N.A. Kharitonova[1], I.A. Belyayeva[1], P.V. Svirin[2], A.N. Evdokimova[1]
[1] Scientific Center of Children's Health, Moscow, Russian Federation
[2] Morozov municipal pediatric clinical hospital of the Department of Health of Moscow, Russian Federation

Practical Aspects of Developmental Care over Neonates with Neonatal Thromboses

Contacts:
Nataliya Alexandrovna Kharitonova, PhD in Medicine, senior research fellow at the premature infant unit of the Scientific Center of Children's Health (Federal State Budgetary Research Institution)
Address: 2/1 Lomonosovskiy Av., Moscow, 119991; **tel.:** +7 (499) 134-15-19; **e-mail:** Kharitonova.doc@yandex.ru

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Increase in the incidence of neonatal thromboses is associated not only with the possibility for women characterized by tendency to high thrombosis to carry pregnancy, but also with the increase in enforced use of invasive treatment methods, such as catheterization of central and peripheral veins and umbilical vessels. This article is aimed at bringing peculiarities of epidemiology, pathogenesis and diagnosis, clinical manifestations and treatment of neonatal thromboses to the attention of practicing physicians. The article present tactics of treating 4 children with thrombi of varying genesis and localization based on clinical observations. The decision to start heparin therapy is made on the individual basis depending on the child's maturity at birth, thrombus localization, presence or absence of complications and nature of the concurrent pathology. The given clinical cases informatively demonstrate reasonability of a multidisciplinary approach to diagnosing and treating patients with this pathology, the need in strict selection of doses of the used drugs and continuous monitoring of coagulogram parameters in the setting of the therapy.
Keywords: *thrombosis, neonates, treatment.*

INTRODUCTION

Thrombosis is a pathological condition characterized by the development of a thrombus with a complete or partial vascular occlusion and a disorder (or a significant threat of a disorder) of blood circulation in tissues or organs.
Thrombosis is becoming increasingly frequent in neonates in recent years. It is mostly caused by the fact that women suffering congenital thrombophilia, antiphospholipid syndrome, and other diseases causing increased predisposition to thrombus formation, can now deliver children successfully. A certain contribution is made by the forced usage of invasive treatment of severe perinatal pathology in neonates, as such treatment requires catheterization of central and peripheral veins and umbilical vessels [1, 2]. A discussion of treatment of neonates suffering neonatal thrombosis seems topical given the high risk of life-threatening condition development caused by thrombus formation and how difficult it is to select a proper therapy and control its effectiveness.

Epidemiology

The frequency of thrombosis in children is 5.1 per 100,000 neonates [3] or 24 per 1,000 visits to neonatal intensive care units [4]. 80% of thrombi are formed due to the use of central catheters [5, 6].
Localization of thrombi in neonates may differ. 10% of all the identified venous thrombi are located in the kidneys; 1/4 of those are formed bilaterally [6]. 13% of children have thrombosis due to the functioning of umbilical catheters [7]. Venous thromboses in the brain are identified in

41 children out of 100,000; arterial cerebral thromboses are diagnosed in 28 to 90 children per 100,000 neonates [9].

Pathogenesis

The neonatal period features several physiological peculiarities that condition an increased frequency of thrombosis in neonates as compared to older children [1, 10]. The frequency of thrombus formation is increased when one or several acquired factors are involved [4, 7, 8], which is why the pathogenesis of the disease in children is almost always combined [1, 7].

The primary factors facilitating increased thrombus formation in neonates

1. Peculiarities of the homeostatic system:
- low activity of most components thereof;
- imbalance of procoagulants and the inhibitors thereof. When a child is born, the K-dependent factors II, VII, IX, and X, as well as factors XI and XII, are reduced [10-12], whereas the activity of antithrombin III is close to the normal range of older children [1].

2. Use of central catheters. The frequency of thrombus formation due to catheterization of peripheral veins has not been calculated; however, studies have shown that catheters are an important thrombosis risk factor [1].

3. Genetically conditioned deficiency of natural anticoagulants:
- homozygote and heterozygote deficiency of proteins C and S and antithrombin III (2-5% frequency) [11].

