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Hemorrhagic Syndrome in Babies

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Hemocoagulation disorders are one of the urgent issues of pediatrics. Hemorrhagic syndrome development in infants is associated with severe complications, severe health disorders and reduced survivability parameters. The article presents the issues of etiology, pathogenesis, clinical presentation, differential diagnosis and treatment of hemorrhagic syndromes in infants. The authors describe quantitative and qualitative differences in the plasma hemostatic system in premature infants, term neonates, infants and adult patients. The article presents the main diagnostic algorithms based on using both routine tests for examining plasma hemostasis and the second-level (confirmatory) tests available at most pediatric medical establishments. The article describes current approaches to the therapy of hemorrhagic conditions in children of a few months of age. An additional examination of the hemostatic system of the children with minimal manifestations of hemorrhagic syndrome, as well as of the patients with liver diseases, cholestatic syndrome, cystic fibrosis and/or chronic gastrointestinal diseases, undergoing a long-term antibiotic therapy is required for timely and accurate diagnosis and correction of hemorrhagic conditions. Vitamin K deficiency prevention is recommended for risk group children. The article is exemplified with three clinical observations.
Keywords: *hemostasis, vitamin K, hemorrhagic syndrome, children.*

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INTRODUCTION

The issue of bleeding, especially of latent forms of the disease, remains relevant in the field of pediatrics, as impaired blood coagulation in children is often found in children nowadays. This is due to peculiarities of the hemostatic system in children. Hemorrhagic disease usually develops as a result of vitamin K-dependent blood coagulation factor deficiency. Absence of preventive administration of vitamin K preparations to neonates may lead to the development of hemorrhagic disease due to the action of adverse endogenous and exogenous factors. Hemorrhagic syndrome manifests itself with increased bleeding due to vitamin K-dependent blood coagulation factor deficiency. Low activity of blood coagulation factors is also related to functional deficiency of the liver characteristic of infants. Hemostatic disorders are mixed at

some diseases due to overlay of disseminated intravascular coagulation (DIC) and associated with infectious-septic, immune, destructive or neoplastic processes.

PECULIARITY OF HEMOSTATIC SYSTEM IN CHILDREN

It is known that synthesis of hemostatic system proteins begins as early as during the intrauterine stage of development; however, they are not sufficiently mature to penetrate the placental barrier. Concentration of most plasma blood coagulation factors may be measured after 10 weeks of intrauterine fetal development; it becomes higher as the fetus develops. However, the activity of vitamin K-dependent factors in fetuses and neonates is lower than in adults and increases gradually reaching the appropriate level by the 6^{th} month of life. Plasma levels of the von Willebrand factor and factor XIII in neonates are almost identical to the reference levels in adults. In a fetus, activity of factors V and VIII is low at the first gestational months and reaches the adult norm by birth. Fibrinogen concentration is considerably lower in fetuses than in adults; it also increases gradually. Healthy children have a fibrinogen level similar to the adult norm at birth; however, this parameter may increase during the 1^{st} week of life. The most significant thrombin inhibitor among AT-III, heparin cofactor II and α2-macroglobulin is the latter. Umbilical blood also features a circulating fetal anticoagulant similar to glycosaminoglycan dermatan sulfate. Its plasma concentration is ca. 0.29 mcg/ml, molecular mass – 150 kDa. It may promote increase in the activity of heparin cofactor II. Duration of a fetal anticoagulant's circulation in a neonate's blood is unknown; however, it is identified in a premature infant's blood within a week. The plasma protein C concentration at birth is considerably lower than in adults and does not increase within the first six months of life. The total protein S concentration is also low. Activation of the coagulation system at birth does not lead to a significant consumption of blood coagulation factors and does not cause low activity of a range of hemostasis components. Activity of the fibrinolytic system in neonates features diverse trends. On the one hand, the level of fibrinolytic products in a neonate's plasma increases during labor due to activation. As is evident from the foregoing, neonates and infants feature a wide range of values of the hemostatic system parameters.

Vitamin K very poorly penetrates the placenta. Primary hemorrhagic disease is caused by low vitamin K concentration in a fetus (does not exceed 50% of the adult level). After birth, vitamin K comes in low amounts with breastmilk; active production thereof by intestinal microflora starts on the 3^{rd}-5^{th} day of a child's life.

BIOLOGICAL ROLE OF VITAMIN K

Vitamin K is necessary to activate the process of γ-carboxylation of the residual glutamine acid in prothrombin (factor II), proconvertin (factor VII), antihemophilic globulin B (factor IX) and Stuart-Prower factor (factor X), as well as in the plasma system of proteins C and S and osteocalcin.

