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Review

Thrombosis in children: Which test to whom, when and how much necessary?

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Abstract

Pediatric thrombosis is multifactorial, and usually risk factors either congenital or acquired are present. After 2000, systematic reviews and meta-analysis on pediatric venous thromboembolic disease and inherited thrombophilia revealed elevated thrombotic risks in these children. In this review, we discuss thrombosis and new literature in various pediatric patient groups and the usefulness of thrombophilia testing.

Keywords: Childhood trombophilia, diagnosis of thrombosis, treatment of thrombosis

What is thrombosis?

Thrombosis is the abnormal formation of a clot composed of blood elements inside a vessel. It develops as a result of disruption in the delicate balance between the procoagulant, anticoagulant, and fibrinolytic systems (1-4). Three changes described by Virchow (5) in 1856 are involved in the formation of thrombosis:

1. Changes in blood flow (rheology, stasis)
2. Changes in the vascular wall
3. Changes in the blood levels of coagulation factors and their inhibitors

Although endothelial injury and platelet functions are important in arterial thrombosis, stasis and disorders of the coagulation-fibrinolytic system come to the forefront in venous thrombosis (5-7). In the pediatric age group, thrombosis occurs most frequently before the age of 1 year and in adolescence (1-5). The incidence of childhood thrombosis is 0.07-0.14/10,000 in the general population. This incidence has been reported to be 5.3/10,000 in children presenting to hospital, 0.51/10,000 in all newborns and 0.24/10,000 in children in neonatal intensive care units (1-4). With survival of many patients who were being lost very early in the past years, more frequent use of catheters and use of interventional procedures that trigger formation of thrombosis, the current incidence of thrombosis in children has shown a 70% increase (from 34/10,000 to 58/10,000) (8, 9).

The morbidity and mortality rates are high, although it occurs more rarely compared with adult thrombosis and does not develop in the absence of a triggering factor; the rate of mortality related with direct venous thromboembolism (VTE) is 2.2%, the frequency of post-thrombotic syndrome is 12.4%, and the recurrence rate for thrombosis is 8.1% (10).

The diagnosis of thrombosis is made more frequently and more easily in children due to noninvasive diagnostic methods [Doppler and ultrasonography (US), echocardiography, computed tomography (CT) and magnetic resonance imaging (MRI)]. Therefore, the concept of 'childhood thrombotic diseases' is currently recognized and is included in the differential diagnosis of many conditions, whereas it had been regarded as a morbidity of adulthood until the 2000s. Both pediatricians and patients have started to become conscious in this area.

Variance in age groups and the underlying diseases renders it difficult to conduct thrombosis studies in children

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(etiology, research, prevention) and to establish treatment guidelines. Therefore, most guidelines related with childhood thrombosis have been prepared with inspiration from adult studies.

What is the role of the tests for hereditary thrombophilia in thrombosis?

Performing hereditary thrombophilia tests is a common clinical approach in individuals with thrombosis or in their families. The incidence of hereditary disorders causing a tendency to venous thromboembolism is 5-10% in the general population and as high as 40% in individuals who have had VTE (3-8, 11, 12). Therefore, important groups including the Subcommittee for Perinatal and Pediatric Thrombosis of the Scientific and Standardization Committee (SSC) of the International Society of Thrombosis and Hemostasis (ISTH) recommended hereditary thrombophilia testing in all patients with thrombosis from the end of the 1990s when hereditary factors were discovered to the beginning of the 2010s (1, 4, 5, 13-16).

In daily practice, hereditary thrombophilia testing is performed because of VTE in 42% of cases, because of arterial thrombosis in 15-23%, and because of congenital complications in 13-17% (6-8). Individuals in whom hereditary thrombophilia testing is performed because of the presence of a family member who carries a risk factor for hereditary thrombophilia or who has had VTE constitute 12-16% of individuals tested (8). Considering the number of patients with thrombosis, it seems that a considerably high amount of money and effort is spent for hereditary thrombophilia tests; it was shown that 22,000 tests were performed for factor 5 Leiden (FVL) and 20,000 tests were performed for prothrombin mutation (PTM) in 2007 in Italy (population 60 million), and 20,378 tests were performed for FVL in the same year in Australia (population 20 million) (8).

