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# MANAGING PATIENTS DIAGNOSED WITH THROMBOPHILIA FOLLOWING AN ACUTE THROMBOTIC EPISODE

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***Trombofilia Thrombophilia is a pathological condition characterized by excessive tendency to hypercoagulability occurring as a result of a hereditary and/or acquired predisposition and is based on changes in coagulation balance. Due to the lack of conclusive evidence supporting clinical testing benefits for inherited thrombophilia, future studies are likely to focus on new strategies to identify and classify patients with hypercoagulability states. Most recommendations for antithrombotic therapy in children are based on extrapolation of results from randomised studies in adults or from small cross-sectional clinical trials and mainly retrospectives in children. Although antithrombotic therapy in children usually follows the same indications as in adults, the distribution of diseases requiring antithrombotic therapy differs in children and adolescents.. Patients with thrombophilia and a history of thrombotic event (such as deep vein thrombosis, pulmonary thrombembolism, or stroke) may benefit from various lifestyle changes as well as drug treatment to reduce the risk of future thrombotic episodes and improve overall cardiovascular health. However, it is important to note that specific recommendations may vary depending on the individual's medical history, the severity of thrombophilia, and any other associated pathologies. The identification of risk factors associated with thrombophilia could lead to the indication of prophylaxis for asymptomatic patients with a family history of early thrombosis and high-risk thrombophilia. These strategies would have the advantage of being able to assess the interaction between inherited and acquired factors and could probably lead to individualised thrombotic risk profiling.***

***Keywords: thrombophilia, acute thrombotic episode, children, hypercoagulability, antithrombotic therapy, prophylaxis, screening, individualized profile***

## INTRODUCTION

Thrombophilia represents a group of conditions characterized by an excessive tendency to hypercoagulability resulting from a hereditary and/or acquired predisposition and is based on changes in coagulation balance. Thrombotic events in children have become an increasingly common problem, especially in pediatric hospitals, their prevalence varying quite a bit due to significant differences in the populations studied and the tests performed [1].

Thrombophilia testing rarely influences the management of an acute thrombotic episode in a child with a thrombotic event. The decision to institute anticoagulant treatment is made on the basis of clinical criteria, weighing the risks and benefits, which do not depend on genetic thrombophilia [2].

Thrombophilia can be hereditary or acquired and can occur through two mechanisms: decreased activity of endogenous anticoagulants (including deficiency / dysfunction of antithrombin, C and S proteins) or increased activity of procoagulant factors [3].

## PROCOAGULANT STATUS

There are many clinical contexts in which the balance between pro and anticoagulant factors tilts in favor of coagulation. The Virchow triad (endothelial lesion, altered blood flow, hypercoagulability) summarizes primary events or changes that together allow and favor the formation of a thrombus [4].

Testing for thrombophilia is recommended for pediatric patients who have experienced the following: purpura fulminans (PC-Ps); infants with spontaneous venous thrombembolism (AT III-Pc-Ps); children or adolescents with spontaneous/relapsing VTE or associated with another transient risk factor (not related to the presence of a central venous catheter) (AT III- Pc-Ps – APCR – F. V Leiden – PT 20210, lupus antibodies, anti-cardiolipin); children or adolescents with arterial thrombosis (AT III-Pc -Ps – APCR – F. V Leiden – PT 20210, homocysteinemia); children undergoing chemotherapy (l-asparaginase) (AT III-Pc-Ps); asymptomatic children with significant family and collateral history (parents with thrombophilia) (AT III-Pc-Ps – APCR – F. V Leiden – PT 20210) [5-12].

When screening for thrombophilia, a number of laboratory investigations are conducted, including protein S (Ps), protein C (Pc), antithrombin (AT) III, activated protein C resistance (APCR), lupus anticoagulant, homocysteine, and coagulation factors VIII and IX levels. Molecular tests are also carried out to detect hereditary thrombophilias, such as factor V Leiden mutation, factor II mutation, MTHFR gene polymorphisms, PAI gene mutation, and gene F XIII mutation.

The most severe forms of the disease are associated with major thrombophilias, which include homozygous factor V Leiden mutation, homozygous F II mutation, homozygous MTHFR 677 gene polymorphism, and antithrombin III deficiency.

The MTHFR gene has two common variations: C677T and A1298C.

Patients who have the C677T variant may have a family history of cardiovascular diseases, such as stroke, acute myocardial infarction, or deep vein thrombosis. They are also more likely to have hyperhomocysteinemia.

Patients with the A1298C variant may experience mental health problems due to neurotransmitter secretion disorders. These problems can affect their ability to manage emotions or stress levels, increase sensitivity to pain, impair concentration, and even hinder their ability to learn or relax.