The first speculation of a factor affecting blood coagulation was made in 1929. Danish biochemist singled out a liposoluble vitamin named vitamin K (koagulation vitamin) in 1935 due to its role in blood coagulation. In 1943 the scientist received a Noble Prize for this discovery [1, 2]. In Russia, a water-soluble analog of vitamin K (Vicasol) was synthesized by A.V. Palladin in 1944. The main form of vitamin K – vitamin K1 (phylloquinone) – is found primarily in vegetables (cauliflowers, Brussels sprouts, spinach, lettuce, zucchinis and soybeans); vitamin K2 (menaquinone) – in bovine liver and porcine kidneys. It is found in smaller amounts in butter, cheese, eggs, corn oil, oatmeal and peas. Vitamin K is also found in many vegetables, fruits, cereals, milk and bread in small amounts. Vitamin K2 is also produced by intestinal microflora. See the list of factors contributing to development of vitamin K deficiency below (table 1).

Vitamin K-dependent blood coagulation factors as non-functioning molecules identified in literature as proteins induced by vitamin K absence (PIVKA) may be found in blood in normal

amounts due to liver carboxylation malfunction [3]. However, they are unable to provide quality hemostasis; this leads to a hemorrhagic disease.

Table 1. Initiating agents of vitamin K deficiency development

Mother	Child
• Intake of specific drugs during pregnancy (indirect anticoagulants, anticonvulsants, broad-spectrum antibiotics, antitubercular agents) • Gestosis • Hepatopathies and enteropathies • Labor-induced pathology	• Prematurity • Lack of or insufficient breastfeeding • Antibacterial therapy • Lack of prevention • Suppression of vitamin K-producing intestinal microbial flora • Treatment with antibiotics, sulfanilamides, salicylates • Long-term absence of food fats required for vitamin K absorption • Impaired vitamin K absorption • Biliary atresia • Cystic fibrosis of the pancreas • Hereditary deficiency of vitamin K-dependent factors associated with point mutations in the gamma-glutamyl carboxylase (*GGCX*) and vitamin K epoxide reductase

HEMORRHAGIC DISEASE OF THE NEWBORN

An increased rate of hemorrhagic disease of the newborn (HDN) with late onset due to the absence of preventive measures against vitamin K deficiency at maternity hospitals has been observed lately [4]. Usually hemorrhagic syndrome in children takes a form of hemorrhagic disease. There are three forms of HDN:

• **Early-onset:** a rare form characterized by bleeding symptoms in the 1st day of life; may develop due to mother's intake of the drugs affecting neonatal production of vitamin K.

• **Classic:** usually develops on the 2nd-5th day of life in breastfed neonates with impaired intestinal absorption.

• **Late-onset:** develops at the age of 2 weeks – 6 months in the event of inadequate vitamin K supply (low breastmilk vitamin K concentration) or insufficient vitamin K absorption caused by hepatic and bile duct disorders.

Clinical manifestations. Early-onset hemorrhagic disease of the newborn (eHDN) may start to develop intrauterine; intracranial hemorrhages, cephalohematomas, skin hemorrhages and umbilical hemorrhages are identified in such children at birth. HDN develops in healthy children at the age of 5-7 days in 0.25-0.5% cases [5]. The initiating agents are severe asphyxia and birth trauma. eHDN may manifest itself as a skin hemorrhagic syndrome in the subjacent areas (buttocks, subaponeurosis hemorrhages), pulmonary hemorrhages, hemorrhages into abdominal cavity organs (especially frequently in liver, spleen and adrenal glands) and melena.

The possible initiating agents of late-onset hemorrhagic disease (lHDN) are malabsorption syndrome (longer than one week), biliary atresia, hepatitis, cholestatic jaundice, cystic fibrosis of the pancreas. Clinical manifestations of lHDN: intracranial hemorrhages, major skin ecchymosis, melena, hematemesis, injection site bleeding. Most children with lHDN have not been receiving vitamin K immediately after birth.

Table 2. Laboratory parameters at various hemorrhagic syndromes in infants

Parameters (for a Stago automatic coagulation analyzer)	Healthy infants	Vitamin K deficiency	Hepatic coagulopathy	DIC (stage II, III)	Thrombocytopenia without DIC	Hemophilia
Platelet count (x 10^9/l)	150-400	Normal	Normal	Low	Low	Normal
Prothrombin	12-16	High	High	High	Normal	Normal

time (seconds)						
Thrombin time (seconds)	14-21	Normal	High	High	Normal	Normal
APTT (seconds)	28-36	High	High	High	Normal	High
Fibrinogen (g/l)	1.6-4.0	Normal	Normal or slightly low	Low	Normal	Normal

Note. DIC – disseminated intravascular coagulation, APTT – activated partial thromboplastin time.

