DEFICIENCIES IN ANTICOAGULANT PROTEINS

OVERVIEW

- Familial deficiencies in anticoagulant proteins are found in less than 10% of all patients with VTEs.
- All anticoagulant deficiencies are associated with a heterogeneous group of genetic variations that either:
  - reduce plasma protein levels, or
  - alter the protein structures in such a way that they are rendered dysfunctional.

RISK OF RECURRENCE

- The risk of a recurrent venous thromboembolism in this group of patients differs based on which anticoagulant protein is deficient.
  - antithrombin III deficiency – recurrence risk 2 to 5%
  - deficiencies in protein C, or protein S – recurrence risk is between 5 and 10%.

ANTITHROMBIN III DEFICIENCY (ATIII DEFICIENCY)

Function of ATIII

- ATIII is the primary inhibitor of thrombin and other procoagulants important in fibrin formation.
- A decrease in ATIII activity impairs the neutralization of thrombin and other procoagulants, which leads to a propensity for VTE's.

Prevalence and Risk for VTE

- The prevalence of ATIII deficiency in the general population is low when compared to the prevalence of factor V Leiden and prothrombin G20210A.
- ATIII deficiency accounts for approximately 2% of patients with VTE's
- The risk for a single VTE may be higher than 2 to 5%
- The risk for a recurrent VTE is 2 to 5%

PROTEIN C DEFICIENCY

Function of Protein C

- Protein C is activated by thrombin when it binds (with Protein S) to thrombomodulin.
- Activated protein C (APC) is responsible for inactivating factors Va and VIIIa, which results in decreased thrombin generation and enhances fibronolytic activity.
- There are two distinct types of protein C deficiency, however distinguishing between types does not have clinical relevance
- Homozygous protein C deficiency is associated with extremely low levels of protein C and neonatal purpura fulminans.

Prevalence and Risk of VTE

- The prevalence of protein C deficiency in the general population is 1 in 200 to 1 in 300.
- There is up to a 10-fold increased risk for VTEs when an individual is deficient in protein C. However, many individuals with Protein C deficiency are asymptomatic.
- Protein C deficiency accounts for approximately 3.7% of patients with VTE's.
- The risk of a recurrent venous thromboembolism in this group of patients is between 5 and 10%.

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PROTEIN S DEFICIENCY

Function of Protein S

- Protein S acts as a cofactor by enhancing the affinity of APC (activated protein C) for negatively charged phospholipids, which enhances the inactivation of factors Va and VIIIa.
- There are two types of protein S deficiency. However, distinguishing between types is typically not clinically relevant.
- The homozygous state is rare and presents with purpura fulminans.

Prevalence and Risk of VTE

- The prevalence of protein S deficiency in the general population is approximately 1 in 100 to 1 in 1000.
- Patients with protein S deficiency present with VTEs at younger ages.
- Approximately 50% of individuals with protein S deficiency have a VTE by age 27 years