The data collected for children with thrombosis have caused concerns about the advantage of hereditary thrombophilia testing despite this much money and effort and caused us to ask the questions "who should we test, which test should we use, and when should we perform testing?" In this review, we aimed to demonstrate which pediatric cases of thrombosis required hereditary thrombophilia testing in light of the literature. In this way, we hope that unnecessary effort, money, and time will not be spent.

What is thrombophilia?

The presence of tendency to thombosis is called thrombophilia. Patients who spontaneously develop thrombosis in the absence of clinical triggering factors, who develop excessive VTE in comparison with the triggering factor, who develop recurrent thrombosis, and who develop thrombosis at a young age constitute the thrombophilia group. In addition, carrying hereditary factors that cause the formation of thrombosis may also be interpreted as thrombophilia. An individual may have thrombosis without positive laboratory findings or positive laboratory findings may be present in the absence of thrombosis (17).

Is thrombosis in children a hereditary disease?

Acquired and hereditary factors are involved in the development of the picture of thrombosis. The risk of thrombosis may increase in individuals who carry one or several hereditary thrombophilia factors, but these individuals may not have any thrombosis attacks for a life time. Presence of long asymptomatic periods between thrombosis episodes in individuals with recurrent thrombosis attacks is important in terms of showing the fact that hereditary factors alone are not sufficient and acquired factors are also important in the development of thrombosis (1-10, 17-19).

It has been shown that acquired factors cause thrombosis more frequently and more efficiently compared with hereditary factors in childhood thrombosis (1-8). Thrombosis in children in the absence of any triggering factor occurs very rarely (less than 5% of all cases of thrombosis). Revel-Vilk et al. (20) found the rate of hereditary thrombophilia as 13% in 171 children who were found to have VTE. Generally, acquired factors including use of a catheter, malignant diseases, infection, heart disease, and nephrotic syndrome can be demonstrated in the majority of cases of childhood VTE (4, 8, 17). Hereditary factors are only important in the adolescence age group and in children who develop VTE in the absence of triggering factors; the rate of hereditary thrombophilia is 60% in these cases (20).

Racial differences are important in terms of thrombosis. In studies conducted in Canada, France, Italy, and England, carrying a risk factor for thrombophilia was found to have varying degrees of contribution to thrombosis (4-10). There is an inadequate number of studies in this area in Turkey. Multi-center prospective studies including homogenous patient groups will be invaluable because they will reflect our country's data.

Recommendation: *Possible triggering acquired factors should be investigated carefully before hereditary factors in all children with thrombosis. If there is no acquired triggering factor and there are other family members who have had thrombosis, these children should be examined in terms of hereditary thrombophilia factors.*

Is familial history important in children with thrombosis?

Familial history is less determinative for thrombophilia in adult thrombosis, whereas the presence of a family history of

thrombosis in children has shown to be the most important marker in multivariate analyses (21). The presence of a family history of thrombophilia provides important clues for performing hereditary thrombophilia testing. Individuals with a family history of early stroke and myocardial infarction (<45 years), thrombophlebitis episodes or pulmonary emboli after delivery carry a high risk in terms of thrombosis.

Recommendation: *Family history of thrombosis should be taken carefully in all children in whom hereditary thrombophilia tests are planned because of thrombosis or any other reason.*

What is the value of hereditary thrombophilia tests in children with thrombosis?

In the examination of hereditary thrombophilia, the most common tests performed include antithrombin (AT), protein C (PC), protein S (PS), FVL and PTM tests. Homozygous AT, PC, PS deficiency or the presence of all these in association is described as 'high-risk thrombophilia' and FVL or PTM carrier state is described as 'low-risk thrombophilia' (1-7, 12). It has been shown that children with AT deficiency have a 8.73-fold increased risk for VTE (95% CI: 3.12-24.42), children carrying multiple mutations carry a 8.89-fold increased risk (95% CI: 3.43-23.06) and children with PTM have a 2.63-fold increased risk (95% CI: 1.61-4.29) (5). These rates are similar to those found in adult studies (12).

