GUIDELINES
FOR STUDENTS
INDEPENDENT WORK
IN THE PRACTICAL CLASSES PREPARING

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Poltava 2016.
The subject of the lesson: Hemophilias. Thrombocytopenic purpura

1. The theme topicality. The theme "Hemophilia" is very important for future doctors in their professional activity; it influences positively on the students in their attitude to the future profession and forms professional skills and experience as well as taking the principle of the knowledge of the subject under study.

2. The main goals:
   - To have general knowledge of the theme studied
   - To understand, memorize and use the knowledge received
   - To learn the etiopathogenesis, classifications, clinics, diagnostics, principles of treatment
   - To be able:
     - to derive previous and clinical diagnosis,
     - to complete the plan of additional investigation,
     - to interpret the results of additional data,
     - to prescribe the treatment.

3. Basic knowledge, abilities and skills necessary for studying theme.

   Interdisciplinary integration

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<th>Subject</th>
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<td>Previous subject (pathophysiology, propedeutics; pharmacology)</td>
<td>Basic terms</td>
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<td>Pathogenesis</td>
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<td>Following subject</td>
<td>etiopathogenesis, classifications, clinics, diagnostics, principles of treatment</td>
<td>to derive clinical diagnosis, to interpret the results of additional data; to prescribe the treatment</td>
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4. Materials for self-training

4.1. The main terms, subjects and its introductions

<table>
<thead>
<tr>
<th>Subject</th>
<th>Introduction</th>
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<tr>
<td>Hemophilia</td>
<td>Congenital blood coagulation disorder, inheritance is sex linked, males are affected while females act as carrier.</td>
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<tr>
<td>Hemophilia A</td>
<td>Occurs as a result of low level or either absence of factor VIII C.</td>
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<tr>
<td>Hemophilia B</td>
<td>(Christmas’ disease) occurs as a result of deficiency of factor IX C.</td>
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<tr>
<td>Hemophilia C</td>
<td>May be defined as a bleeding disease caused by deficiency of factor XI C (Rosental syndrome).</td>
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4.2. Self preparation at class. Practical skills the student must be able to do:
1. To survey a patient.
2. To make a differential diagnostic and formulate the clinical diagnosis.
3. To estimate the results of lab studies and procedures.
4. To write out the recipe: Cryoprecipitate, recombinant factor VIII et all.

**Theme contents:**

**Hemophilia** - congenital blood coagulation disorder, inheritance is sex linked, males are affected while females act as carrier. Some cases do not have any family history and presumably result from spontaneous genetic mutation.

**Sex** - males are affected while females act as carrier.

**Age** – early onset in babies about 6 month old.

**Pathogenesis**

The antihemophilic factor (AHF) or factor VIII coagulant protein is a large (265 kDa) single-chain protein that regulates the activation of factor X by proteases generated in the intrinsic coagulation pathway. It is synthesized in liver and circulates complexed to the von Willebrand factor (vWF) protein. Factor VIII molecule is present in low concentration (10 mkg/L) and is susceptible to proteolysis. The gene for factor VIII is on the X chromosome and carrier detection and prenatal diagnosis are well established.

**Hemophilia A** occurs as a result of low level or either absence of factor VIII, primary synthesized by liver, but other organs such as spleen, kidney may also contribute to the plasma level. The factor VIII gene is localized on the X chromosome and that’s why hemophilia A is sex-linked disorder. All daughters of patient with hemophilia are obligate carriers and sisters have a 50% chance of being carrier. If a carrier has a son, he has a 50% chance of having hemophilia, and daughter has a 50% chance of being carrier. 33% cases do not have family history.

Lack of factor IX is known as **hemophilia B** (Christmas’ disease). It is also X-linked recessive trait.

**Hemophilia C** is occurs in patients with lack of factor XI (Rosental syndrome).

**Clinical**

Spontaneous bleeding, profuse bleeding after trauma, dental extraction, surgery manipulation. Sometimes may be nasal, pulmonary hemorrhage, and from gastrointestinal, genitourinary systems’ organs. It may be complains of joint enlargement, disorder.

