A child with hemorrhagic syndrome

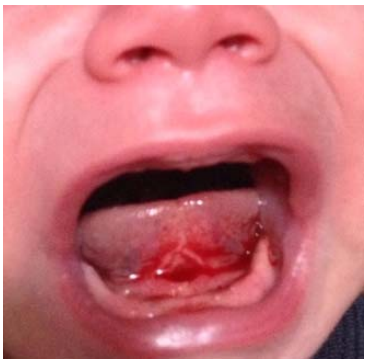

Fig. 1. Bleeding from the lingual frenum area

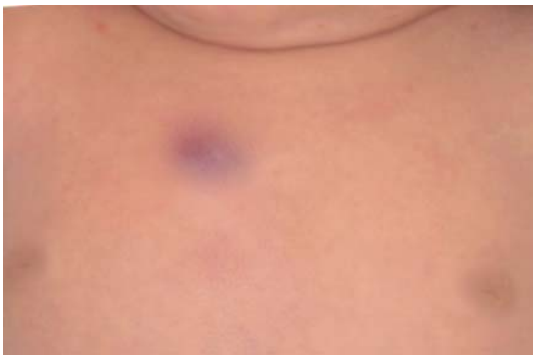

Fig. 2. Ecchymosis on the front surface of the chest skin

Three days ago a 1-and-a-half-month old girl arrived with profuse bleeding from the tongue frenulum. The bleeding continued despite local mouth treatment. Two days ago her stool acquired a dark color. Perinatal history is not burdened. The **Girl was on home birth, has not been observed by a pediatrician.**

On examination: **height - 55 cm (50th percentile), weight - 3650 gr (3rd percentile), pale skin, two ecchymosis: one on the chest and the other on the back, 1.5-2 cm in diameter, profuse bleeding from the frenulum (Fig. 1,2), the spleen is not palpable, liver +0.5 cm from the edge of the costal arch.**

General blood analysis: **leukocytes 13.7×10^9/l, erythrocytes 3.96×10^{12}/L, hemoglobin 122 g/L, platelets 636×10^9/l.**

Coagulogram: **prothrombin time (PTT) > 240 s (normal < 13.1 s), activated partial thromboplastin time (APTT) > 128 s (normal < 37.1 s), fibrinogen 3 g/l, D-dimer 0.23 mcg/ml, Willebrand factor - 157%, factor IX - 2% (normal 60-150).**

Biochemical blood analysis: **transaminases, total protein, and albumin are normal. Bleeding time is normal, clotting time - considerably lengthened. Bleeding from the place of venipuncture for 30 min.**

What is the probable diagnosis?

1. Glanzmann thrombasthenia.
2. Idiopathic thrombocytopenic purpura (ITP).
3. Coagulopathy associated with a deficiency of vitamin K.
4. Hereditary Von Willebrand disease.
5. Hemophilia B.

Correct answer: 3. coagulopathy associated with a deficiency of vitamin K.

In general, such symptoms as petechiae, purpura, bleedings from mucous membranes and nasal bleedings, are more characterizing for the pathology of vascular-platelet hemostasis, and extensive bleeding into the muscles, cavities and joints - for violations of the plasma reactions. However, all the diseases listed among the answers, could make their debut in infancy as ecchymosis - prolonged bleeding from venipuncture sites and mucous membranes. Below there are the distinctive features that suggest the correct diagnosis.

Glanzmann thrombasthenia and idiopathic thrombocytopenic purpura (ITP) are pathologies of the hemostasis platelet component. Herewith, platelet aggregation is disturbed (bleeding time is lengthened), whereas coagulation tests (aPTT, PTT) and the level of clotting factors are normal in contrast to the results of research in our patient. In the case of Glanzmann thrombasthenia - a rare genetic disorder in which there is a quantitative or qualitative deficiency of the fibrinogen receptor GPIIb-IIIa (its other name - integrin αIIbβ3) of platelets, - the number and size of platelets is not changed [1]. However, the function of platelets is disrupted: the laboratory notes there is a decrease of platelets with adenosine diphosphate, adrenaline, and collagen aggregation, whereas the response to ristomycin is normal (we did not carry out an in-depth study of platelet function in our patient, as an infringement of plasma hemostasis was revealed, which was the key to other diagnoses). Glanzmann thrombasthenia debuts in the first months of life in the form of petechiae, ecchymosis, and bleeding from the mucous membranes.

A mandatory sign of ITP is thrombocytopenia, which is not observed in our patient. Thrombocytopenia herewith is linked with antibodies to the antigens of platelets (mostly to GPIIb-IIIa, GPIb-V-IX) formation, which leads to the sequestration of platelets in the spleen and their phagocytosis by macrophages [2]. The activation of a megakaryocytic germ in the bone marrow is not enough to compensate for the platelet number. In most cases, acute idiopathic thrombocytopenic purpura is mild - in the form of petechiae and ecchymosis - and passes on its own, but there are described cases of intracranial hemorrhage at platelet numbers going lower than 10×10^9/L, which happens in 0.5-1% of cases [2].