There are several genes that play a role in coagulation balance, in addition to the common mutations and polymorphisms such as factor V Leiden, MTHFR gene polymorphism, and prothrombin mutation. These include:

- CBS 844ins68 gene polymorphism, which can cause hyperhomocysteinemia

- Glycoprotein IIIa, a membrane receptor that binds to various ligands in circulation and is involved in clot formation. Heterozygotes for allele b have been found to be resistant to antithrombotic drugs, such as aspirin.

- ACE-DEL/INS (angiotensin convertase) polymorphism, which is associated with homeostasis and changes in blood flow

- ApoE (ApoE4) polymorphism is associated with deep vein thrombosis, particularly in the lower limbs [13].

Paraclinical tests are not recommended during an acute episode, excluding cases of purpura fulminans. The examination was not conducted during periods of anticoagulant therapy with heparin or dicumarins (warfarin) less than 2 days after stopping heparin or 15 days after stopping dicumarins. The examination was conducted no earlier than 30 days after discontinuation for patients who had received hormonal therapy. Pregnant adolescents were examined no earlier than 90 days postpartum [14].

Paraclinical tests were performed at least 3 months after a thrombotic event. In the case of infants up to 6 months, normal values of hemostasis factors for each age stage were taken into account for interpreting the results. If hereditary thrombophilia was confirmed, parents were also tested.

## MATERIAL AND METHODS

A total of 67 patients, ranging from 3 months to 17 years of age, were analyzed in this study. Of the patients, 54% were male. The majority of patients were referred by a pediatric neurologist following an acute thrombotic episode, or by a pediatrician due to nonspecific symptoms such as headaches, nosebleeds, and bruising, as well as accompanying coagulation abnormalities. Additionally, many patients had a significant family history of thrombophilia, with either one or both parents having previously been diagnosed with the condition.

Out of the patients in the study, two were born through IVF. One patient had arteriovenous malformations in their brain. Two patients developed cerebral thrombosis after contracting SARS-CoV-2. Two patients were diagnosed with deep vein thrombosis in the ilio-saphenous-popliteal axis, one of which occurred after a femoral venous catheter was inserted. Two patients experienced thrombembolism and pulmonary infarction.

For patients diagnosed with thrombophilia, fasting homocysteine levels were monitored. 12% of patients had elevated levels, with a maximum of 24.7 umol/L (normal range < 10 umol/L). The activity of factors VIII and IX were also measured. 59% of patients had values over 200%. AT III activity was within normal limits for all patients at the time of examination. Protein C and S values were also within normal limits. 18% of patients had a positive result for lupus anticoagulant, while anticardiolipin antibodies were negative for all cases. Anti-beta2glycoprotein 1 antibodies were also negative for all cases.

## TREATMENT

When it comes to antithrombotic therapy in children, recommendations are often based on extrapolation from studies conducted in adults or from small cross-sectional clinical trials, which are mainly retrospective in nature. While the indications for antithrombotic therapy in children usually follow those for adults, the distribution of diseases requiring such therapy in children and adolescents is different. Additionally, some predisposing factors for thromboembolism are unique to children and adolescents. Most indications for antithrombotic therapy in children arise due to an underlying medical condition or intervention aimed at managing such a condition. The management of antithrombotic therapy in children is different from that of adults because of ongoing physiological changes that can affect the clotting process and influence how the body responds to antithrombotic therapy [15].

When treating patients who have experienced a thrombotic episode, it is important to work with a team of healthcare professionals, including a pediatrician, hematologist, vascular/cardiovascular surgeon, and pediatric neurologist/neurosurgeon, as needed.

Testing for thrombophilia is usually not a factor in treating a child who is experiencing a blood clot. The decision to use anticoagulant therapy is based on clinical criteria and the risks and benefits associated with it, rather than genetic factors [2].

It is uncertain how long newborns and children with a first thrombotic event should receive anticoagulation treatment. The ACCP guidelines suggest that newborns with VTE should be monitored or treated with anticoagulants for 6 weeks to 3 months, whereas older children should receive 3 to 6 months of anticoagulants [2]. However, these recommendations are grade 2C and are based on low-quality evidence, so they may not be the best option.

It is unclear whether the presence or absence of an inherited thrombophilia should affect the duration of therapy for a child with VTE, as there is not enough data on the subject, and existing guidelines do not address it [2].

To manage and prevent venous thrombosis in children, LMWH (Enoxaparin/Fraxiparin) should be used as a starting point for treatment. If rapid anticoagulation is necessary, heparin can be used as well (2C).

