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Review Article

Inherited and Acquired Thrombophilia

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Aim of the Study: The aim of this study is to review the indications for thrombophilia testing, diagnostic criteria, and therapeutic options, with a particular focus on congenital thrombophilia.

Keywords: Diagnostics; Genetic Testing; Thrombophilia; Thrombosis

Congenital Thrombophilia

Congenital thrombophilia results from genetic defects of proteins involved in hemostasis. It is diagnosed in approximately 3-8% of the population, depending on the study group and the parameter assessed.

The Most Common Forms of Congenital Thrombophilia Include: Congenital deficiencies of natural anticoagulants: antithrombin III, protein C, protein S. Mutations in genes encoding coagulation proteins: Factor V G1691A (Factor V Leiden) and Prothrombin G20210A

Less Common Causes Include: Homozygous homocystinuria, selected types of dysfibrinogenemia, increased activity of coagulation factors VII, IX, and XI

The prevalence of congenital defects is estimated as follows:

- Antithrombin III deficiency: 0.02-0.17%
- Protein C deficiency: 0.2-0.3%
- Protein S deficiency: 0.5%
- Factor V Leiden mutation: 2-5%
- Prothrombin G20210A mutation: 2-3% in the European population [1,2]

Clinical Manifestations of Congenital Thrombophilia

The clinical course is variable and may differ among individuals with the same risk factor. Some patients will develop thrombotic complications, while others remain asymptomatic. The risk of thrombosis is highest in individuals with genetic risk factors combined with additional triggers, such as:surgery,immobilizatio n,pregnancy [3]

In Patients with Congenital Thrombophilia, the Risk of Thrombotic Events Increases with Age

- Before the age of 45, thrombotic events occur in 60-80% of patients with natural anticoagulant deficiencies
- Recurrence is more common in patients with multiple risk factors

The Most Frequent Manifestations Include

- Deep Vein Thrombosis (DVT) of the lower limbs, often complicated by Pulmonary Embolism (PE)
- Thrombosis in atypical locations, such as upper extremity veins, abdominal veins, or cerebral venous sinuses
- Arterial thrombosis, most commonly affecting cerebral vessels, and less frequently coronary arteries
- Superficial thrombophlebitis, which occurs 6-fold more often in heterozygous Factor V Leiden carriers and 4-fold more often in heterozygous prothrombin G20210A carriers than in healthy individuals
- Neonatal purpura fulminans, caused by homozygous protein C or S deficiency

- Warfarin-induced skin necrosis, typically during the first days of therapy in heterozygous protein C deficiency (less often protein S deficiency)
- Familial clustering of Venous Thromboembolism (VTE)
- Recurrent thrombotic events

Congenital Thrombophilia and Pregnancy

Thrombophilia poses a particular risk to pregnant women. It may result in obstetric complications, including:recurrent miscarriages,Intrauterine Growth Restriction (IUGR),stillbirth. The risk of deep vein thrombosis in pregnant women with natural anticoagulant deficiencies is approximately 8 times higher than in healthy women. For heterozygous Factor V Leiden, the estimated incidence of thrombotic complications is 1:400-500 pregnancies, compared to 0.13-0.7:1000 in healthy women. In cases of recurrent miscarriage, late pregnancy loss, IUGR, or placental abruption, congenital thrombophilia should be included in the diagnostic workup [4,5].

Diagnostics of Congenital Thrombophilia

Diagnostic evaluation includes

- Clinical assessment: detailed history and physical examination
- Laboratory testing: antithrombin III, protein C, protein S, and optionally factor VIII activit
- Genetic testing: Factor V Leiden G1691A and Prothrombin G20210A mutations
- Imaging: Doppler ultrasound, magnetic resonance imaging, and vascular studies

Congenital thrombophilia is a significant risk factor for a first thrombotic event, but thrombosis is multifactorial, and not all carriers will experience thrombosis. Screening tests are not recommended, as the presence of thrombophilia does not necessarily predict recurrence or alter management.

Diagnostic evaluation should be selective and individualized.