The clinical features are similar in the case of all the types of hemophilia, but in patients with hemophilia B bleeding is usually not so severe because factor IX is more stable than factor VIII.

**Physical**

General patient’s condition is usually satisfactory. In case of prolonged and recurrent hemorrhages and loss much of blood general condition may be middle, grave or hard grave.

The posture of the patient is active with restriction due to the pain and walking difficulties in affected joints and muscles caused by spontaneous bleeding. The skin is pallor with hemorrhages: petechia, ecchymoses, hematoma.
Hemarthrosis begins spontaneously without any apparent trauma. The most commonly affected joints are knees, elbows, ankles, and hips. Bone destruction occurs due to recurrent subperiosteal hemorrhages.

Lab Studies
Clinical blood analysis
- Activated partial thromboplastin time increased;
- Whole blood coagulation time is raised;
- Factor VIII d'olling assay (VIII C) reduced;
- Immunological methods show normal VIII R, AG;
- Bleeding time and prothrombin time tests are normal;
- Carrier females have half the clotting activity (VIII C) expected for the level of VIII R, AG.

Imaging Studies
X-ray examination
- Brodening of femoral condyles;
- Sclerosis, osteophyte and bony cysts;
- Atrophy of muscles.

Computer tomography scan
- Intracerebral hematoma.

TREATMENT
Tenets regarding the treatment of bleeding in hemophilia patients include the following:
- Symptoms often precede objective evidence of bleeding;
- Signs of bleeding may not appear until several days after well-documented trauma. Early treatment is more effective, less costly, and can be lifesaving;
- Avoid the use of aspirin or aspirin-containing drugs, which impair platelet function and may cause severe hemorrhage. Cyclooxygenase inhibitors can be used, as they do not impair platelet function.

The goals are to control symptoms, and to prevent recurrent bleeding or other complications. The treatment is based on lifestyle modification and control of blood coagulating level.

Lifestyle modifications include the following:
- Very important to change the profession rightly
- The patients had got full information about the disease of their child.
- Schoolboys had to be free from physical training classes.

Pharmacologic therapy – intensive therapy by antihemorrhagic drugs – the main treatment and method of prophylaxis of most hemophilia complications.

MEDICATION
The goals of pharmacotherapy are to prevent complications and to reduce morbidity.

Plasma products enriched in factor VIII reduce the degree of orthopedic deformity and permit virtually any form of elective and emergency surgery.

Cryoprecipitate, which contains about half the factor VIII activity of fresh-frozen plasma in one-tenth the original volume, is simple to prepare and is produced in hospital or regional blood banks.
Patients with hemophilia should receive either monoclonal purified or recombinant factor VIII to minimize viral infection risk and exposure to irrelevant proteins.

Each unit of factor VIII infused, defined as the amount present in 1 ml normal plasma, will raise the plasma level of recipient by 2%/kg of body weight. Factor VIII has a half-life of 8 to 12 h, making it necessary to infuse it continuously or at least twice daily to sustain a chosen factor VIII level.

In patients with mild hemophilia an alternative treatment is desmopressin (DDAVP), which transiently increases the factor VIII level. Desmopressin will increase the factor VIII level two-to threefold. Although generally safe, it occasionally causes hyponatremia or may precipitate thrombosis in elderly patients.

Epsylon-aminocaprionic acid – 4-6g four times daily for 3 or 4 days after dental extraction.

Tranexamic acid – longer-acting antifibrinolitic just before surgery dental manipulation and continue for at least 2 to 3 days.

**Prognosis**

- Most patients with hemophilia do well with medications, although a relapse after cessation of medical therapy is common and indicates the need for long-term maintenance therapy.
- Identifying the subgroup of patients who may develop the most serious complications of the disease and treating them aggressively is important.

**Thrombotic thrombocytopenic purpura**

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening multisystem disorder that is considered a true medical emergency. Moschcowitz first described TTP in 1924 when he observed that a 16-year-old girl had anemia, petechiae, and microscopic hematuria. She died of multiorgan failure, and, at autopsy, disseminated microvascular thrombi were prevalent. These thrombi remain the hallmark of the pathologic diagnosis. Since that time, advances in the pathophysiology, etiology, and medical management of TTP have been noteworthy.