There are controlled studies showing that the risk of development of stroke and thromboembolic complications is higher in children carrying hereditary thrombophilia risk factors (4, 5). However, the literature also includes studies conducted by Canadian, Dutch, and German study groups with controversial results (4, 7, 8, 18). For example, it was reported that hereditary thrombophilia testing was unnecessary in the presence of thrombosis in children and newborns in one study (4, 22). Another study recommended PTM examination and even screening of siblings and parents in children with arterial-venous thrombosis (4, 23). When the data of both studies were examined, it was observed that the median age was 2.3 months in one study and 6 years in the other, and the presence of catheters was very different between the two studies (77% in one study and 18% in the other) (4).

Although studies related with the effect of hereditary risk factors determined as a result of screening tests at the time of treatment or maintenance of prophylaxis were conducted, clear results that resulted in definite judgements could not be obtained (24-29).

Until 5-6 years ago, it had been recommended that methylenetetrahydrofolate reductase (MTHFR) mutation examinations should be performed and homocysteine levels should be measured in patients with thrombosis. However, Simone et al. (24) showed that this had no contribution to thrombosis. Therefore, these tests should no longer be included in thrombosis panels. In fact, it is very difficult to convince many patients who are unnecessarily concerned and in panic because they have been found to have the MTHFR gene mutation that this is not a dangerous mutation in daily practice.

The emergency treatment approach is the same in all patients with thrombosis. Therefore, knowing hereditary thrombophilia risk factors is not very helpful for physicians in the acute thrombosis phase. The conditions for which hereditary tests are important in children with thrombosis include homozygous deficiency of AT, antiphospholipid antibody syndrome (APAS), homozygous or combined heterozygous PC, PS or AT deficiency, and newborns and children with clinical purpura fulminans, disseminated intravascular coagulation (DIC) or large vessel thrombosis. In these patients, early diagnosis and replacement treatment (FFP or AT, PC concentrate) may be lifesaving. However, these cases occur considerably rarely in clinical practice (4, 30).

Recommendation: *Hereditary thrombophilia testing should be performed in the emergency period if the result will direct or change treatment. Otherwise, the patient should be monitored and this decision should be made in the follow-up.*

In adult studies, it has been shown that all hereditary thrombophilia factors cause predisposition to venous thrombosis and there is no hereditary that causes an increasing tendency to arterial thrombosis except for hyperhomocysteinemia (5-10, 17-19). There is still no consensus on the issue of which patient groups should be tested for hereditary thrombophilia.

In view of all this information, our general recommendation for children with thrombosis is as follows: *Hereditary thrombophilia examination should be performed, if thrombosis is found, recurs, and occurs in abnormal regions in a pediatric patient and if the family history is positive.*

However, performing hereditary thrombophilia testing is controversial in some clinical conditions. Considering the great impact of acquired factors in the development of thrombosis in children, the decision for hereditary thrombophilia testing should be made by taking 'the special clinical condition' that triggers thrombosis into account.

What should be taken into consideration when examining hereditary thrombophilia tests in children with thrombosis?

Factor 5 leiden and PTM among the hereditary thrombophilia tests should be examined as genetic mutation

analyses and the possibility of erroneous diagnosis is low for these tests. However, it is difficult to qualitatively perform AT, PC, and PS tests in which blood levels are measured and erroneously low blood levels are confronted more frequently compared with actual deficiency (31). Many different clinical conditions may cause reduction in PC, PS, and AT levels;

Low levels of protein C and PS may be found with the use of vitamin K antagonists and oral contraceptives (OC), hepatic diseases, nephrotic syndrome, hemodilution, and pregnancy.

Low levels of AT may be found with the use of heparin, hepatic disease, nephrotic syndrome, hemodilution, and after use of L-asparaginase and in disseminated intravascular coagulation (DIC) syndrome.

It should also be kept in mind that the blood levels of AT, PC, and PS will be reduced in relation with consumption in the acute thrombosis period. The measurement of blood levels of AT, PC, and PS in the parents instead of the patient in the acute period will be supportive for an accurate diagnosis. The diagnosis should never be based on a single laboratory result and the possibility of transient or erroneously low levels should be excluded by performing at least one more test. Repeating the tests 3-6 months after the diagnosis of thrombosis in the period during which an anticoagulant is not used would be an appropriate approach (4, 8, 31-33).

What are the special clinical conditions in the investigation of hereditary thrombophilia in children?