The optimal timing for laboratory testing is approximately 12 weeks (3 months) after a thrombotic event, since:

- Factor VIII activity may be elevated in the acute phase
- Antithrombin III activity may be decreased

Genetic testing is not time-dependent, as it is performed on DNA material. Testing for common polymorphisms in MTHFR and PAI-1 genes is not recommended, as their association with thrombosis risk and impact on treatment is not clearly established [6,7].

Indications for Thrombophilia Testing

- Venous thrombosis at a young age (<50 years)
- Atypical site thrombosis
- Recurrent thrombosis
- Thrombosis triggered by a minor risk factor (e.g., short-term immobilization)
- Positive family history of VTE
- Thrombosis associated with hormonal contraception or hormone replacement therapy
- Recurrent pregnancy loss (>3 miscarriages), IUGR, fetal demise, placental abruption
- Thrombosis during pregnancy or the postpartum period
- Neonatal thrombosis

Acquired Thrombophilia

Acquired thrombophilia develops secondary to other conditions or environmental factors. [8-11]

Major risk factors include:

- Antiphospholipid Syndrome (APS)
- Malignancies
- Acquired resistance to activated protein C, e.g., during pregnancy, postpartum, or with Hormonal Therapy (OCP or HRT)
- Infections, including COVID-19, which carries a high thrombotic risk, as well as other bacterial and viral infections
- Elevated coagulation factors VIII, IX, XI
- Elevated fibrinogen levels

Diagnostic workup for acquired thrombophilia includes:

- Clinical risk assessment
- Serological testing, e.g., ELISA for APS antibodies
- Coagulation testing: APTT and PT

Antiphospholipid Syndrome (APS)

APS is an autoimmune disorder characterized by a predisposition to venous and arterial thrombosis, classified as acquired thrombophilia.

The pathogenic factor is the presence of antibodies against protein-phospholipid complexes with prothrombotic properties.

Key Diagnostic Antibodies Include

- Lupus Anticoagulant (LA)
- Anti-Cardiolipin Antibodies (aCL)
- Anti-Beta-2 Glycoprotein I Antibodies (anti-β2GPI)

APS Diagnosis

APS is diagnosed based on ACR/EULAR 2023 classification criteria:

- ≥3 points from clinical domains
- ≥3 points from laboratory domains [9]

At least two positive tests 12 weeks apart are required to confirm persistent antibody presence and exclude transient positivity. A positive antibody result must be correlated with clinical manifestations to establish the diagnosis of APS [9,12].

Management of Thrombophilia

Treatment depends on the type of thrombophilia and clinical presentation.

Acute Management

- Low-Molecular-Weight Heparin (LMWH)
- Followed By Vitamin K Antagonists (VKAs) or Novel Oral Anticoagulants (NOACs) [10,12]

Lifelong Secondary Thromboprophylaxis is Recommended

- After the first VTE episode in severe thrombophilia
- After the second VTE episode, or if two thrombophilia causes coexist
- NOACs are preferred for congenital thrombophilia due to lower bleeding risk
- VKAs are recommended for APS [10,12]

Chronic anticoagulation is not indicated for asymptomatic carriers of congenital thrombophilia. Prophylactic LMWH is considered during high-risk periods (major surgery, trauma, pregnancy), especially in anticoagulant deficiencies. Routine prolonged anticoagulation (>3 months) is not recommended after a first provoked VTE (e.g., trauma, major surgery) in congenital thrombophilia. However, it may be considered based on patient preference and acceptable bleeding risk 0.5-2% per year [10,12,13].

Such a strategy is suggested for:

- Antithrombin deficiency
- Homozygous Factor V Leiden or Prothrombin G20210A mutation
- Pulmonary embolism with intermediate or high mortality risk

Conclusion

Congenital and acquired thrombophilia represent significant clinical challenges. Accurate diagnosis and risk stratification are crucial for effective management. Appropriate treatment and prophylaxis can substantially reduce the risk of life-threatening thrombotic complications. With the increasing availability of genetic testing and modern anticoagulants, effective diagnosis and individualized therapy are now achievable for patients with thrombophilia.

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