This life-threatening condition may have a positive outcome if recognized early and medical intervention is initiated early. Thrombocytopenic purpura is a syndrome with diagnostic criteria developed in 1966 by Amorosi and Ultmann. They reviewed 255 patients previously reported and 16 other patients. They outlined a pentad of clinical features including microangiopathic hemolytic anemia, thrombocytopenia, neurologic abnormalities, fever, and renal dysfunction.

2. The aims of the training course:

To know:
- etiology and pathogenesis of thrombocytopenic purpura
- classification
- the basic syndromes
- differential diagnosis
- main principles of treatment

To be able:
- to take anamnensis from a patients
to survey the patient, to reveal and to give the estimation to the changes of the patient’s condition
- to draw up a plan of additional investigations to estimate their results
- to prescribe proper treatment

**Pathophysiology**

The TTP syndrome is characterized by microangiopathic hemolysis and platelet aggregation/hyaline thrombi whose formation is unrelated to coagulation system activity. Platelet microthrombi predominate; they form in the microcirculation (ie, arterioles, capillaries) throughout the body causing partial occlusion of vessels. Organ ischemia, thrombocytopenia, and erythrocyte fragmentation (ie, schistocytes) occur. The thrombi partially occlude the vascular lumina with overlying proliferative endothelial cells. The endothelia of the kidneys, brain, heart, pancreas, spleen, and adrenal glands are particularly vulnerable to TTP. The liver, lungs, gastrointestinal tract, gallbladder, skeletal muscles, retina, pituitary gland, ovaries, uterus, and testes are also affected to a lesser extent. No inflammatory changes occur.

**Mortality/Morbidity**

The mortality rate associated with TTP approached 100% until the 1980s; the drop in mortality rate since that time is attributed to earlier diagnosis and improvement in therapy with plasma exchange.

- Presently, the mortality rate is approximately 95% for untreated cases.
- The survival rate is 80-90% with early diagnosis and treatment with plasma infusion and plasma exchange.
- One third of patients who survive the initial episode experience a relapse within the following 10 years.

**Race.** No significant racial difference exists.

**Sex.** This condition is more common in women than in men, with a female-to-male ratio of 3:2.

**Age.** TTP is most common in adults, although it can occur in neonates to persons as old as 90 years. The peak occurs in the fourth decade of life, with a median age at diagnosis of 35 years.

**History.** The pentad of findings associated with TTP is rarely found, and the current clinical factors leading to the diagnosis include the following:

1. Thrombocytopenia
2. Schistocytosis
3. Elevated serum lactate dehydrogenase (LDH) levels (often markedly elevated)
4. Absence of other disease entities that could explain the thrombocytopenia and microcytic hemolytic anemia

Patients with thrombotic thrombocytopenic purpura (TTP) present with nonspecific complaints.

- Prodrome resembling a viral, flulike illness
  - Fever (60%)
  - Fatigue/generalized malaise
  - Arthralgias
- Hematologic changes
- Thrombocytopenia, with petechial hemorrhages in the lower extremities and a lack of bleeding
- Anemia - Hemoglobin levels less than 10 g/dL
- Neurologic changes
  - Altered mental status (36%) - Patients can present with confusion, generalized headaches, altered mental status, focal deficits, seizures, visual disturbances, and coma. Symptoms may wax and wane secondary to the microhemorrhagic and microocclusive vascular changes in the brain. CNS bleeding is an ominous sign.
    - Seizures (16%)
    - Hemiplegia (12%)
    - Paresthesias (4%)
- Cardiac changes
  - Heart failure
  - Arrhythmias
- Abdominal pain (24%) - May be related to gastrointestinal ischemia
- A patient can present with some or all of the characteristics of the classic pentad, which includes the following:
  - Thrombocytopenia
  - Fever
  - Renal changes (88%) with gross hematuria (15%)
  - Neurologic deficit
  - Hematologic changes
- Microangiopathic hemolytic anemia (MAHA)