Before hormone-OC treatment

Hereditary thrombophilia testing is still being ordered before hormone or OC treatment in many patients, though its redundancy has been shown and it is not recommended in many studies; however, this issue is still controversial (4, 8, 10, 12, 17). We recommend that hereditary thrombophilia testing before hormone-OC treatment should be performed according to "a carefully taken personal and family history of thrombosis." Accordingly;

Recommendation: *1- We do not recommend hereditary thrombophilia testing before hormone-OC treatment in individuals who do not have a positive personal or family history of thrombosis.*

2- We recommend hereditary thrombophilia testing before hormone-OC treatment in individuals who have a positive family history of thrombophilia and first-degree relatives with high-risk hereditary characteristics for thrombophilia (AT, PC, PS deficiency).

3- We do not recommend hereditary thrombophilia testing before hormone treatment in individuals who have first-degree relatives who are FVL or PTM carriers (low thrombophilia risk) and do not have a history of thrombosis. However, we raise the awareness of these families in terms of thrombosis and recommend that they should pay special attention to dehydration.

Patients with malignancy

In patients with leukemia, steroid treatment, L-asparaginase treatment, and use of catheters cause thrombosis. Until the beginning of the 2000s, it had been recommended that hereditary thrombophilia testing should be performed at the time of diagnosis in patients with leukemia, but studies showed that thrombosis developed in the first one month in 34% of patients leukemia with catheters, but it was clinically asymptomatic and no hereditary factors were found in any patients (34). Albisetti et al. (35) found that the possibility of thrombophilia was lower in patients with malignancy who were found to have catheter-related thrombosis compared with patients who did not develop thrombosis (4%, 12%).

Recommendation: *We think that it is unnecessary to perform hereditary thrombophilia testing in children with leukemia or malignancy unless the child is symptomatic or has a positive family history of thrombosis*

Neonatal period

Catheter-related thrombosis in newborns: Newborn patients with thrombosis are generally not included in thrombosis studies conducted with children. The incidence of VTE in newborns has been reported as 5.1/100,000 births (36). Park et al. (37) found the risk of thrombosis in the neonatal period as 9.2% in a literature review published in 2016 in which the years between 1948 and 2012 were examined. In neonatal thrombosis, acquired causes are found with a higher rate compared with the causes of hereditary thrombophilia; at least one cause is present in 95% and catheters are blamed most commonly (36, 38). In newborns, catheter-related thrombosis is a rare but serious problem. Although previous studies have emphasized that 89% of cases of neonatal thrombosis are related with catheters, new studies show an association with catheters with a rate of 54% in venous thrombosis and with a rate of 27% in arterial thrombosis (34). The reason of the reduction of catheter-related thrombosis in newborns is explained by prophylactic administration of heparin and use of more appropriate catheters and better care of catheters. Endothelial injury, presence of foreign body, disruption of laminar blood flow, inflammation, and infusion of hypertonic solutions are blamed in the etiology of catheter-related thrombosis. In the meta-analyses of Young et al. (22),

AT, PC, and PS deficiency was not found in any newborn with catheter-related thrombosis. One patient was found to be heterozygous for FVL. Similarly, hereditary thrombophilia factor was not found in any newborn with catheter-related thrombosis in another study (23). Berfeloe et al. (39) found FVL with a rate of 5% and PTM with a rate of 11% in cases of catheter-related thrombosis; however, the number of subjects was very low in this study. There are many studies that conflict with each other in this issue in the literature (22, 23, 34, 39).

In newborns, thromboses occurring in umbilical and peripheral catheters constitute 80% of all cases of thrombosis. Thrombosis is most commonly found in the hepatic vein, right atrium, and vena cava inferior. In treatment, low-molecular-weight heparin may be used efficiently in combination with thrombolytic drugs. Although use of prophylactic heparin does not prevent the development of thrombosis, it prolongs the catheter usage time and reduces the possibility of occlusion (37, 40).

