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RECURRENT THROMBOSIS IN AN ADOLESCENT WITH ANTIPHOSPHOLIPID SYNDROME AND MULTIPLE RISK FACTORS

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Abstract

Inherited thrombophilia increases the risk of a first thrombotic event and venous thromboembolism. Coexistence of inherited thrombophilia and autoimmune disorders (antiphospholipid syndrome) can lead to severe recurrent venous thrombosis. A sixteen-year-old boy with a family history of pulmonary embolism developed multiple venous thromboses (deep vein thrombosis) and severe post-thrombotic syndrome. The first thrombotic event occurred after trauma. The patient was considered carries for inherited thrombophilia. Subsequent investigations revealed deficiency of protein C, S and persistence of lupus anticoagulant. High level of homocysteine was also determined. Each episode of acute respiratory viral infection resulted in thrombosis. Post-thrombotic syndrome occurred due to the failure of recanalization. Failure of recanalization is now recognized as an independent predictor of recurrent deep vein thrombosis. Doppler ultrasound detected jugular vein thrombosis and left and right femoral vein thrombosis. Anticoagulants were prescribed, but they did not prevent the thrombosis. The patient took warfarin (INR=2.5-3.0, sometimes 4.0), but it was not effective. Thus, the patient was considered to have inherited thrombophilia and antiphospholipid syndrome disorder combination. Low molecular weight heparin was prescribed for the prevention of thrombosis (Anti-X-a=0.6-1.0), and hydroxychloroquine was prescribed as a mild immunosuppressive drug.

Venous thromboembolism is a rare disease in children. Commonly, it is a multifactorial condition caused by both genetic and acquired risk factors. Patients with family history and early-onset thrombosis need screening for inherited thrombophilia, autoimmune disorders or oncology. In addition, the impact of risk factors must be taken into consideration. The length of treatment and preventive therapy remains unclear and depends on the risk factors.

Keywords: *recurrent thrombosis, children, inherited thrombophilia, antiphospholipid syndrome, lupus anticoagulant.*

Introduction

Thrombotic complications are the cause of high mortality, not only in the elderly. Currently, more researches are devoted to the study of this problem in the young population. Among the most frequently mentioned reasons is the combination of genetic predisposition and various risk factors. Thus, thrombosis has multifactorial nature. Episodes of thrombosis in young population often develop due to hereditary predisposition, such as mutations in the genes of blood coagulation and fibrinolysis. Trigger factors include infections, trauma, surgery, presence of a central venous catheter. Among the diseases with common involvement of thrombosis are oncological, systemic connective tissue diseases, more often systemic lupus erythematosus, autoimmune disorders, particularly the carriage of antiphospholipid antibodies. Significant risk factors include intake of estrogenic drugs, glucocorticoids and smoking [*Ishola T et al., 2016*]. Uncovering the causes of thrombosis is important for the treatment and subsequent prevention.

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Here is the history of a patient with recurrent thrombosis caused by a combination of several contributing factors.

Patient T.A., 16 years of age, was admitted with complaints of migrating red spots on the legs, painful on pressure. Life history: a boy born from the second pregnancy proceeding with anemia. At birth: weight – 3440 *g*, height – 52 *cm*. Early psychomotor development is age appropriate. Breastfed up to 1 year and 5 months; vaccinated in accordance with the national calendar. Early physical and psychomotor development is age appropriate. Allergy: to milk, citrus causing a rash; allergy to aspirin, pentoxifylline, causing a rash. Family history: paternal grandfather died of a pulmonary embolism, maternal grandmother has polyarthritis, and maternal grandfather has lung cancer.

History of the disease: The first event of the disease occurred in August 2012, after the infected wound of the left foot was complicated by infiltration and pigmentation along the vessel on the left lower leg. For about a year, the infiltration was not reduced, but the patient had no subjective complaints, had not seen a doctor and was not treated. The cause of the infiltration was not found. In August of 2013, the patient developed acute condition with a high fever, severe pain in the left side of the head accompanied by dizziness, vomiting, ringing in ears. He was treated for acute respiratory viral infection, received antibiotic therapy with no efficacy.