Von Willebrand disease is a common hereditary hemorrhagic pathology associated with a deficiency or dysfunction of a protein called Von Willebrand factor. It is involved in the primary vascular-platelet hemostasis by mediating platelet adhesion to subendothelial structures (to collagen) and subsequent platelet aggregation. Another important function of the Von Willebrand factor is the binding of free factor VIII and its protection from proteolytic degradation by the protein C - Protein S system, i.e. participation in the secondary plasma hemostasis [3]. Since plasma glycoprotein is involved in platelet adhesion and aggregation, in case of its deficiency or violation of functions, the bleeding time is prolonged. Prothrombin time should be normal, because this test reflects the external cascade of the clotting work, i.e. a function of factor VII, as well as of factors X, V and of prothrombin. The interaction of these factors in Von Willebrand's disease is not disrupted. APTT, on the contrary, shows the effectiveness of the internal blood clotting cascade, i.e. of factors XI, IX, VIII, as well as of factors X, V and of prothrombin. Since Von Willebrand factor is essential for protecting the Factor VIII from premature destruction, in case of hereditary blood disease there is a deficiency of factor VIII, and aPTT can be prolonged [3]. In our patient we see lengthening of both PTT and aPTT, whereas the bleeding time and the level of Von Willebrand factor are normal. These figures contradict the diagnosis of Von Willebrand disease.

Hemophilia B is a coagulopathy associated with factor IX deficiency. This disease is sex-connected and can develop only in boys. In hemophilia B, the external blood clotting cascade is not disrupted, and the value of the VWP should be within the normal range. Due to the lack of factor IX, the intrinsic pathway of blood clotting suffers, and aPTT is lengthened. Bleeding time and platelet numbers are not changed. Clinical manifestations of hemophilia B in infancy are prolonged bleeding and hematomas after injury and surgery; bleedings from the umbilical

wound; intracranial hemorrhages [4]. Despite a significant reduction of Factor IX in our patient, she cannot have haemophilia B.

The girl in the presented clinical case has a late form of coagulopathy associated with a deficiency of vitamin K. The prerequisites to diagnosis are anamnestic data, namely the lack of vitamin K deficiency prophylaxis (the child was born at home, and was not observed by a pediatrician) and of breastfeeding. Bleeding of mucous membranes and spontaneous ecchymosis, which is very typical for this pathology, were observed in the patient. Laboratory tests also spoke in favor of this diagnosis. In vitamin K deficiency, glutamine residues' of several clotting factors carboxylation is violated, which is necessary for their operation. Vitamin K-dependant factors are II, VII, IX and X, protein C and protein S. Consequently, both internal and external clotting cascades become disrupted and the PTT and APTT become prolonged. The platelet hemostasis link does not suffer. [5]

An early form of coagulopathy associated with vitamin K deficiency occurs within the first 24 hours after birth, the classic form - during the first week after birth, and the later - in children aged 2 weeks - 6 months. Breast-feeding, liver disease, and malabsorption syndrome predispose the later form's development. In breast-fed infants who did not receive vitamin K deficiency prophylaxis at birth, the frequency of coagulopathies associated with a deficiency of vitamin K is 4,4-7,2 of 100 000 [5]. Since the physiological need for vitamin K is 1 mcg/kg per day, infants under the age of 1 year need 5-10 mcg/day, while in breast milk there is no more than 1-4 mcg/l of this anti-hemorrhagic biologically active compound. In addition, vitamin K passes through the placenta in insufficient amounts, which also predisposes children of the first months of life to a deficiency of this substance. Natural sources of vitamin K_1 (phylloquinone) are greenleaved vegetables, greens (kale, parsley, spinach), some legumes and vegetable oils (canola, olive), and of vitamin K_2 (menaquinone) - bacterial activity of the gastrointestinal tract and animal liver [6].

In addition to these manifestations of the late form of coagulopathy associated with vitamin K deficiency was the bleeding of mucous membranes, gastrointestinal hemorrhages and ecchymosis, intracranial hemorrhage developed in 50% of cases, with the mortality rate up to 20% [5-7]. Treatment consists of a single intramuscular injection of 1-3 mg of vitamin K, severe cases may require transfusion of fresh frozen plasma at a dose of 10-20 ml/kg.

Prevention of vitamin K deficiency is necessary for all children. There are several schemes of prophylaxis [5]:

- 1 mg of vitamin K intramuscularly at birth (further reception is not required);
- 1 mg of vitamin K *per os* at birth, and further - in the case of breast-feeding - 1 mg 1 time per week orally for up till the age of 12 weeks, or 2 mg at the age of 1 and 4 weeks.

Standard deficiency of vitamin K prophylaxis schemes can be ineffective if the child has liver disease or malabsorption syndrome (especially for schemes with taking vitamin K orally) [5-8].

It should be remembered that the therapy with menadione - a synthetic analogue of vitamin K - or vitamin K_3, might be associated with the development of hemolytic anemia, indirect hyperbilirubinemia and kernicterus [5].

So, if a child has spontaneous bleeding, ecchymosis, intracranial hemorrhage, laboratory observed elongated PTT and aPTT with normal (or increased) number of platelets, while his/her age is less than 6 months, and he/she did not receive any preventive vitamin K, the most likely diagnosis is coagulopathy associated with vitamin K deficiency [5-8]. The diagnosis confirmation is rapid (within hours): the coagulogram normalizes after a parenteral injection of 1 mg of vitamin K. In our patient, bleeding from the lingual frenum area stopped 2 hours after the vitamin K injection; after 12 hours, all coagulogram indexes had normalized. No neurological disorders were noted. According to laboratory data, the child did not have signs of liver disease and changes in stools, which might have indicated malabsorption. Subsequently, the weight gain has normalized.

It must be remembered that the "harmless" bleeding of skin and mucous membranes in case of vitamin K deficit may be a harbinger of intracranial hemorrhages, so urgent diagnosis and treatment are needed.

Yu.S. Lashkova
Scientific Center of Children's Health, Moscow, Russian Federation

CONFLICT OF INTEREST

The author has indicated she has no financial support / conflict of interest relevant to this article to disclose.

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