4. Other congenital and acquired prothrombotic factors are
- congenital cardiovascular defects leading to polycythemia, rheological disorders and hypoxia;
- prenatal infection, sepsis, water deprivation, hepatic pathology, antiphospholipid syndrome. The titer of antiphospholipid antibodies was identified in 5% of neonates with developed thrombosis [1, 13].

Many of the mentioned acquired risk factors result in a reduced activity of natural anticoagulants and an increased activity of procoagulants, which is crucial for thrombosis development in neonates [1].

Clinical presentation

Clinical manifestations of thrombosis are divided into acute and residual, or late [1, 14, 15]. The primary clinical manifestations of thrombosis are presented in tb. 1 on the basis of their localization.

Alongside with intense clinical symptoms, thromboses may also have a symptomless course, in which case they are “accidentally” identified in the process of instrumental tests.

Diagnosis

Neonatal thrombosis diagnosis is verified by means of computer and magnetic resonance imaging (CI/MRI), as well as by ultrasonography (US), which is the most available and most frequently used technique for the visualization of thrombi in neonates. However, comparative analysis has shown that the US sensitivity is not sufficient [16], which is why angiography remains the “golden standard” of thrombosis diagnosis despite its invasive nature [1].

Treatment

Treatment of most neonatal thromboses starts with heparins (tb. 2) [1, 17, 18]. Duration of heparin therapy depends on its effectiveness and the nature of thrombosis.

The primary approaches to diagnosis and therapy of neonatal thromboses is presented in the following clinical cases.

CLINICAL CASE 1

A term boy of the 2nd pregnancy accompanied by anemia in the 3rd trimester and of the 1st term delivery by a 26-year-old mother suffering gardnerellosis and endometritis.

The boy had survived severe intranatal asphyxia. APGAR score – 3 out of 5. Minor hemorrhage was observed twice during the neonatal period. By the 7th postnatal day, the boy's condition stabilized. Neurosonography did not identify any pathological signs; however, the clinical presentation involved torpor, posseting, absence of sucking reflex, and flat weight curve, which made more detailed tests imperative.

The child underwent *MRI*. The MR image helped to visualize thrombosis of the sinistral transverse venous sinus at the stage of partial recanalization (Fig. 1).

Examination of the ocular fundus identified multiple small reabsorbing hemorrhages.

Molecular genetic examination identified genetic factors that may reduce the fibrinolytic activity:

— methionine synthesis reductase: homozygote state;

— 5,10-methylenetetrahydrofolate reductase: heterozygote state.

The child was *examined* by a *neurosurgeon* who concluded that the patient does not need surgical intervention and recommended dynamic monitoring.

Treatment. Heparin therapy was not carried out due to a partial recanalization of the thrombus as well as the absence of pathological changes in the coagulogram.

Dynamic monitoring identified a complete recanalization of the thrombus with the recovery of blood circulation.

Prognosis and follow-up: the child requires dynamic monitoring by hematologists due to high risk of thrombosis.

CLINICAL CASE 2

A term boy of the 3rd pregnancy accompanied by candidiasis, hydramnion, anemia, and the 2nd term delivery by a 24-year-old mother with compromised gynecological history: colpitis and cervical erosion.

On the second day after birth, the infant underwent surgical intervention due to adenomatosis of the upper sinistral lung lobe. After the intervention, he received a prolong infusion therapy via a central catheter.

On postnatal day 11, edema and cyanosis of the lower limb were identified.

Ultrasonography identified a thrombus in the lumen of the inferior vena cava. The thrombus could be traced up to the mesogastric area.

Molecular genetic examination identified genetic factors that may slightly reduce the fibrinolytic activity:

— inhibitor of plasminogen activator type 1: heterozygote;

— 5,10-methylenetetrahydrofolate reductase: homozygote.

Coagulogram shows a reduction in the activated partial thromboplastin time (APTT).

Treatment. Unfractionated heparin (UFH) treatment, intravenous administration; the initial dose was 28 units per kilogram per hour subsequently increased to 33 units per kilogram per hour with monitored APTT.

Dynamic monitoring identified lysis of the thrombus after 7 days of heparin use. Given the choice of adequate heparin dose and the stabilization of the child's status, the therapy was changed to subcutaneous administration of low-molecular heparin (Fragmin) in the dose of 120 units per kilogram BID over 6 weeks.