In September 2013, the saphenous vein infiltration in the left calf increased. The examination allowed diagnosing thrombosis of saphenous vein in the left lower leg. All this was complemented by the pain in the neck and painful palpable cords in the neck veins. The general blood test revealed high indices of erythrocyte sedimentation rate 30-60 *mm/h*, C-reactive protein up to 36 *mg/l*, hyperfibrinogenemia – 9 *g/l*. The low level of protein C – 10% was found to be the cause of thrombosis though D-dimer was within the norm. Anticoagulant, antibiotic therapy was initiated though without efficacy. The patient continued to have high fevers, intense headaches, pain in the lower limbs. Phlebitis appeared in the sites of injections. Differential diagnosis was initiated between antiphospholipid syndrome, systemic vasculitis, and hereditary thrombophilia. Laboratory tests showed that the level of anticardiolipin antibodies was in norm, antibodies to β-2 glycoprotein-1 were not found, the level of anti-neutrophil antibodies, antinuclear antibodies were normal. The soft tissues ultrasound revealed a partial thrombosis of saphenous vein. Doppler ultrasound of superior vena cava revealed thrombotic mass in *v. cefalica*. MRI of the brain reported internal asymmetric hydrocephalus.

In October 2013, the patient had a deterioration, suddenly developed fever, severe headaches. Meningitis was ruled out. At the same time, right subclavian vein phlebitis was detected at the site of the catheter. In November 2013, a genetic research was conducted. Mutations in methylenetetrahydrofolate MTHRF T677, factor V Leiden, FIIG20210A fibrinogen gene were studied. The results of the genetic examination showed protein S bordering deficiency (53.6%), carriage of homozygous G1639A mutations in VKORC 1 Vitamin K epoxide reductase gene, heterozygous mutation of I/D in angiotensin converting enzyme gene. Other detections included lupus anticoagulant carriage, a significant increase in homocysteine level – 19.3 *mmol/l*, and a slight increase in lipoprotein a – 32 *mkmol/l*. However, other mutations, especially the folate cycle enzymes and the mutations in the gene of plasminogen activator inhibitor were not studied. Doppler ultrasound of the neck vessels reported non-occlusive thromboses of internal jugular veins, left subclavian vein and brachiocephalic segments. Anticoagulation therapy with Dalteparin sodium (10000 *U/day*) was initiated, but together with the therapy the infiltration along the left femoral vein appeared again.

In January 2014, the patient was examined for headaches. The MRI of the brain revealed thrombosis of the transverse and sagittal sinus on the right. He was hospitalized in April 2014 with a diagnosis of hereditary thrombophilia. The status reported: left lower leg is 1 *cm* larger than the right one, expansion of the venous network of the left calf. The neurological status stated memory decrease, secondary to the disease, dysphonia, tongue deviation to the left. Muscle tone is symmetrically reduced; moderate reduction of Achilles reflexes and the cutaneous abdominal reflexes, pathologi-

