsible for venous thrombosis.

Inheritance

The main inherited causes of CVT[9] are listed in Table 1. All are inherited as an autosomal recessive trait.

Genetic risk and external factors

Patients with inherited thrombophilias are at an increased risk of CVT. The lifetime risk of venous thrombosis[10] based on inherited factors is given in Table 2. The risk is increased manifold if there are concomitant external risk factors like surgery, trauma, prolonged immobilization, pregnancy and puerperium[11], oral contraceptives[12], antiphospholipid antibodies and hyperhomocysteinemia.[13] The use of oral contraceptives (OCs) significantly increases the risk of CVT. Martinelli et al compared the prevalence of CVT in carriers of the G1691A and G20210A mutations who used OCs, and found that the use of OCs was more frequent among women with CVT (96%) than amongst controls.[14] Women with inherited thrombophilias should avoid using OCs particularly if they have a past or family history

Table 1. Genetic causes of Cerebral venous thrombosis.[9]

Disorder	Gene	Inheritance	General population %	With CVT %
Activated protein C resistance	Leiden Factor V mutation	Autosomal recessive (AR)	2-15	5-20
Prothombin 20210	Prothombin	AR	0.1	1 - 5
Protein C deficiency	Protein C gene	AR	0.2 - 0.4	3 - 6
Protein S deficiency	Protein S gene	AR	0.03 - 0.13	1 - 5
Increased factor VIII	von Willebrand factor defiency	AR	10	25
Antithrombin III deficiency	Antithrombin III	AR	Rare	3 - 8
Plasminogen deficiency	Plasminogen activator - I	AR		
Lipoprotein	Apolipoprotein (a)	AR		
Marfan Syndrome	Fibrillin 1	AR	0.03	
Fabry disease	Alpha-galactosidase	AR		
Sickle cell syndrome	Globin genes	AR		
Heparin cofactor II	Heparin cofactor II	AR	Rare	? 5
Platelet collagen receptor	Platelet collagen receptor	AR		
Factor XII	Factor XII	AR		

Table 2. The lifetime risk of venous thrombosis based on inherited factors.[10]

Inherited factor	Increase in lifetime risk above general population risk
Single factor V mutation	4-7%
One prothrombin G20210A mutation	2.8%
Two factor V mutations	80%
Combined Factor V and G20210A mutation	20%
Factor V mutation plus use of OCs	30%
Protein C deficiency	3-7%
Protein S deficiency	2-20%
Antithrombin III deficiency	9-50%

of venous thrombosis. Hormone replacement therapy also increases the risk of venous thrombosis.[13]

Inherited thrombophilias as a cause of foetal and neonatal CVT

Approximately 25% of ischaemic cerebrovascular disease in children is due to CVT. In 70% an acquired etiology can be identified. In 30% no cause can be determined.[15]

Table 3. Suggested testing for maternal/fetal Thrombotic disorders.

Protein S
Protein C
Antithrombin III
Factor V Leiden
Prothrombin G20210A
Lipoprotein (a)
Homocysteine
Anticardiolipin IgG/IgM (maternal only)

It has recently been established that genetic thrombotic disorders are significant risk factors for neonatal stroke. Factor V Leiden, prothrombin G20210A mutation, increased factor VIIIc, protein C & S deficiency and antithrombin III deficiency have all been reported to cause neonatal stroke due to CVT.[16] Table 3 lists coagulation profile testing suggested for mother and baby for neonatal stroke and neonatal CVT:

Conclusion

Cerebral venous thrombosis may cause significant neurological morbidity and mortality in young adults and children. FVL is the most common genetic risk factor, followed by the prothrombin gene mutation G20210A. Inherited thrombophilias with concomitant acquired risk factors may increase the risk of CVT manifold. Asymptomatic relatives of an affected patient may be tested and treated in high risk situations. Prophylactic treatment for asymptomatic carriers is not recommended as the risks outweigh the benefits. Maternal and foetal testing is suggested when CVT occurs in neonates.

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