Prognosis and follow-up: the child requires dynamic monitoring by a hematologist and a surgeon.

CLINICAL CASE 3

Premature girl, the first of dichorial biamniotic twins, of the 3rd pregnancy initiated by means of extracorporal insemination and embryo transplantation (the first two pregnancies ended in

spontaneous abortions) accompanied by threatened abortion in the 3rd trimester due to arterial hypertension and of the 1st preterm surgical delivery at week 35-36 with the pelvic presentation of the 1st embryo by a 32-year-old obese mother.
During the early neonatal period, infusion therapy was administered to the girl via an umbilical catheter. No clinical manifestations of thrombosis were observed.
Ultrasonography identified hepatomegaly. The sinistral lobe was 45 mm, the dextral lobe was 55 mm, the hepatic parenchyma was not changed, the size and vessels of the spleen were normal. The portal vein of the liver was widened to 5.5 mm. A 3 mm thrombus was identified in the umbilical vein.
Treatment. No heparin therapy was carried out, because coagulogram parameters were within the normal range at the moment of examination, and the process was not spread across the portal vein system.
Dynamic monitoring identified complete thrombus lysis.
Prognosis and follow-up: it is recommended for the girl to undergo dynamic monitoring carried out by surgeon, hepatologist, and hematologist, as she is at risk of portal hypertension.

CLINICAL CASE 4
Term girl of the 2nd pregnancy (the first child died of sepsis at the age of 5 days) accompanied by threatened abortion in the 1st trimester, anemia in the 2nd trimester, hydramnion in the 3rd trimester, and chronic thrombohemorrhagic syndrome and of the 2nd term delivery by a 24-year-old mother suffering severe multigene thrombophilia (mutations of 7 genes, including the Leiden factor) as well as cervical erosion and colpitis.
No clinical signs of thrombosis were identified in the child.
Ultrasonography identified an unmoving echogenic 6 x 3 mm formation in the sinistral pulmonary branch. The right atrium contained a mural 7 x 3 mm formation in the entry area of the inferior vena cava (Fig. 2)
Coagulogram identified an APTT reduction.
Molecular genetic examination identified genetic factors that may significantly reduce the fibrinolytic activity:
— coagulation factor V (the Leiden factor): heterozygote;
— subunit IIIa of thrombocyte integrin aIIbβ3: heterozygote;
— fibrinogen β: heterozygote;
— methionine synthesis reductase: heterozygote.
Treatment. Due to the high risk of thromboembolism, the thrombolytic therapy was being selected at the intensive care unit. The initial heparin dose was 28 units per kilogram per hour (Fig. 3).
Later, the dose was increased to 34 units per kilogram per hour under a strict control of the APTT level. Coagulogram parameters were subject to dynamic monitoring. Due to the low level of antithrombin III and insufficiency of heparin therapy, the child had to undergo transfusion of fresh-frozen plasma twice. After the girl's condition stabilized and the thrombi reduced in size (Fig. 4), the therapy was replaced by subcutaneous administration of dalteparin sodium under a strict control of anti-Xa heparin activity with a target value of > 0.5 units per ml.
At the age of 1.5 months, acute inguinal hernia incarceration developed in the child and required an urgent surgical intervention. Due to the high risk of hemorrhages, dalteparin sodium therapy was withdrawn and resumed on the second day after the intervention. The dose amounted to the half of the previously achieved dose and was later increased to the target value of anti-Xa heparin activity.
After the proper dose of low molecular heparin was selected, the child was discharged to be outpatiently monitored by a hematologist. Subcutaneous administration of dalteparin sodium for 6 weeks after discharge was recommended.
Dynamic monitoring identified residual thrombosis phenomena with a replacement with connective tissue and absence of hemodynamically significant disorders.

Prognosis and follow-up: the child requires dynamic monitoring by hematologists due to genetic burden and high thrombosis risk.