cal foot signs (Babinski, Rossolimo, Zhukovski, Bechterev-1). Meningeal signs: the inability to straighten the legs in the knee joints (more on the right). Radicular syndrome: moderate Lasegue sign on the right. Doppler ultrasound of the lower limbs showed signs of occlusive thrombosis of common and external iliac veins on the left. Vascular ultrasound of the superior vena cava and extracranial brachiocephalic veins indicated occlusive thrombosis of the upper right jugular vein, recanalization of the top jugular vein, left subclavian vein, left brachiocephalic vein right brachiocephalic vein. Laboratory tests revealed a slight deficiency of protein S, lengthening of activated partial thromboplastin time. The dose of low molecular weight heparin (Anti-Xa=0.63) was increased. No data about systemic disease of the connective tissue were obtained. After hospitalization the patient was outpatiently taking low molecular weight heparins. However, secondary to acute respiratory viral infection, the redness of the skin on the inner surface of the left thigh reappeared and was painful on palpation. He was admitted to hospital in November 2014 with complaints of painful red nodes on the inner surface of the left thigh. The examination uncovered an infiltrate of 5×5 *cm* and a more lateral infiltrate of 1×1 *cm* on the inner surface of the upper third of the left thigh. Similar palpable knots were localized in the distal femoral epiphysis and were painful on palpation. According to Doppler ultrasound of the inferior vena cava: occlusive thrombosis of the left external iliac vein, thrombosis in the stage of minimal recanalization of the left superficial femoral vein. Occlusive thrombosis of the great saphenous vein in the upper third of the thigh and of the great saphenous vein flow in the upper third on the left. Doppler ultrasound of vascular system of the superior vena cava revealed post-thrombotic occlusion of the internal jugular veins on both sides. Occlusal thrombosis of brachiocephalic vein on the left. The patient was consulted by a geneticist, who suspected hereditary thrombophilia and recommended examination of relatives. The dose of low molecular weight heparin (Anti-Xa=0.89) was increased, and the patient took it for a month. Later warfarin (controlled international normalized ratio) was prescribed. Periodically, new elements of infiltration appeared on arms and legs.

Early in September 2015, the patient developed headaches in the left parietal-temporal part, tinnitus, low-grade fever, red subcutaneous nodes in the left lower limb, pain in the neck on the left. On readmission he underwent the differential diagnosis between vasculitis and antiphospholipid syndrome. The tests showed erythrocyte sedimentation rate up to 25 *mm/h*, neutrocytosis – 73%, fibrinogen 8.5 *g/l*, increase in C-reactive protein to 24 *mg/l*, protein C – 38%, protein S – 27.7%, a positive lupus anticoagulant. Doppler ultrasound of lower limb vessels showed signs of occlusive thrombosis of the left great saphenous vein in the thigh with no signs of flotation and with a mobile top of a blood clot in the lower third.

The therapy with warfarin was continued at the dose of 2.5 *mg/day* (INR=2.5-3.0), topically Troxevasin. In October 2015, painful red nodes appeared on the lower limbs: on the calves, the inner surface of the foot. The rashes were regarded as nodosum erythema. After Nimesulide and Suprastin therapy the nodes were partially resolved, but 3 days later, painfulness, induration, swelling, and redness reappeared along the saphenous vein of the left shin. With suspicion of phlebothrombosis the patient was hospitalized. The preliminary diagnosis was systemic vasculitis. Assumption of antiphospholipid syndrome. The status report: pigmentation at the sites of former phlebitis and phlebothrombosis, an infiltrate linear along the veins on the medial surface of the left lower leg, dense, painful swelling of the surrounding soft tissues, increased venous pattern in the shins. The ripple on feet was satisfactory and the limb was warm to the touch. The tests revealed erythrocyte sedimentation rate up to 40 *mm/h*, neutrocytosis – 76%, fibrinogen 8.5 *g/l*, increase in C-reactive protein up to 26 *mg/l*. Doppler ultrasound of the lower legs showed that the small subcutaneous vein in the middle third of the left tibia was thrombosed.

Non-occlusive thrombosis: with regard to the recurrent vascular changes and the increase in C-reactive protein and erythrocyte sedimentation rate, the condition was seen as a systemic vasculitis. Prednisolone was prescribed at the dose of 35 *mg/day* (0.7 *mg/kg/day*) from 22 November 2015 with the dose reduction to 10 *mg/day* in March 2016. The patient is now taking warfarin 2.5 *mg/day*

(INR 2-3, occasionally up to 4.5). However, the appearance of painful knots along the vessels still remains in the centre of attention.