Diagnosis. Diagnosis is established on the basis of a combination of anamnestic (presence of HDN risk factors) and clinical data and confirmed with laboratory examinations: reduction in the vitamin K-dependent coagulation factor activity, hypocoagulation via the internal pathway (increased activated partial thromboplastin time [APTT]), hypocoagulation via the external pathway (increased prothrombin or thromboplastin time [PT]), Quick prothrombin value below 60%. At the same time, the levels of fibrinogen, von Willebrand factor and platelets remain within the range of reference values.

When diagnosing HDN, vitamin K-dependent hemorrhagic conditions should be differentiated from the other diseases accompanied by hemorrhagic syndrome and impaired blood coagulation system. See data on the hemostatic parameters at various hemorrhagic syndromes in infants below (table 2).

Correction of disorders at vitamin K deficiency. Intravenous administration of a vitamin K preparation is recommended. Prothrombin time and APTT usually normalize within 4 hours after an intravenous infusion. Absence of either clinical or laboratory improvement indicates that a child is probably suffering not HDN, but a hepatic or some other pathology, including hereditary coagulopathy. The administrable vitamin K dose is 1 mg/kg. In Russia, the most frequently used preparation is menadione sodium bisulfite (Vicasol) – vitamin K3, which is less efficient than phylloquinone (vitamin K1). Term neonates are prescribed the drug in the dose of 5 mg, premature infants – 2-3 mg BID 12 hours apart. Sometimes menadione is administered TID in order for the vitamin K-dependent coagulation factor level to exceed 30% of the adult level.

Prevention. Intramuscular administration of vitamin K soon after birth is an effective measure of preventing HDN. The recommended dose of vitamin K for premature infants is 0.5 mg/kg, for term infants – 1 mg/kg [6]. In some countries specialists continue to assume that administration of vitamin K in the dose of 2 mg for 2-3 days to healthy term infants is enough in case of an absolutely smooth gestation course. However, oral use of vitamin K is not sufficiently effective for preventing late-onset HDN. The scientists believe that weekly intake of 1 mg of vitamin K by all breastfed children will become an effective means of preventing late-onset HDN [7]. The children receiving total parenteral nutrition, long-term antibiotic therapy and having signs of malabsorption require the same approach. Children with jaundice, premature infants, children receiving broad-spectrum antibiotics are recommended a single intramuscular administration of vitamin K every 5-7 days for preventive purposes.

CLINICAL CASE 1

Male Gleb R., 7 months of age, date of birth: March 21, 2014.

The child of the 2nd pregnancy. Birth weight – 3 110 g, length – 50 cm. Gestation course: ARVI (in weeks 20 and 28), arterial hypertension. Pyelectasis diagnosed at the age of 25 weeks. 2nd labor, gestational week 37.

Anamnesis: the child has been followed up at a department of surgery; diagnosis: "Obstructive megaloureter on the left, condition after surgery, urinary fistula, uroplania". At the age of 4 months: lumbotomy on the left, kidney revision, heminephrectomy of the lower segment; at the age of 5 months: paranephric abscess on the left, urinary fistula, paranephric abscess puncture, relumbotomy on the left, lancing of the paranephric abscess, wound drainage. At the age of

6 months: repeated hospitalization due to hyperthermia up to 39 oC, anxiety and anorexia. Diagnosis: "Urinary fistula, uroplania". Therapy: Sulperacef.
The child was hospitalized to the department of urology at the research institute of pediatric surgery of the Scientific Center of Children's Health (SCCH) on September 23, 2014, due to aggravated condition. The child was transferred to the resuscitation unit on September 24, 2014, due to severity of the condition caused by respiratory failure events, hypochromic and microcytic anemia and hemorrhagic syndrome. General condition: severe. Body temperature: 37.2 ^{o}C. Conscious. Cutaneous coverings: pale, clean. Mixed dyspnea, up to 40 respiratory movements per minute. Auscultation: diminished breath sounds in the posteroinferior regions, no identifiable rales. Muffled heart tones, tachycardia. Heart rate – 154 bpm. Tendency towards arterial hypertension. Distended and soft abdomen (on palpation). Unobstructed urination; transparent light urine. Drainage – straw-colored, with hypostasis. Significant bleeding from blood sampling sites (hand, finger).