**Causes**
- Pregnancy and the postpartum state account for 10-25% of cases of TTP.
  - TTP usually presents before 24 weeks’ gestation and can be distinguished from other thrombotic microangiopathic disorders in that thrombocytopenia occurs without DIC.
  - Central nervous system (CNS) findings occur early and are disproportionate to alterations in blood pressure, renal dysfunction, or hepatic compromise.
  - The course of the syndrome is not altered by termination of pregnancy.
  - Improvement in survival rate is due to aggressive treatment with plasmapheresis or plasma transfusion.
- Thrombotic microangiopathic disorder is uncommon but occurs in greater frequency in patients with HIV-1 infection; it may be the initial presenting syndrome.
  - The usual presentation is thrombocytopenia, MAHA, renal abnormalities, and neurologic dysfunction.
  - Serum LDH level is extremely elevated (ie, >1000 U/L); LDH level also is elevated with *Pneumocystis carinii* infection, high-grade B-cell lymphoma, and sulfa drug reactions.
Management consists of plasma exchange, antiplatelet agents (eg, dipyridamole, sulfinpyrazone, aspirin, dextran), and splenectomy for refractory cases. Survival rate and prognosis are poor.

- TTP often is associated with cancer.
  - Anemia and thrombocytopenia occurring with TTP may be out of proportion to that expected from cancer and chemotherapy reactions.
  - LDH level is elevated, and Coombs test result is negative.
  - In the cancer patient, coagulation factor consumption is often low.
  - Both TTP and DIC can be present in the same patient and may be difficult to distinguish.
  - Cancer chemotherapeutic agents associated with TTP include mitomycin C, tamoxifen, bleomycin, cytosine arabinoside, and daunomycin.
- Noncancer chemotherapeutic and other drugs suspected of causing TTP include immunosuppressive agents (eg, cyclosporine A), crack cocaine, ticlopidine, oral contraceptives, penicillin, and rifampin.
- Toxins associated with TTP include the following:
  - *Escherichia coli*
    - *E. coli* O157:H7 is a toxin-producing bacteria.
    - *E. coli* toxin is found in undercooked foods.
    - *E. coli* toxin is associated with diarrhea and outbreaks of HUS in children and to a lesser degree associated with TTP.
    - *E. coli* toxin is concentrated in the renal and brain endothelium.
  - Spider and bee venoms

Lab Studies. Thrombotic thrombocytopenic purpura (TTP) is a clinical diagnosis with no pathognomonic laboratory test findings. In the past, a pentad of signs and symptoms was associated with TTP: thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, renal failure, and fever. Current clinical practice diagnostic criteria include thrombocytopenia, schistocytosis, and significant elevations in serum LDH levels to suggest the diagnosis of TTP. Measuring protease activity as a single test to distinguish TTP from HUS is not practical at this time. The absence of in vitro tests capable of detecting abnormalities in all the molecular interactions required for the cleavage of ULVWF multimers by ADAMTS-13 in vivo is a limitation.

*Laboratory tests helpful in making the diagnosis include the following:*

- Complete blood count (CBC)
  - Thrombocytopenia and anemia are noted.
  - Evidence of thrombocytopenia may precede the appearance of fragmented RBCs and LDH elevation by several days.
- Peripheral blood smear - Fragmented RBCs (ie, schistocytes) are consistent with hemolysis. Schistocytes on a blood smear is the morphologic hallmark of the disease, but no guidelines exist as to the number of schistocytes required to differentiate TTP from other thrombotic microangiopathies.
- LDH level - Extremely elevated, mostly as a consequence of LDH from ischemic or necrotic tissue cells rather than due to hemolysis
- Indirect bilirubin level - Elevated
- Reticulocyte count - Elevated
- Prothrombin time (PT) and activated partial thromboplastin time (aPTT) - Normal
- DIC panel (eg, fibrinogen, D-dimer) - The results are usually normal. Increasing D-dimer levels are the most specific DIC parameter and reflect fibrinolysis of cross-linked fibrin.
- Pregnancy test - Helps identify the 10-25% of patients with TTP who are pregnant or postpartum
- Creatinine level - Mildly elevated (46%)
- HIV testing - Helps identify patients with HIV in whom TTP is the presenting symptom
- Urinalysis - Proteinuria and microscopic hematuria