In March 2016, he was admitted to the University Children's Hospital for diagnosis confirmation. On admission: condition close to satisfactory, signs of hormonal Cushing syndrome, height – 168 *cm*, weight – 58.5 *kg*; multiple acne vulgaris on the face, expansion of the venous network on the skin of the chest, a longitudinal section of hyperpigmentation at the site of former thrombosis on the front surface of the left thigh. The left lower leg is 1 *cm* larger than the right one along the circle, small infiltrates on the legs along the saphenous veins, physical signs of internal organs without features. The clinical and laboratory evaluation data did not reveal any systemic connective tissue disease or vasculitis. The coagulogram draws attention to the activated partial thromboplastin time lengthening and a positive lupus anticoagulant. In the instrumental examination, according to Doppler ultrasound of the lower limbs, there is a complete occlusion all over the left external iliac vein with the initial signs of recanalization.

The lumens of total femoral, femoral, deep femoral veins and popliteal veins are not expanded and are painted unevenly due to parietal hypoechoic and hyperechoic platelet. The lumen passability is from 30% to 90%. The lumen of the internal jugular vein is not differentiated due to the occlusion.

Doppler ultrasound data of 15.03.2016 are shown in the table and figure (a, b).

Taking into account the Doppler ultrasound data, the patient is regarded as threatened by pulmonary embolism. The boy underwent CT of the chest, and no pathological changes were detected. According to echocardiogram, the pulmonary artery pressure is normal. In the absence of data for a systemic disease, it was recommended to reduce the prednisolone dosage to total cancellation. However, taking into consideration the persistent

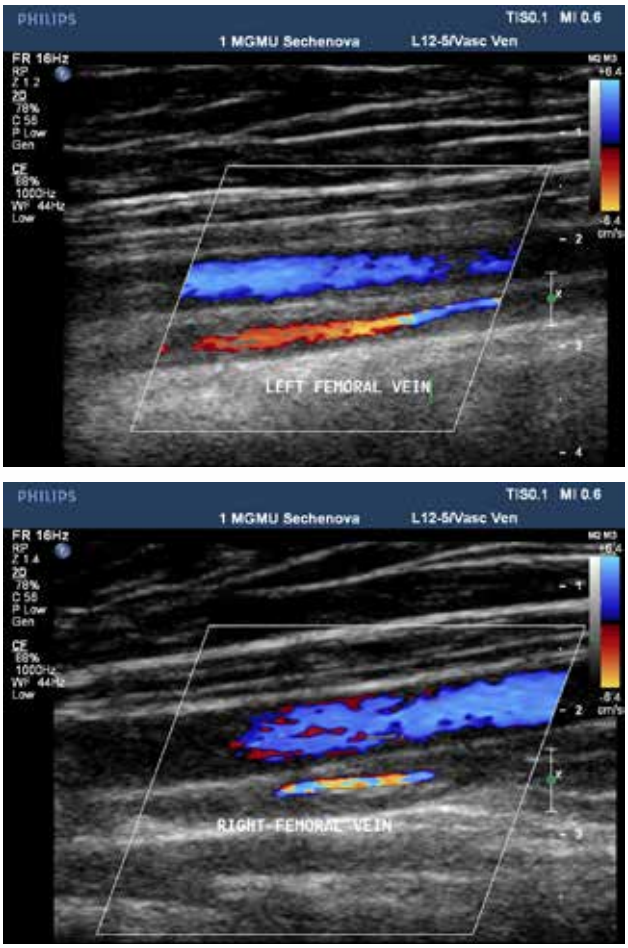

FIGURE. *Dopplerography of lower limb veins with complete occlusion of iliac veins*

TABLE

Results of duplex scanning of neck vessels and lower limb veins

Internal jugular veins at both sides	Lumen is not differentiated. Post-thrombotic occlusion
Large and small saphenous veins of the thigh	The lumen is not expanded. Painted with no signs of acute disorders of patency. No varicose
External iliac veins	On the left: occlusion all over the vein, the initial recanalization in individual segments. On the right: the veins are completely passable
Common femoral veins on both sides	Not expanded, unevenly painted due to hypoechoic and isoechoic parietal thrombotic masses, lumen passability from 30% to 90%
Femoral veins on both sides	
Popliteal veins on both sides	

circulation of lupus anticoagulant, Plaquenil was prescribed for a long term therapy. With regard to the recurrent thrombosis during warfarin therapy even at a sufficient interval of INR 2.5-3.0 and the drastic fluctuations of INR, the drug was canceled. Heparin was prescribed again with the subsequent prescription of low molecular weight heparins.