CONCLUSION

The presented cases prove that when fibrinolytic therapy is prescribed and selected for a neonate with thromboses, it is imperative to take into consideration maturity of the child at birth, localization of a thrombus or thrombi, clinical peculiarities of the disease, and the nature of the combined perinatal pathology. The dose of medicines, dynamic in-vitro monitoring, and multidisciplinary approach to diagnosis and treatment of neonatal thromboses ought to be selected on the individual basis. The process should involve neonatologists/pediatricians, hematologists, neurosurgeons, vascular surgeons, and hepatologists.

Thus, the issue of neonatal thromboses is a subject matter not only of neonatology; it requires attention of many experts over the course of subsequent ontogenesis.

CONFLICT OF INTEREST

The authors have declared absence of reportable financial support / conflict of interest.

REFERENCES

1. P.V. Svirin, S.A. Rumyantsev, L.E. Larina, A.V. Suvorova, A.P. Zharkov. Lecheniye neonatalnykh trombozov. *Neonatologiya*. 2013; 1: 76-85
2. Y.V. Zhirkova, I.A. Belyayeva, Y.I. Kucherov. Perkutannaya kateterizatsiya tsentralnykh ven u novorozhdennykh. Ed. by Academician of the RAS and the RAMS A.A. Baranov. *Moscow: Pediatr*. 2013. 30 p.
3. P.A. Zharkov. Vliyaniye nositelstva protromboticheskikh polimorfizmov na risk razvitiya trombozov u detey. *PhD in Medicine: thesis abstract. Moscow*. 2013.
4. L.Z. Barkagan. Narusheniye gemostaza u detey. *Moscow: Meditsina*. 1993. 176 p.
5. M.Y. Chuchin. Tserebalniy sinus-tromboz v detskom vozraste. *Pediatriya*. 2005; 2: 63-70.
6. P.A. Zharkov. Vliyaniye nositelstva polimorfizmov genov svertyvayushchey sistemy krovi i folatnogo obmena na risk razvitiya trombozov u vzroslykh i detey. *Voprosy prakticheskoy pediatriyi*. 2012; 5: 26-32.

Table 1. Clinical manifestations of thrombosis [1, 8, 12, 13]

Localization	Acute clinical manifestations	Residual clinical manifestations
Renovascular thrombosis	A palpable formation in the abdominal cavity, hematuria, proteinuria	Stable hypertension, renal failure, renal hypoplasia
Vena cava inferior thrombosis	Edema and color change of lower limbs; respiratory distress syndrome and arterial pressure rise possible	Lower limb pain, abdominal pain, phlebeurysm, limb ischemia signs
Vena cava superior thrombosis	Vena cava superior syndrome: cyanosis, facial and neck edema	Vena cava superior syndrome: cyanosis, facial and neck edema. Ectasia of subcutaneous veins, teleangiectasia, headache, constricting pain behind the breastbone, increased intracranial pressure, and edema of periorbital tissue
Portal vein thrombosis	Symptoms of hepatic dysfunction, hepatosplenomegaly	Development of portal hypertension syndrome, hepatosplenomegaly, gastroesophageal hemorrhages
Limb vein thrombosis	Edema, pain, burning sensation, and hyperemia	Development of visible subcutaneous collaterals, limb growth retardation, post-thrombotic disease
Pulmonary artery thromboembolism	Significant deterioration of ventilation/perfusion ratio, oxygenation deficiency, signs of dextral heart failure	Hypertrophy of dextral heart compartments, clinical manifestations of pulmonary hypertension
Mesenterial vessel thrombosis	Signs of necrotic enterocolitis	Perforation with peritonitis development
Central thromboses	Strokes and thromboses of venous sinuses are manifested via cerebral symptoms, i.e. spasms and torpor. Local symptoms not likely to occur	Neuropsychic maldevelopment, cognitive disorders, paresis and paralysis

Table 2. The peculiarities of treatment strategy and control over heparin therapy effectiveness

