GENETIC COAGULATION DEFECTS

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Normal hemostasis in response to blood vessel injury results from sequential activation of coagulation enzymes and culminates in formation of a stabilized fibrin clot. Complex natural mechanisms are known to exist for deterring this process. The principal components that suppress intravascular clotting thereby ensuring unobstructed blood flow are the coagulation inhibitors and the fibrinolytic system. When defects of these components occur the disrupted balanced between procoagulant and anticoagulant activities in blood may lead to thrombosis.

The purpose of this presentation is to review and summarize current knowledge regarding hereditary defects in coagulation inhibitors and evaluate the extent to which these disorders contribute to the risk of thromboembolism in man.

HEREDITARY DEFICIENCY OF ANTITHROMBIN III

Antithrombin III, a 58-kd plasma glycoprotein produced by hepatocytes represents the primary inhibitor of serine proteinases that participate in the intrinsic and common pathways of blood coagulation. It is estimated that about 85 percent of thrombin potentially generated in plasma and most of the available factor Xa are neutralized by antithrombin III. Catalytically active thrombin, and possibly other enzymes, cleave a specific arginine385-serine386 bond in the C-terminal portion of the antithrombin III molecule, which leads to formation of a stable inactive equimolar complex between the inhibitor and the active serine center of the protease. With time active thrombin may slowly dissociate from the complex releasing the antithrombin III moiety which no longer has an inhibitory activity. Both the inhibition of enzymes and the formation of an inactive antithrombin III derivative are markedly enhanced by heparin.

As early as 1914 Howell suspected that thrombosis might be prevented by a natural plasma protein. More than half a century later, Egeberg described a familial disorder characterized by low levels of antithrombin III in blood and a high incidence of venous thromboembolism. Subsequently, a number of families with similar characteristics have been reported. The disorder is inherited as an autosomal dominant trait but appears to be heterogeneous. In most cases antithrombin III
is qualitatively normal but is present in plasma at about 50 percent of the normal concentration. It's catabolic rate as well as its distribution between plasma and noncirculatory compartments remain unchanged; the defect lies in the synthesis of the protein which occurs at half the normal rate\textsuperscript{15}. Studies of families with this so-called "classical" form of deficiency provided evidence for the linkage between the antithrombin III locus and the locus of the Duffy blood group in the heterochromatic region of the long arm of chromosome 1 \textsuperscript{16,17}. The location of the structural antithrombin III gene in human chromosome 1 was recently confirmed by genetic mapping\textsuperscript{18}. With the use of recombinant-DNA techniques a common DNA polymorphism within the gene was identified\textsuperscript{19}. While in some families the deficiency is associated with structural gene deletion, in other families both parental antithrombin III genes are detectable in the affected members\textsuperscript{19,20}. The disorder has a relatively low frequency of occurrence and is estimated to appear in approximately 1 in 5,000 persons\textsuperscript{21}. Males and females are equally affected. According to Vikydal et al\textsuperscript{22}, inherited antithrombin III deficiency occurs in less than 2 percent of all patients presenting with venous thromboembolism. Clinically, the deficiency is characterized by recurrent thromboembolism with onset at a relative early age often in the absence of other predisposing factors. Exceptional subjects may have arterial thrombosis. We have investigated 43 deficient members of six unrelated families. Cumulative risk of thrombosis in this group exceed 90 percent (Fig 1). This flagrant thrombotic tendency emphasizes the importance of procoagulant-anticoagulant balance, particularly in areas of prolonged venous stasis. Total homozygous deficiency in man is unknown and is most likely incompatible with survival beyond fetal life.

Fig. 1. Cumulative incidence of thromboembolism related to age, as estimated in a population of 43 subjects with "classical" type of hereditary antithrombin III deficiency.