**Imaging Studies**
- CT scan of the head to assess for intracranial bleeding and infarcts

**Other Tests**
- Bone marrow or gingival biopsy samples diagnostic lesions in 30-50% of cases.

**Emergency Department Care**
The classic pentad is rarely complete at presentation. Current clinical criteria for initiating therapy are as follows:

1. Thrombocytopenia
2. Schistocytosis
3. Elevated serum LDH levels
4. Absence of other disease entities that could explain the thrombocytopenia and microcytic hemolytic anemia

Early recognition and management are essential for patient survival.
Understanding the pathophysiology of thrombotic thrombocytopenic purpura (TTP) is ongoing and too early to have clearly defined evidence-based standard procedures that may be applicable for all patients. Intravenous (IV) plasma exchange, also called plasmapheresis, is the present standard of treatment for TTP. During the plasma exchange, the inhibitory antibodies are removed and the plasma is replenished with the deficient protease. Delay in starting the plasma exchange is correlated with treatment failure. If a delay is unavoidable, begin plasma infusion until the plasma exchange is available.

- Use a device with a wide-bore, 2-lumen catheter at the femoral site. Use blood-cell separators so that the patient's plasma is removed and replaced by fresh frozen plasma (FFP). Start with a single plasma volume and exchange FFP at a rate of 40 mL/kg of body mass. A plasma exchange twice a day may be necessary for resolution of thrombocytopenia and neurologic complications if the response to the initial daily exchange is poor.
- Infusion of FFP (30 mL/kg) is used as a temporizing measure until the patient can be transferred to a facility where plasma exchange is available.
- The standard replacement fluid is FFP. However, success with cryosupernatant has been reported. Cryosupernatant is the residual plasma fraction after the separation of cryoprecipitate.
Glucocorticoid-steroid and antiplatelet agents are used. Steroids often are administered prior to plasma exchange. Steroids have no proven added benefit over plasmapheresis alone, but some patients respond to high-dose prednisone (200 mg/d) alone, without plasma therapy.

Antiplatelet agents are used, but hemorrhage is a concern and these agents' benefit has not been proven. Aspirin and dipyridamole are recommended by some, but their use is controversial. Other antiplatelet agents (eg, ticlopidine, prostacyclin) have variable outcomes.

Splenectomy is performed occasionally to treat patients who do not respond to plasma exchange or that relapse chronically. Some patients benefit from splenectomy. The response may be due to the removal of the site of sequestration of the RBCs and platelets. Another possibility is that the spleen is a major site of microvascular occlusive lesions in severe TTP.

Treatment of refractory or relapsing TTP includes vincristine, a second-line therapy with an unknown mechanism of action. Vincristine is occasionally given to treat resistant cases, but it has no proven benefit. Dosing is 1 mg/m², with a maximum dose of 2 mg, given weekly.

Supportive care for end-organ damage may be required. Hemodialysis is required occasionally for renal failure. Angiotensin-converting enzyme (ACE) inhibitors, nitroprusside, or esmolol may be required to control severe hypertension.

Anticonvulsants, such as phenytoin, may be required to control seizures.

Platelet-depleted packed RBCs may be necessary for severe hemolytic anemia.

Platelet transfusion is contraindicated because it is associated with rapid deterioration. The platelet aggregation worsens with platelet transfusions. In some studies, extensive platelet aggregates were found throughout the CNS on postmortem examination.

Desmopressin (DDAVP) is contraindicated because it acts by releasing ULVWF from the endothelium into the circulating blood.