Unfractioned heparin (UFH)	Low molecular heparin: dalteparin sodium, reviparin sodium, enoxaparin sodium
Uninterrupted intravenous influsion	Subcutaneous administration BID-TID
Loading bolus dose – 75 units per kilogram (10 minutes) Maintenance dose – 28 units per kilogram (one hour); subject to further adjustment Target values: APTT increase in 2-2.5 times	For treatment, the initial dose is 100-120 units per kilogram administered subcutaneously twice; subject to further adjustment based on the results of anti-Xa heparin activity within the target range of 0.4 to 0.8 units per ml (blood sampled 3 to 4 hours after administration) For prevention, the daily dose is half of the

	effective therapeutic dose and is administered once
Control is based on the APTT appraisal After the dosage is selected and adjusted, APTT should be controlled on the basis of severity of clinical thrombosis manifestations When treating life-threatening thrombosis in a child in severe condition, APTT should be controlled on a daily basis; in less severe cases, it may be measured once in 2-3 days Control is obligatory when the drug is replaced	Blood is sampled to determine the anti-Xa heparin activity 4 hours after administration The anti-Xa heparin activity is measured once in 2-4 days until target values are achieved, and 1-4 times per month after stabilization has been achieved
It is not recommended to use the drug for more than 3 weeks due to possible development of complications, i.e. osteoporosis and heparin-induced thrombocytopenia	Can be used for a longer period (more than 3 weeks)
In case of resistance to UFH therapy, antithrombin III or FFP is administered to aid natural anticoagulants. APTT is then measured once a day or once in 2 days, including measurement before and after administration	-

Note. APTT stands for activated partial thromboplastin time, FFP stands for fresh frozen plasma, anti-Xa stands for anticoagulant activity.

Fig. 1. Thrombosis of the sinistral transverse venous sinus at the stage of partial recanalization

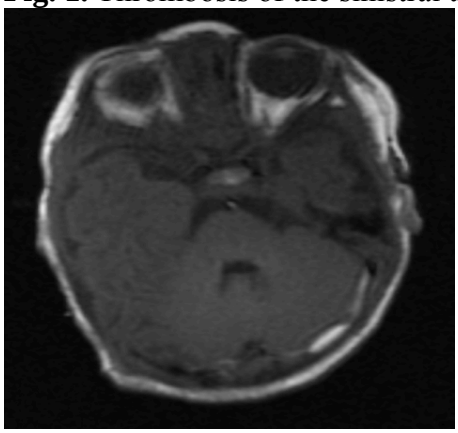
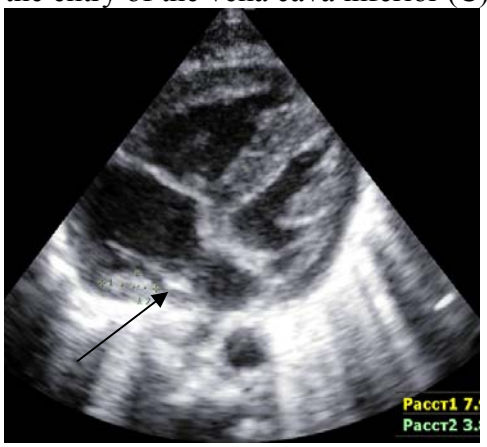
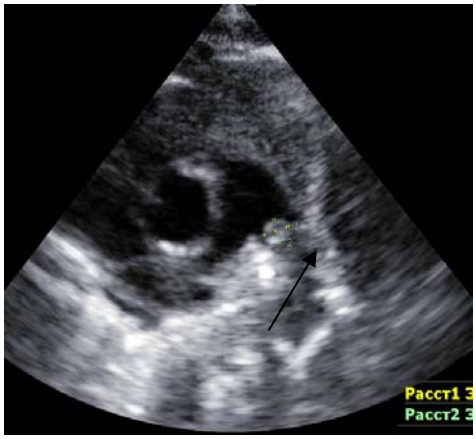


Fig. 2. Ultrasonographic image of thrombi in the area of the sinistral pulmonary vein (A, B) and the entry of the vena cava inferior (C)



A



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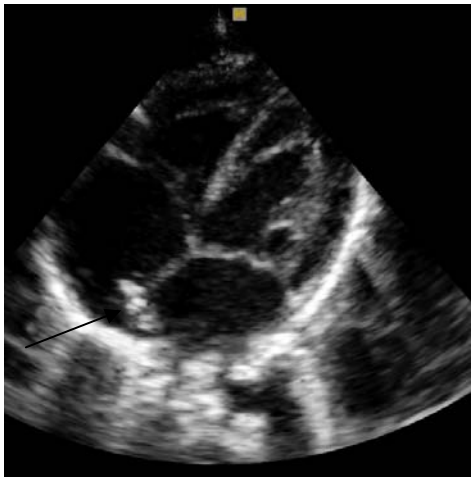