Treatment may then be continued with warfarin/acenocoumarol or LMWH (1B) for up to 3 months for secondary venous thrombosis or up to 6 months for idiopathic thromboses (1C). For children under 1 year of age, LMWH is preferred [2,16].

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Patients with thrombophilia and a history of thrombotic event (such as deep vein thrombosis, pulmonary thromboembolism, or stroke) may benefit from various lifestyle changes to reduce the risk of future thrombotic episodes and improve overall cardiovascular health. However, it is important to note that specific recommendations may vary depending on the individual's medical history, the severity of thrombophilia, and any other associated pathologies [17,18].

1. Adherence to treatment: If anticoagulant drugs are prescribed, it is essential that they are administered as directed by the prescribing doctor.
2. Regular medical follow-up: regular consultation by a pediatric hematologist, cardiologist, neurologist, cardiovascular surgeon is essential to monitor the evolution of pediatric patients, to adjust treatment if necessary and to determine immediate risk factors that may evolve to a new acute thrombotic episode.
3. Healthy diet: it is recommended to adopt a healthy diet for the cardiovascular system, rich in fruits, vegetables, whole grains, lean proteins and healthy fats. It is recommended to limit the intake of saturated and trans fats, added sugars and sodium. A balanced diet can help control weight, blood pressure, and cholesterol levels.
4. Physical activity: it is recommended to perform regular physical activity. Regular exercise helps improve circulation, maintain a healthy weight, and improve overall cardiovascular health.
5. Weight management: it is important to maintain a weight within normal limits for age, through a combination of a balanced diet and regular exercise. Obesity can increase the risk of acute thrombotic events and other cardiovascular complications.
6. Hydration: Proper hydration supports blood circulation and helps prevent complications related to dehydration.
7. Avoiding smoking, especially for adolescent patients.
8. Avoiding alcohol consumption.
9. Sleep management: age-appropriate sleep periods.
10. Compression stockings: In case of overweight patients it may be recommended to wear compression stockings to help improve blood flow.
11. Travel precautions: in case of travelling for long periods of time (especially by plane), precautions are recommended to prevent the formation of peripheral venous thrombosis, such as proper hydration, periodic movement and wearing compression stockings.
12. Medical alert: Informing medical staff about the diagnosis of thrombophilia and about any medications that the patient takes chronically, before undergoing any medical procedures or surgeries, as well as in case of severe infections requiring hospitalization and installation of a central or peripheral venous catheter.

Omega-3 fatty acids, commonly found in fatty fish and certain plant sources, have been studied for their potential health benefits, including cardiovascular health. While omega-3 fatty acids are generally recognized for their anti-inflammatory and cardiovascular benefits in adults, their specific effects in children with thrombophilia are less studied. Thrombophilia is a condition characterized by an increased tendency to form blood clots, and managing it usually involves a multifaceted approach.

Potential benefits of omega-3 fatty acids in children with thrombophilia may include:

1. Anti-inflammatory effects: Omega-3 fatty acids have anti-inflammatory properties that could help alleviate inflammation associated with thrombophilia and contribute to overall cardiovascular health.
2. Blood flow and platelet function: Omega-3 fatty acids can support healthy blood flow and normal platelet function, which could play a role in reducing the risk of clots.
3. Lipid profile: Omega-3 fatty acids can help improve lipid profiles by increasing HDL cholesterol levels and reducing triglyceride levels.
4. Vascular health: Omega-3 fatty acids can have a positive impact on blood vessel health and endothelial function.

While omega-3 fatty acids have potential benefits, it is important to approach their use in children with thrombophilia with caution and under the guidance of the treating physician, with the help of a dietitian. Factors to consider include:

- Drug interactions: Omega-3 fatty acids, especially in high doses, may have anticoagulant effects. This potential interaction with anticoagulant drugs should be considered especially for children with thrombophilia who are already receiving anticoagulant medication.
- Dosage and source: The appropriate dose and source of omega-3 fatty acids for children with thrombophilia should be determined based on the child's individual needs and under the guidance of a specialized dietitian who can develop a balanced, personalized diet that may contain foods such as fatty fish (salmon and mackerel), flaxseed, chia seeds and walnuts.

Research has shown that folic acid may have positive effects on endothelial function. The endothelium plays a crucial role in regulating blood vessel tone, blood flow, and various processes related to cardiovascular health. Studies have found that endothelium dysfunction is linked to the development of thrombotic events.