**Test evaluation and situational tasks.**

Choose the correct answer/statement:

1. In the pathogenesis of idiopathic thrombocytopenic purpura main role belongs to:
   A. Immune mechanisms
   B. Toxic effects
   C. Reduction of platelet production
   D. Genetic disorders
   E. Mechanical platelets trauma

2. Which of the following manifestations of hemorrhagic syndrome are the most typical for hemophilia?
   A. Hemarthrosises
   B. Bleeding from mucous membranes
   C. Hematuria
   D. Stroke
3. Which of the following drugs is fundamental in the treatment of hemophilia A?
A. Factor VIII concentrate
B. Cryoprecipitate
C. Hemostatic sponge
D. Preserved blood
E. Factor IX concentrate

4. Which of the following drugs are the primary in conservative treatment of idiopathic thrombocytopenic purpura?
A. Corticosteroids
B. Blood transfusion
C. Heparin
D. Cryoprecipitate
E. Dicynonum

5. The diagnosis of thrombocytopenic purpura is confirmed by:
A. Thrombocytopenia
B. Leukocytosis
C. Anemia
D. Accelerate ESR
E. Changes in coagulation

6. Which of the following manifestations of hemorrhagic syndrome is the most characteristic of thrombocytopenic purpura?
A. Petechiae
B. Hemarthrosises
C. Hematuria
D. Subcutaneous hematoma
E. Bleeding from mucous membranes

7. Which of the following factors related to the plasma coagulation factors?
A. Fibrinogen
B. Heparin
C. Plasminogen
D. Platelets
E. Serotonin

8. Which of the following drugs is fundamental in the treatment of hemophilia A?
A. Factor VIII concentrate
B. Aminocaproic acid
C. Factor IX concentrate
D. Prednisolone
E. Heparin
9. The cause of hemophilia B is:
   A. Deficiency of coagulation factor IX
   B. Deficiency of VIII and IX coagulation factors
   C. Deficiency of VII and VIII clotting factors
   D. Deficiency of VI coagulation factor
   E. Deficiency of XII coagulation factor

10. Which of the following manifestations of hemorrhagic syndrome are the most typical for hemophilia?
   A. Post-traumatic and spontaneous bleeding, hemarthrosis
   B. Hemorrhagic petechial rash, abdominal pain, hematuria
   C. Spontaneous bleeding from the mucous membranes
   D. Nosebleeds
   E. Papular, petechial rash, symmetrically located in the limbs

**Real-life situations to be solved:**

1. A woman aged 42, complains of the bruising on his legs, long menorrhagia, general weakness, noise in my head. Objectively: pale skin, massive punctulate and spotty rash on the legs and body. Tachycardia. Systolic murmur at all points of auscultation. BP - 75/50 mm Hg. In blood test: RBC - 2.9x10^12/l, HGB - 80 g/l, color index - 0.9, leukocytes - 6.5x10^9/L, platelets -20.0x10^9/l. ESR- 12 mm / h Duration bleeding by Duke - 12 min. In the bone marrow - the increased number of young immature megakaryocytes no signs of platelet separating. Other indicators are normal. Which disease correspond to the data of clinical and laboratory signs?

2. A 18-years old patient K. was hospitalized to the therapeutic department with renal bleeding continuing more than a day. From anamnesis it is known that the patient has a hereditary pathology of intrinsic blood clotting pathway, it was diagnosed in childhood, repeatedly treated in the hematology hospital, where he received treatment with cryoprecipitate and fresh frozen plasma. Objectively: skin is pale-pink color, elbow joints, knee and ankle joints are deformed, active and passive movements are severely limited. The complete blood test: erythrocytes - 4.6x10^12/l, Hb – 115 g/l, the color index – 0.75; MCV – 80.6 fl, platelets 224x10^9/l, white blood cells – 4.4x10^9/l, bands 4%, segments 60%, eosinophils 1%; basophils 0%, lymphocytes 30%, monocytes 5%, ESR – 3 mm/h. The duration of bleeding by Duke is 4 minutes, the Lee-White coagulation time: start – 15 minutes, the end – 25 minutes and continues. The complete urine analysis – red color, 1020, leukocytes 2-4 in the view, the red blood cells are on the whole field of view. In coagulogram: prothrombin time 12.7 sec, fibrinogen 3.9 g/l, APTT – 55.9 sec, blood coagulation factor VIII – 4%, blood coagulation factor IX – 97.8%. What is the most likely diagnosis?

**Recommended literature:**

_A. Main:_

**A. Main:**

**B. Additional:**

Composed by as. Lymanets T.V.