C

Fig. 3. Heparin thrombolytic therapy pattern

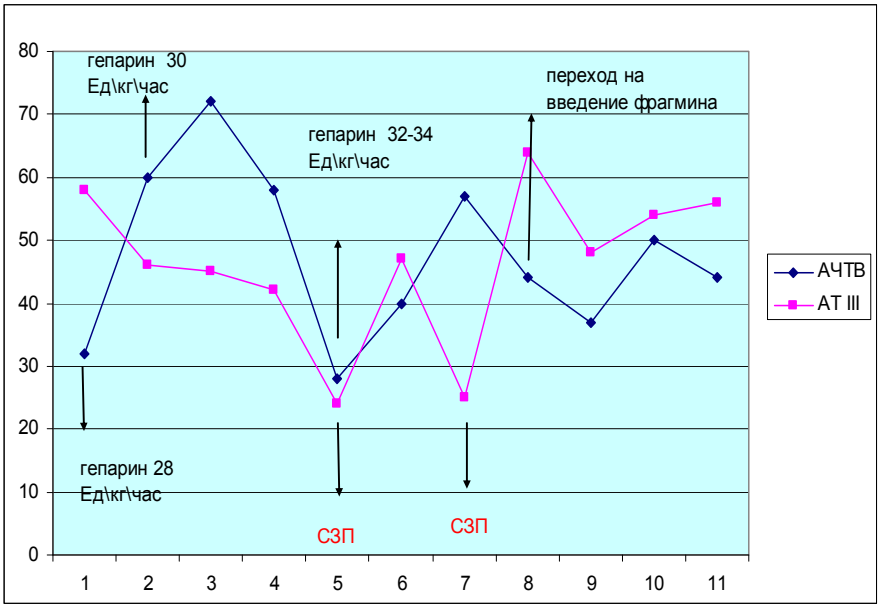
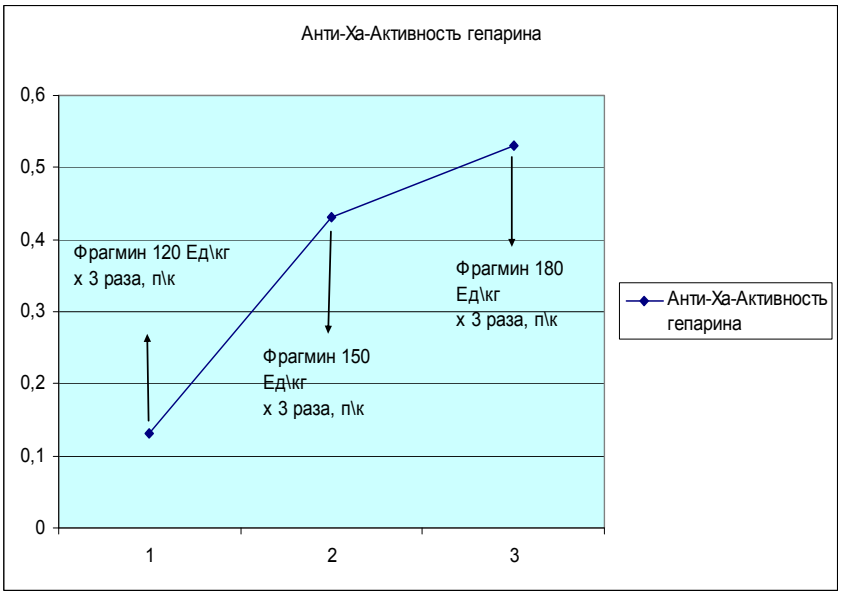


Fig. 4. Algorithm of selecting an effective dalteparin sodium dose



RUSSIAN	ENGLISH
Гепарин	Heparin
Ед/кг/час	Units per kilogram per hour
Переход на введение фрагмина	Introduction of fragmin
АЧТВ	APTT
СЗП	FFP
Анти-Ха-Активность гепарина	Anti-Xa heparin activity
п/к	subcutaneously