Folic acid is involved in homocysteine metabolism, and taking supplements can help lower homocysteine levels. High homocysteine levels have been associated with endothelial dysfunction, oxidative stress, and inflammation, all of which can contribute to the development of atherosclerosis and impaired endothelial function.

Taking 0.5-5.0 mg of folic acid daily has been shown to decrease plasma homocysteine levels by approximately 25%.

Various studies have investigated the potential benefits of folic acid supplementation on endothelial function, and positive effects have been indicated by them.

There are three ways in which folic acid supplementation can benefit endothelial function:

1. Vasodilation: Studies have shown that folic acid can improve the vasodilation process in individuals with endothelial dysfunction.
2. Nitric oxide production: Folic acid has the potential to enhance the production of nitric oxide, which helps relax blood vessels and regulate blood flow. Nitric oxide is essential for maintaining endothelial function.
3. Reducing inflammation and oxidative stress: Folic acid's ability to decrease homocysteine levels may help reduce inflammation and oxidative stress, both of which can negatively impact endothelial function.

Antiplatelet treatment: Aspirin, dipyramol and indomethacin are probably the most widely used antiplatelet treatments among children. Low doses of aspirin (antiplatelet doses) usually have minimal side effects in children, but aspirin should generally not be prescribed to children <16 years of age unless there are convincing clinical indications. Particular concerns about Reye's syndrome usually appear to be related to higher doses of aspirin (>40 mg/kg) [15].

Aspirin is commonly used for its antiplatelet effects, meaning it helps prevent blood platelets from aggregating and thrombus formation. While aspirin may be beneficial for certain medical conditions, its use in children with thrombophilia should be approached with caution and under the careful guidance of the treating physician.

Before considering aspirin use, it is important that a child with thrombophilia undergoes a thorough medical evaluation, including the child's medical history, risk factors, benefits, and potential risks of aspirin therapy.

The antiplatelet effects of aspirin may help prevent certain thrombosis, but it may not be appropriate for all cases of thrombophilia.

The type and severity of thrombophilia can influence the decision to use aspirin. In some cases, anticoagulant drugs (Fraxiparin, Enoxaparin, acenocoumarol) might be more suitable for preventing a thrombotic event.

Doses of aspirin for children are usually lower than those for adults and depend on the age, weight, and medical condition of the child. Antiplatelet doses are 1-5 mg/bkg/day [15].

It is very important to consider that aspirin can increase the risk of bleeding, including gastrointestinal bleeding and, in rare cases, intracranial hemorrhage. In the case of children with thrombophilia, the balance between hemostasis and thrombosis can be extremely fragile, so the risk-benefit balance is important.

The patients registered by the Pediatric Clinic of Fundeni Clinical Institute were monitored hematologically and by radiology follw-up throughout the antithrombotic treatment, in collaboration with the pediatric neurologist, cardiologist and vascular surgeon. Most patients received initial treatment with Enoxaparin at a dose of 1 mg/kg/dose at 12h and subsequent prophylactic treatment with 0.5 mg/kg/dose at 12h for a period of 3 to 6 months, with further favourable outcome. There are currently no studies that can prove the efficacy/benefit of aspirin use in the case of thrombosis prophylaxis in children (2C) [2,13].

Patients received adjuvant treatment with:

- Folic acid - 2.5-5 mg/day
- Vitamin B6 (0.1-2 mg/day) and B12 (0.9-2.4 mcg/day) depending on age
- diet and lifestyle changes (performing light physical activity, avoiding highly processed foods and concentrated sweets, energy drinks / high caffeine content)

No new thrombotic events were documented during monitoring.

## CONCLUSIONS

Identifying inherited thrombophilia can help provide information about why your child developed thrombosis, especially if the event was unprovoked. The identified person may be more likely to receive thromboprophylaxis during future high-risk situations.

Anticoagulant prophylaxis, which can greatly benefit hospitalized patients, is unfortunately not being utilized enough. Knowing if a patient has an inherited thrombophilia can improve treatment plans and help family members understand their potential risks.

While clinical testing for inherited thrombophilia hasn't been conclusively proven to be beneficial, future studies may focus on new strategies to identify patients with hypercoagulability states.

These strategies could involve worldwide coagulation tests, molecular assays, gene expression profiling, or single nucleotide polymorphisms. By assessing inherited and acquired factors, these approaches could lead to personalized thrombotic risk profiling.

Identifying thrombophilia may prompt prophylaxis for asymptomatic patients with a family history of early-onset thrombosis and high-risk thrombophilia.

This could reduce the overall costs of treating acute episodes and complications, and improve treatment compliance and patients' quality of life. It is important to develop a monitoring protocol for patients with thrombophilia to achieve these benefits.

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