Recommendation: *We do not recommend hereditary thrombophilia testing in newborns with catheter-related thrombosis in light of the current information.*

Non-catheter–related thromboses in newborns: The most common non-catheter–related thrombosis in newborns is renal vein thrombosis (RVT). Approximately 57% are bilateral and the thrombus extends to the vena cava inferior in more than half of all cases. Perinatal asphyxia, intrauterine growth retardation, sepsis, and polycythemia are risk factors. Its incidence is 2.2/100,000. The possibility of hereditary thrombophilia is higher in newborns with renal vein thrombosis compared with newborns with catheter-related thrombosis. In two comprehensive studies conducted in relation with this issue, the presence of hereditary thrombophilia was found with a rate of 43% in one study and at 68% in the other study (35, 37). Additional acquired risk factors including asphyxia, sepsis, diabetic mother, and catheters are also present in addition to hereditary thrombophilia in patients with renal vein thrombosis (4, 8, 40, 41).

Recommendation: *We recommend hereditary thrombophilia testing in newborns with renal vein thrombosis.*

Children with heart disease

In children with heart disease, venous (52.5%), arterial (35.6%), venous and arterial (11.9%) thrombosis may be observed. The most important cardiac risk factors for the development of thrombosis include congenital heart disease and cardiomyopathy. The other important acquired risk factors include surgery, angiography, presence of catheter, infection, and hypoxia. The contribution of hereditary thrombophilia to thrombosis is considerably low in children with cardiac disease (4, 42).

Recommendation: *Hereditary thrombophilia testing has no advantage in thromboses in children with congenital heart disease.*

Children with nephrotic syndrome;

In children with nephrotic syndrome, thrombosis secondary to AT and PS deficiency may develop and its rate has been reported as 9-36%. In patients with nephrotic syndrome with thrombosis, hypoalbuminemia (83%) and infection (31%) are blamed more than hereditary thrombophilia (10,43).

Recommendation: *Hereditary thrombophilia testing has no advantage in children with nephrotic syndrome who develop thrombosis.*

Stroke-transient ischemic attack

When stroke and transient ischemic attack is found in the neonatal period, AT, PC, and PS deficiency should be considered specifically. However, it should be kept in mind that AT, PC, and PS are physiologically low in newborns and one should pay attention to this aspect when making the diagnosis. It would be more appropriate to reevaluate the patient after thrombosis recovers and the blood levels reach the adult level (after the age of 6 months-1 year) (4, 8, 32).

Studies have shown that the incidence of stroke and transient ischemic attack in newborns and children is increased 7.06-fold (95% CI: 2.44-22.42) in AT deficiency, 8.76-fold (95% CI: 4.53-16.96) in PC deficiency, 3.20-fold (95% CI: 1.22-8.40) in PS deficiency, 3.26-fold (95% CI: 2.59-4.10) in FVL mutation, 2.43-fold (95% CI: 1.67-3.51) in PTM, 1.58-fold (95% CI: 1.20-2.08) in MTHFR mutation, 6.95-fold (95% CI: 3.67-13.14) in the presence of APA, 6.27-fold (95% CI: 4.52-8.69) with an increase of lipoprotein (a) and 11.86-fold (95% CI: 5.93-23.73) in the presence of combined hereditary thrombophilia risk factors (4, 20, 44, 45).

Generally, the presence of thrombophilia has been reported with a rate of 20-50% in childhood strokes, similar to VTE. In older children, PC deficiency, increased lipoprotein (a), FVL and PTM are risk factors for the recurrence of stroke (4).

Recommendation: *It would be appropriate to perform hereditary thrombophilia testing in children with findings of stroke and transient ischemic attack.*

Do hereditary thrombophilia tests have an impact upon anticoagulant treatment-prophylaxis time?

In patients with thrombosis, treatment is administered for 2-6 weeks and subsequently, prophylactic anticoagulant treatment is administered for 3-6 months to prevent recurrence of thrombosis. Another objective of hereditary thrombophilia testing in children is to determine which

patients may develop recurrence of thrombosis (46-49). There is no controlled study related with the advantage of prolonging thrombosis treatment and prophylaxis according to the results of hereditary thrombophilia tests in children (4, 5, 8, 17). In adult studies, the relative impact of the presence of hereditary thrombophilia on recurrent thrombosis [RR (relative risk)] is 1,4-2,5 and it has been advocated that it is not a very appropriate approach to decide the time of anticoagulant prophylaxis according to the presence of hereditary thrombophilia in adults (47).