Laboratory examination

Clinical blood assay: hemoglobin – 66 g/l, erythrocytes – 3.66 x 10^{12}/l, platelets – 388 x 10^{9}/l.
Coagulogram: Quick prothrombin value – 0%, prothrombin time > 240 seconds, international normalized ratio – 0, thrombin time – 18.3 seconds, fibrinogen – 2.23 g/l, APTT – 77.9 seconds, D-dimer – 0.22 mcg/ml. Coagulation factors VIII, IX, II, VII an X – 168, 5, 4, 4 and 2%, respectively.
Treatment. Packed red blood cells, Meronem + Vancomycin, Caspofungin, Vicasol (5 mg/day). The day after: normalization of coagulogram parameters (Quick prothrombin value – 90%, prothrombin time – 13.9 seconds, international normalized ratio – 1.06, thrombin time – 17.3 seconds, fibrinogen – 1.59 g/l, APTT – 29 seconds, D-dimer – 0.37 mcg/ml, plasminogen – 75%, protein C – 47%; coagulation factors IX, II, VII and X – 65, 64, 74 and 82%, respectively).

CLINICAL CASE 2

Female M., 7 months of age. Cystic fibrosis (mixed). Severe course. Chronic blue pus infection.
The child of the 3rd pregnancy, delivered in week 36 by means of cesarean section. Birth weight – 2 500 kg, length – 47 cm. APGAR score – 4/5. Not vaccinated. Breastfed until the age of 2 months. Ailing since birth. Diagnosed with "intrauterine infection, prematurity (36 weeks), respiratory distress syndrome, enterocolitis" on the 3rd postnatal day. The child was transferred from the maternity hospital to the neonatal pathology unit.
Examination (7 months): poor physical development (disharmonic due to insufficient body weight). Given pronounced manifestations of respiratory failure in the setting of cystic fibrosis, the child was transferred to the resuscitation unit for follow-up and treatment in order to correct electrolytic disorders.
At admission to the resuscitation unit: extremely severe condition; cutaneous coverings: pale, with moderate cyanotic discoloration in the nasolabial triangle. Pronounced participation of subsidiary muscles in respiration, retraction of complaint thoracic areas. Muffled and regular heart tones. Respiration by means of an oxygen mask. Saturation in the setting of oxygen supply – 100%. Heart rate at rest – 112 bpm, at stress – up to 146 bpm.
Acid-base balance and blood gases: pH – 7.3, pCO_2 – 44, pO_2 – 153.
Blood assay: hypochromic anemia (hemoglobin – 70 g/l), leukocyte count – 15 x 10^{9}/l, hypokalemia – 2.76 mmol/l, hyponatremia – 123 mmol/l. Nasal bleeding and catheter site bleeding were observed.
Coagulogram: Quick prothrombin value – 48%, PT – 35 seconds, APTT – 70 seconds, von Willebrand factor – 130%. Coagulation factors IX, VII, II and X – 11, 7, 10 and 14%, respectively.

Treatment. Vicasol (1 mg/kg), Dicynone. Positive dynamics on day 2. Hemorrhagic syndrome was arrested; coagulogram demonstrated normalization of hemostatic parameters: PT > 14 seconds, APTT – 38 seconds, factor IX – 42%, factor VII – 48%.

CLINICAL CASE 3

Female S., 1 month of age. The child was delivered on term by means of emergency cesarean section (hypoxia); birth weight – 3 130 g. APGAR score – 8/9. Vitamin K was not administered in the maternity hospital; the girl was discharged on day 6. Unremarkable umbilical wound. Breastfed. Medical examination revealed ankyloglossia. Examination by a maxillofacial surgeon at the age of 1 month led to an injury of the mouth cavity mucosa. Bloody issue from the mouth appeared 1 week later; it gradually aggravated in a course of 3 days. Ecchymosis on the chest and the back appeared at the same time, as well as dark brown coloring of the stool. The girl was taken to the consultation department with corresponding complaints.
Examination: singular hematomata on bodily skin, petechiae.
Coagulogram: PT > 240 seconds, APTT > 128 seconds, von Willebrand factor – 157%, factor IX – 2%.
Treatment. Injection of 1% menadione solution (Vicasol) in the dose of 1 mg/kg twice 12 hours apart. Examination after 1 day indicated absence of mouth cavity mucosal bleeding; clinical blood assay was unremarkable: platelet count – 636 000; coagulogram: normalization of parameters: PT – 13.1 seconds (11.5-15.3 seconds), APTT – 37.1 seconds (29.1-35.5 seconds). Within the subsequent 7 days the girl was receiving tableted mendaione in the dose of 2 mg per day. Hemorrhagic syndrome was arrested within 24 hours. 2-week follow-up: normal condition of the child, no mucosal bleeding, clean skin, normal stool.

CONCLUSION

It is necessary to examine children with minimal manifestations of hemorrhagic syndrome, inject a preventive dose of vitamin K to the children undergoing long-term antibiotic treatment, especially the children with cystic fibrosis, as well as to the risk group children (see table 1). Periodic monitoring of children with hepatic diseases, cholestatic syndrome and/or chronic gastrointestinal diseases involves additional examination of the cholestatic system in order to timely diagnose and correct hemorrhagic conditions.

CONFLICT OF INTEREST

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