Based on history, clinical, laboratory and instrumental examination, the boy has been diagnosed: antiphospholipid syndrome, thrombosis of the common femoral, femoral and popliteal vein, lupus anticoagulant, post-thrombotic syndrome, threat of pulmonary embolism, a transient decrease in natural anticoagulants protein C and S, hyperhomocysteinemia, lipoproteinemia, homozygous mutation in VKORC 1, Vitamin K epoxide reductase gene.

Thus, the teenager has recurrent thrombosis, thrombophlebitis with inflammatory activity, post-thrombotic syndrome. The reason for this condition was the combination of hereditary and acquired risk factors. It is known that the boy has a burdened family history: paternal grandfather died of a pulmonary embolism. Cohort study of thrombosis incidence in relatives of children with thrombosis and congenital deficiency of natural protein C, S anticoagulants, anti-thrombin III showed that these children have a 20-fold increased risk of venous thromboembolism [*Holzhauer S et al., 2012*]. The boy's first episode of thrombosis occurred after an infected foot wound. Infections are the trigger in a third of patients with thrombosis. Our patient repeatedly developed recurrent thrombosis secondary to acute respiratory viral infection [*Ishola T et al., 2016*].

Moreover, the child had other risk factors for thrombosis. A significant increase in homocysteine level is considered as an independent risk factor. Homocysteine is an inducer of endothelial dysfunction and has prothrombogenic activity. The patient did not have mutations in MTHRF gene, though mutations in other enzymes of the folate cycle and mutations in the genes responsible for fibrinolysis have not been studied yet.

The combination of natural anticoagulant level decrease together with lupus anticoagulant is a permanent adverse prothrombogenic factor in a child. The fact of continuous detection of lupus anticoagulant is very essential, as in combination with recurrent thrombosis it allows to come up with the diagnosis of antiphospholipid syndrome. The association of lupus anticoagulant with recurrent thrombosis is well known. Persistence of antiphospholipid antibodies is quite steady and, of course, is a negative factor that is associated with a high risk of mortality [*Ames P et al., 2016*]. The literature describes cases in which patients with antiphospholipid syndrome develop signs of systemic lupus erythematosus in the future. However, after repeated examinations, the boy has no criteria for the diagnosis of systemic lupus erythematosus or other systemic connective tissue diseases. Therefore, the prescription of prednisolone was unjustified, because the glucocorticoids cause hypercoagulability. Therefore, prednisolone was cancelled. However, since antiphospholipid syndrome is present, Plaquenil was prescribed for a long-term intake [*De Carolis S et al., 2015*].

Due to a number of relapses of thrombosis, the child has developed a severe post-thrombotic syndrome. According to the criteria of the International Consensus on chronic venous diseases, the boy has thrombotic obstruction with multiple localizations, including lower leg veins, popliteal, femoral, jugular veins [*Kreidy R, 2015*].

From our point of view, relapses of thrombosis were associated with inadequate doses of anticoagulants and adherence to treatment. Insufficient efficacy of warfarin (with adequate INR 2.5-3.0) was partly due to the presence of mutations in the Vitamin K epoxide reductase gene, which complicates the dose selection for the patient, as the dosage increase leads to drastic fluctuations in the INR and may cause bleeding [*Dilge Taskin B et al., 2016*].

With aregard to the foregoing, the boy is at high risk for recurrence of thrombosis and pulmonary embolism and needs indeterminate, long-term preventive therapy.

The selection and the length of anticoagulant therapy in children are not currently determined. However, according to the recommendations of the All-Russian Association of Thromboses, Hemorrhages and Vascular Diseases, patients with relapsing venous thrombosis and pulmonary embolism need lifelong anticoagulation therapy [*Bokarev I, Medvedev A, 2012*].

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