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Essential Thrombocythemia - Principal Analysis in Children and Adolescents

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Abstract: Essential thrombocythemia (ET) is a rare disease in childhood. In this disease, an increase in the number of platelets in the peripheral blood is observed due to atypical megakaryocytes in the bone marrow associated with proliferation. The clinical features of ET course and response to therapy are analyzed in childhood and adolescent patients. ET course was analyzed in 23 patients under 19 years of age. The diagnosis of ET was established on the basis of WHO criteria, which included evaluation of clinical data, laboratory tests (general clinical studies; morphological, genetic, histological studies of bone marrow), instrumental studies and assessment of response to treatment. The average age of manifestation of the disease was 9 years and 9 months, the average indicator was 9 years and 6 months. Organomegaly was detected in 13 (52%) patients, isolated splenomegaly in 7 (37.5%) and hepatosplenomegaly in 6 (37.5%). Bleeding occurred in 6 (19.4%) patients with a significant decrease in ristocetin cofactor activity. Von Willebrand factor (not more than 15%), thrombocytosis (2000 10 9/1). 10 (38.7%) patients had microcirculation disorders (headache, dizziness, indigestion), half of them had thrombocytosis 1000-2000 10 9/1. JAK 2 V6 17F mutation in 3 (9.7%) patients, CALR gene mutation in 7 (29.0%), MPL gene - 1 (3.2%) patient, remaining 13. In (58.1%) patients, habitual driver genes were identified. Translocation t (12:12) was found in 1 (3.2%) patient. Complete or partial response to single-component cytoreductive therapy in young patients was 70-80%. The rate of complete response during therapy with anagrelide and interferons is higher than with hydroxycarbamide therapy (42.9%, 47.4%, and 0%, respectively). Hydroxycarbamide is not used in first-line therapy in children.

In the pediatric population of patients with ET, the "triple negative" group predominated. which made differential diagnosis with secondary thrombocytosis difficult. The risk of bleeding in children is higher than in the adult population, which is due to the large number of patients with severe thrombocytosis. With the development of hemorrhagic syndrome, microcirculation disturbances that do not respond to treatment, antiaggregant agents, we recommend that ANA therapy should be preferred over INF and IIU as the first-line cytoreductive therapy. According to the pharmacokinetic properties, not anagrelid, but interferon and hydroxycarbamide and anagrelid, the potential risk of development of myelofibrosis is high.

Keywords: essential thrombocythemia. children, adolescence, von Willebrand factor activity. chronic myeloproliferative disease, JAK 2, MPL, CALR.

Relevance: Essential thrombocythemia (ET) is a blood disease belonging to the group of Ph-negative myeloproliferative diseases (MPD), which is manifested by an increase in the number of platelets in the peripheral blood due to excessive clonal proliferation of the megakaryocyte lineage of hematopoiesis. Prevalence of ET is 1.03 per 100,000 people (95%) Confidence interval: 0.58-1.80 per

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year in the adult population, and less common in children (under 16 years): 0.004 0.11 per 100,000 people per year [1, 2, 3]. Recent studies have shown a correlation between ET and other Ph-negative MPDs. Somatic, with "driver" gene mutations JAK 2 [4, 5], MPL [6] and CALR [7, 8]. In adult patients, JAK 2 mutations occur in 50-60% of ET cases, CALR in 15-24% of cases, and MPL in 4% of cases, in the remaining 10-20% of cases it causes a "triple" mutation. [9, 10]. suffering from ET. proportion of patients are children and adolescents without JAK2 mutation, nor CALR. neither MPL genes are significantly larger [2, 10]. However, in children with ET, unlike adults, thrombosis is very rare [1, 10, 11]. There is no modern radical therapy for ET and it does not increase life expectancy. Clonal proliferation of hematopoietic stem cells in ET is relatively stable, so the risk of fibrotic transformation is very low and less than 20-10%. The main indication for the treatment of ET is the prevention of thrombotic and hemorrhagic syndromes, but according to systematic data, the risk of such complications in patients is not more than 5% (thrombosis-3.8%), bleeding: bleeding 5%) [10]. Today, leading experts in the field of chronic MPD recommend the use of acetylsalicylic acid for the majority of young patients with ET (in patients with mutated JAK2 MPL) [13]. The purpose of this study is to analyze the clinical features of the possible course of therapy and response to ET in children and adolescents. Recent studies have shown a correlation between ET and other Ph-negative MPDs. Somatic, with "driver" gene mutations JAK 2 [4, 5], MPL [6] and CALR [7, 8]. In adult patients, JAK 2 mutations occur in 50-60% of ET cases, CALR in 15-24% of cases, and MPL in 4% of cases. in the remaining 10-20% of cases it causes a "triple" mutation. [9, 10]. The proportion of ET patients in children and adolescents without JAK2 mutation, neither CALR nor MPL genes is significantly greater [2, 10].