In a pediatric study related with this issue, children who were found to have thrombosis were divided into three groups; anticoagulant treatment was given for three months in one group without performing hereditary thrombophilia testing, for six months in another group without performing hereditary thrombophilia testing, and for three months or six months according to tests result by performing hereditary thrombophilia test. When the results were evaluated, it was observed that the lowest cost and the highest efficiency was obtained in the patient group in which hereditary thrombophilia testing was not performed and anticoagulant treatment was given for three months (46). It was also observed that prolonging anticoagulant treatment in patients who hereditarily carried a high risk of thrombophilia did not provide advantage in terms of recurrence of thrombosis or development of complications. In contrast, some studies have shown that the risk of hemorrhage was higher compared with the risk of thrombosis in children who used anticoagulant treatment for a long time because they carried a hereditary thrombophilia risk factor (13, 22). The other patient group who may develop thrombosis in the absence of a triggering factor and who need long-term anticoagulant treatment comprises patients who are found to have APA. However, these antibodies may be found to be transiently increased in some healthy children and it is not considered very appropriate to give anticoagulant treatment to children with APA in the absence of thrombosis, because thrombosis occurs very rarely in healthy children (0.07/100,000).

Recommendation: *1- Prolonging anticoagulant treatment according to hereditary thrombophilia test result may be helpful in children with thrombosis.*

2- Prolonging the prophylaxis time may be helpful in children who carry a high risk of thrombosis according to hereditary thrombophilia test result (AT, PC, and PS, homozygous FVL or multiple hereditary risks)

Should children of families carrying hereditary thrombophilia factor be investigated?

Another advantage of performing thrombophilia testing in children is the detection of hereditary risk factors in individuals who are as yet clinically asymptomatic. It is known that the risk of thrombosis is higher in individuals who are carriers for PC, PS and AT mutations in presence of triggering factor compared with carriers of FVL or PTM mutations (12). The risk of thrombosis in use of OCs is 4.3% in individuals with a positive family history of thrombosis, 0.7% in individuals with a negative family history of thrombosis, and 0.04% in the general population (9). Thrombosis prophylaxis may be helpful in these individuals in acquired conditions increasing the risk of thrombosis including use of OCs, hormone treatment, pregnancy, and puerperium. Relieving individuals with a positive family history of thrombosis who have normal PC, PS, AT, FVL, PTM tests may lead to an erroneous influence (12). A much higher risk for thrombosis in these individuals who have no hereditary risk factor for thrombosis compared with the general population suggests that there may be other hereditary factors that we do not know yet. However, Franchini et al. (11) did not recommend performing of measurements that have not been proven to be definitely associated with thrombosis including homocysteine, MTHFR, tissue factor pathway inhibitor, coagulation factor level, lipoprotein (a), thrombomodulin, endothelial protein C receptor, angiotensin converting enzyme, protein Z and protein Z-dependent protease inhibitor, and disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS13) in these patients.

Many physicians who care for adults find it appropriate to screen asymptomatic family members of patients with thrombophilia. Screening is more strongly recommended especially in women of childbearing age who carry a risk for VTE. In contrast to adults, the contribution of hereditary thrombophilia in the development of VTE and its complications is still controversial in healthy children. The literature contains a small number of studies examining the frequency of thrombosis in young (aged below 15 years) family members of patients with thrombosis (4-10, 17-19). In one study conducted in this area, young (aged below 15 years) family members of adult patients who had thrombophilia symptoms were followed up for 5 years and no symptomatic or asymptomatic VTE attack was observed in these children, 26% of whom were found to have one or multiple hereditary thrombophilia risk factors. Again, the frequency of thrombosis was not found to be different in these children compared with healthy children, although thrombosis prophylaxis was not administered in the presence of acquired factors (surgery, trauma) (10). This study is valuable in terms of showing that thrombosis prophylaxis is not necessary in children carrying hereditary risk factors even following surgery or trauma.

If tests are being planned to be performed because the child is a member of a family with a history of multiple thromboses, it would be more appropriate to perform

these tests at advanced ages when the risk of exposure to acquired factors is increased because thrombosis related with hereditary thrombophilia alone is very rare in children. In addition, it should be kept in mind that blood levels of PC, PS, and AT, which are high-risk factors for thrombophilia, are physiologically low in childhood because of having an immature hemostasis system and may lead to incorrect diagnoses.

On the other hand, stress caused by the state of carrying a hereditary thrombophilia risk factor may lead to different problems. There are no qualified pediatric studies in this area. However, Cohn et al. (50) showed that carrying a hereditary risk factor increased the percentage of anxiety from 27% to 43% in adults, though it did not cause as much concern as the state of carrying a hereditary risk for breast cancer. It is not easy to convince individuals who have no symptoms to have injections every day in risky periods. This is especially more difficult in pediatric patients.

Recommendation: *It is not necessary to perform hereditary thrombophilia testing in children aged below 15 years in families who carry only hereditary thrombophilia risk factors.*

Thus far, we have summarized the following:

Which children should be examined in terms of thrombophilia?

Should asymptomatic family members be examined?

Should prophylaxis be given to children who carry a risk of thrombophilia especially in periods during which problems may occur?

It is evident that these issues are not clear and there are gaps. Therefore, multi-center controlled studies should be conducted with study groups composed of homogeneous patients and carriers who have not developed thrombosis and long-term, risky periods and problematic conditions should also be monitored in these studies. When pediatricians are confronted with a patient with thrombosis, they should take family history carefully, share the risks with the family, and implement the best treatment approach for each patient by consulting centers that see more patients in this area, if necessary. A good pediatrician should know that they should monitor newborns or children with malignancy who have undergone catheter placement and children who receive chemotherapy including mainly L-asparaginase or children with congenital heart disease in terms of development of thrombosis more closely compared with children who carry hereditary thrombophilia risk factor (4-11).

However, pediatricians avoid anticoagulant treatment in thromboses in children because they are wary of complications, especially in the neonatal period. The majority administer conservative treatment for renal, central nervous system, and even sinovenous thromboses because of the presentation of a single case in most publications, scarcity of studies including large series, great difference between the clinical pictures and courses of thrombosis in adults and children, use of adult guidelines as treatment schedules and adjustment of doses and preparations of medications according to adults; pediatricians have contented themselves with fluid, electrolyte treatment, and adjustment of blood pressure.

Our aim in thrombosis treatment is the prevention of enlargement of thrombosis; pulmonary, central nervous system, and other vital organ emboli; recurrence of thrombosis; and mortality. The rate of mortality related with thrombosis is lower in children compared with adults. This rate has been reported to be 3% in studies conducted in recent years. The risk of pulmonary emboli in patients who have been found to have thrombosis is close to the rate of deep vein thrombosis (20%) (4, 5, 8, 10, 17).

Children with thrombosis should absolutely be evaluated carefully and treated rapidly because the risk of recurrence is high, the possibility of finding an underlying cause is high, and they have a 60-80–year lifetime ahead. The success rate of achieving normal blood flow in the obstructed vessel in children is 50% with anticoagulant drugs and 90% with thrombolytic treatment. The pediatrician's mission is to make the diagnosis and administer treatment, and to implement preventive health service (to prevent the development of thrombosis).

In conclusion, the association between hereditary thrombophilia and VTE is well known in adults. Acquired factors are more predominant in thrombosis in the pediatric age group. It is not yet known what contribution the presence of hereditary thrombophilia factor makes to the risk in children with predisposition to thrombosis who have undergone catheter placement and been diagnosed as having congenital heart disease or nephrotic syndrome. The association between hereditary thrombophilia and recurrence of thrombosis is not clear either. Hereditary thrombophilia test results do not change the treatment plan in children. However, it would be helpful to administer thrombosis prophylaxis in risky periods (e.g., surgery, pregnancy, puerperium, OCs use, immobility) when asymptomatic individuals with AT, PC, and PS deficiency are known in advance. We think that thrombophilia testing will not be helpful in children aged below 15 years because thrombosis related with thrombophilia alone is very rare. We think the following will be helpful for patients:

1. Effective treatment in conditions where fluid loss occurs intensively because of fever, diarrhea and vomiting, and hematocrit increases secondarily predisposing to thrombosis in terms of rheology,
2. Avoiding long-term immobility (surgery, orthopedic problems),
3. Avoiding long journeys,
4. We think that informing about healthy nutrition and lifestyle (avoiding smoking, doing physical exercise) will be as helpful as hereditary thrombophilia testing and thrombosis prophylaxis.

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