However, in children with ET, unlike in adults, thrombosis is very rare [1, 10, 11]. There is no modern radical therapy for ET and it does not increase life expectancy. Clonal proliferation of hematopoietic stem cells in ET is relatively stable, so the risk of fibrotic transformation is very low and less than 20-10%. The main indication for the treatment of ET is the prevention of thrombotic and hemorrhagic syndromes, but according to systematic data, the risk of such complications in patients is no more than 5% (thrombosis - 3.8%, bleeding - 5%) [10]. Today, leading experts in the field of chronic MPD recommend the use of acetylsalicylic acid for the majority of young patients with ET (in patients with mutated JAK2 MPL) [13].

The purpose of this study: to analyze the clinical features of the possible course of therapy and response to ET in children and adolescents.

Materials and methods: 23 patients aged 10-19 who were treated in the hematology departments of Samarkand City Multidisciplinary Medical Center and Samarkand City Multidisciplinary Children's Center during 2019-2022 were selected for the study. (average -10.5 years). 11 of them are boys and 12 are girls. Diagnostic ET is organized according to WHO criteria [15]. All patients were investigated, except for secondary genesis of familial thrombocythemia and increased number of platelets in the blood.

This disease was accidentally detected during a routine examination of the general blood test in patients with a platelet count of more than 450 10 9/1 in three consecutive tests. According to clinical guidelines [14], patients with a platelet count less than 1000 x 109/1 were given antiaggregant therapy was performed. Cytoreductive therapy was carried out only if antiaggregant prophylaxis was ineffective for bleeding or microcirculation disorders. The drugs of choice for cytoreductive therapy in ET patients were pegylated interferon alfa-2a (Peg-INF), hydroxyurea (NU), and anagrelide (ANA). Taking into account the age of children, preference was given to interferon drugs (INF) and phosphodiesterase inhibitors.

The obtained drug was changed to a pegylated form. When any hematological response is achieved.

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the minimum effective dose was reduced step by step. XU was prescribed in the standard 10-30 mg/kg/initial dose. This study used criteria for response to ET therapy proposed by European Leukemia Net and International.

Complete response (CR) criteria are: significant improvement or complete absence of disease symptoms, including significant increase in liver and spleen size within 12 weeks:

- stable remission according to the general analysis, the general blood analysis is determined as follows;
- the number of platelets is 400 × 10 9/1, - the number of leukocytes is 10 × 1091;
- the absence of leukoerythroblastosis for 12 weeks;
- there are no signs of disease development and every no hemorrhagic or thrombotic rashes;
- histological remission of the bone marrow is defined as the absence of hyperplasia of megakaryocytes and absence of reticulin fibrosis for more than 1 time.

A partial response (PR) was defined when all criteria for CR without histologic remission were met on bone marrow biopsy. The first response assessment was performed 12 weeks after the start of therapy, then after 6 months and then 1 time at the age of 6 months.

Coagulation hemostasis was studied: prothrombin time, activated partial thromboplastin time, homocysteine, D-dimer, activity von Willebrand factor was performed automatically.

Statistical analysis. Descriptive statistics include the calculation and comparison of average values and medians with the determination of minimum and maximum values, and the calculation of percentages for various indicators.

Data categories using Microsoft programs Excel and XLSTAT by Addinsoft for visual display of results. diagrams are used. To test the hypothesis of differences between samples due to asymmetry, the non-parametric Mann-Whitney test was applied to the distribution of laboratory parameters. The level of significance was accepted as 0.05.

Results of the study:

1. The first manifestations of the disease in the clinic, an increase in the number of platelets in the peripheral blood analysis, more than 450 10 9/1, were recorded in 7 of the patients under 5 years of age (6 months-5 years). 6-14 years old in 9 patients, 15-16 years old in 3 teenagers, 17-21 years old in 4 patients. The average follow-up period at the time of this study was 4 years (range 1-14 years).
2. The usual mutation of the JAK 2 gene was detected in 5 out of 23 (19.7%) patients whose onset of the disease was at the age of 1, 2, and 8; all boys. Among them, one patient (age 8) had nosebleeds and eating disorders, and the remaining 2 patients were asymptomatic. Only splenomegaly was noted JAK2 gene mutation was identified in 1 patient. In the general blood test, the number of red blood cells in these patients was high - 5.24-5.52 1012 / L ($p = 0.008$ and 0.009). Allele load at diagnosis was 12.5%, 15% and 25%, respectively. CALR gene mutation was detected in 9 out of 31 cases (29.0%).
3. Headache, indigestion, and dizziness were recorded in 4 patients aged 15-19 years when the disease started. Microcirculation disorder- bleeding episodes (spontaneous ecchymoses, nosebleeds, long-term bleeding during tooth extraction) - at 6 months, in one patient who started ET, combined microcirculation disorder and nosebleeds - in one patient who started the disease at the age of 15 years.

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4. Splenomegaly was detected in 5 patients, hepatomegaly was also detected in 3 of them. in 3 patients. organomegaly was not detected during the examination. The hemogram of all patients showed an increase in the number of platelets (950-3300 x 109/1) and neutrophils (3.76 10.91 10 9/1). An increase in the number of leukocytes in 3 patients (10.71-16.03 *). 10 9/1) was also observed.

Allelic genes could not be reliably identified due to the limitations of fragment analysis techniques. An additional mutation of the CALR gene was detected in a patient with ET. E364R causes an amino acid change in the protein sequence. CALR 2 gene mutation type was found in 28 and 19% allelic way in 2 patients (AA. PU), respectively.

Thus, 78% of patients had CALR gene mutations, standard type 1 mutations, and type 2, comparable to the adult population. A somatic mutation of the MPL gene was detected in only one 16-year-old patient. CALR and MPL, the average age of the disease is 10 years (1 year 17 years), of which 9 boys and 9 girls.7 patients had asymptomatic ET. The average age of onset was 5 years (range 1-15 years). Manifestations of microcirculatory disturbances (pain, dizziness) were noted in 6 patients. The average age of onset was 11 years (range 8-17 age), 3 patients had signs of hemorrhagic syndrome in the form of post-traumatic bleeding, menorrhagia, nosebleeds.

In the histological and histochemical studies of the bone marrow, intertrabecular spaces are filled with hypercellular hematopoietic tissue (total cellularity 60-100%), fat cells are unevenly distributed throughout the bone marrow spaces. Erythropoietic cells are scattered and located in the form of small erythron islands: the shift of lekoformula to the left is often noted with the presence of intermediate forms that are not disturbed by cytology. The number of megakaryocytes increased and unevenly distributed spaces along the intertrabecular, very frequently formed clusters up to 10-15 units, had signs of nuclear disruption.

These data may indicate the presence of primary MF in the prefibrotic early stage in the patients, so at least 2 patients (SR, EA) changed the therapy to XU and repeated histological studies after 6 months. There was an inverse relationship between ristocetin and von Willebrand factor cofactor (vWF:RCo) activity in the platelet count.

Manifestation of hemorrhagic syndrome is post-traumatic ecchymosis. bleeding during tooth extraction, frequent nosebleeds and heavy bleeding during menstruation. All patients received cytoreductive therapy. Thus, childhood bleeding occurs with severe thrombocytosis, corresponding to older patients with lower vWF:RCo values [23]. This observation also indicates the importance of not only changes in platelets [21], but also plasma components of hemostasis, as previously shown.

Hemorrhagic syndrome in these patients was not life-threatening, did not require hospitalization and transfusion of blood components. 9 (38.7%) patients suffered from microcirculation disorders manifested by severe headache, dizziness, visual disturbances, periodic pain and heat in the upper fingers. 3 of them (33.3%) patients did not respond to antiplatelet therapy, all patients noted the disappearance of symptoms when cytoreductive therapy was prescribed. 3 (33%) patients did not receive cytoreductive therapy and had symptomatic relief with acetylsalicylic acid. In the analysis, the majority of patients with impaired blood microcirculation had a platelet count between 1000 and 2000 109/1, which was asymptomatic ET. can be compared with thrombocytosis in patients.

The condition of 6 patients with asymptomatic ET under observation without any appointment did not worsen.

Discussion.

The clinical manifestations of ET in the patients included in the study were similar to those previously

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described. [19]. In the studied cohort, 1 patient (PU) developed Hodgkin's lymphoma, representing 2.3% also shows the importance of its components.[20]

Therapy is recommended with caution in patients with extreme thrombocytosis (1500 10 9/1) and/or reduced vWF: RC0 < 30% because of the very high risk of life-threatening bleeding, also life-threatening in children under 12 years of age. the risk of developing Ree's syndrome increases because the risk of bleeding is very high [20-23]. When analyzing the response to therapy, it became clear that the use of INF in the first line was compared with ANA. (44.4% and 40% complete response, respectively).

A study of the pharmacokinetics of ANA when taken on an empty stomach in children and adolescents aged 7-14 years. It showed that a slightly lower response to ANA therapy compared to adult patients is explained by the pharmacokinetics of the drug in children.

The discontinuation rate of Peg-INF due to side effects was 11.1%. However, the data showed that patients achieved a complete hematological remission after drug withdrawal. 100% of patients had flu-like symptoms, toxic hepatitis, other adverse reactions manifested by abdominal pain, psychological disorders (depression) were identified in 9 (50%) patients. dose-dependent, mild, accompanying therapy (hepatoprotectors, antidepressants) and did not require discontinuation of the drug.

All patients using INF were switched to treatment with a long-acting form of the drug, which reduced the number of adverse effects and the route of injection.

Conclusions.

Thus, in children, in contrast to adult patients, ET often occurs with extreme thrombocytosis, which potentially leads to a higher risk of bleeding due to a more profound deficiency of von Willebrand factor.

A milder course of ET in childhood and adolescence: thrombotic and hemorrhagic syndromes require frequent hospitalization and transfusion of blood components. Cytoreductive therapy, which is offered by researchers according to the instructions, consists of the following: hemorrhagic complications; microcirculation disorders that cannot be eliminated by taking antiplatelet agents, the degree of myelofibrosis in the bone marrow is MF 1-2 or more. INF drugs are recommended to be used as a first-line therapy, giving preference to pegged forms that reduce the inconvenience of treatment for children and adolescents. Taking into account the information of the official instructions, 3 years to the drug (benzyl alcohol, part of the drug, can cause neurological and other complications, sometimes leading to death). It is better to offer NU for up to 3 years in patients with intolerance / lack of effect from INF. Carcinogenicity has not been proven and is unlikely [26, 27]. Taking into account the duration of therapy intended for teenage girls, this drug requires not to forget about the teratogenic effect. SP

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