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STUDY OF PERIODIC DISEASE IN CHILDREN UNDER THE CONDITIONS OF A LARGE MEGAPOLIS

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ABSTRACT

Periodic disease (or familial Mediterranean fever) is a hereditary monogenic autosomal recessive disease, characterized by recurrent serositis and frequent amyloidosis development. Previously, periodic disease was considered as a rare pathology, that mostly occurred among representatives of peoples, whose ancestors lived in the Mediterranean area. Over the past few years, the tendencyof morbidity rate growth and geographic expansion of the periodic disease prevalence can be observed due to the increasing number of mixed marriages and migration.

The gene responsible for the development of periodic disease is located in the short arm of the 16th chromosome close to the genes of autosomal dominant polycystic kidney disease and tuberous sclerosis, and encodes the Pyrin protein involved in the regulation of inflammatory processes. The inflamed receptors irritated by mediators cause pain syndrome, and the heat-regulating center affected by a large number of endogenous pyrogens leads to fever. Clinically, the periodic disease occurs at regular intervals (days/weeks/months) and is characterized by common fever attacks. Fever may be accompanied by pain episodes caused by non-specific inflammation in serous and synovial membranes. Any attack is accompanied by laboratory signs of inflammation: leukocytosis, increased erythrocyte sedimentation rate and other inflammatory proteins, increased α- and β-globulin fractions, decreased neutrophil myeloperoxidase activity. The most common symptoms of periodic disease in children are fever and abdominal pain syndrome.

The mainstay of therapy in periodic disease is the prescription of colchicine. This medication has an antimitotic effect against amyloidoblasts and macrophages in periodic disease and stabilizes the neutrophil membrane, preventing the pyrin release. In most cases colchicine completely prevents periodic disease attacks or significantly reduces relapse and severity, prevents the renal amyloidosis, reduces the severity of the symptoms. In the absence of therapy, the greatest danger is the development of renal amyloidosis, which is the only cause of death in patients with periodic disease.

Present article reflects current views on the pathogenesis, approaches to the diagnostics and treatment of periodic disease in children. Demonstrated correlational analysis allows to detect the interrelation of the clinical course and the type of mutation in the MEFV gene, as well as to illustrate modern approaches to the treatment of children with periodic disease.

KEYWORDS: *abdominal pain, hyoscine butylbromide, fever, periodic disease.*

INTRODUCTION

Periodic disease (synonyms: Armenian disease, familial Mediterranean fever, Janeway-Mosenthal paroxysmal syndrome, periodic peritonitis, Reimann's syndrome, Siegal-Mamou disease) is a hereditary monogenic autosomal recessive disease characterized by recurrent serositis and frequent amyloidosis development.

Previously, periodic disease was considered as a rare pathology, that mostly occurred among representatives of peoples, whose ancestors lived in the Mediterranean area, especially Armenians, Sephardic Jews, Arabs, Turks. Occurrence of periodic disease among Sephardic Jews according to

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various estimates ranges from 1:250 to 1:2000 (frequency of the mutant gene carriage ranges from 1:16 to 1:8), among the Armenians – from 1:100 to 1:1000 (frequency of gene carriage ranges from 1:7 to 1:4) [*Harutyunyan V, Hakobyan G, 2000*]. Over the past few years, the tendencyof morbidity rate growth and geographic expansion of the periodic disease prevalence can be observed due to the increasing number of mixed marriages and migration. There are a lot of periodic disease cases in Russia, France, Italy, USA, Bulgaria, Finland, Portugal, Canada, Turkey and Japan, at that, not only in the representatives of the Armenian, Jewish or Arab nations, but also among the indigenous population.

In 1992, E. Pras and co-authors found, that the gene responsible for the development of periodic disease is located in the short arm of the 16th chromosome close to the genes of autosomal dominant polycystic kidney disease and tuberous sclerosis, and encodes the Pyrin protein involved in the regulation of inflammatory processes. Pyrin is a nuclear transcription factor that regulates inflammatory responses of leucocytes, and it also acts as a negative regulator of inflammatory processes in the presence of certain threshold level of its concentration. The baseline of periodic attacks is a spontaneous or provoked degranulation of neutrophils with the release of neuromediators, particularly IL1β, and with the development of aseptic inflammation occurring mainly on the serous and synovial membranes. Currently, there are two hypotheses to explain the development of periodic disease attacks: according to "sequestration" hypothesis, the mutant pyrin is unable to inhibit caspase 1, the enzyme necessary for converting inactive pro-IL1β to the active form. This leads to the overproduction of IL1β and causes inflammation. According to "pyrin inflammasome" hypothesis, pyrin can be involved in the formation of inflammasome (intracellular supramolecular complex involved in the activation of procaspase 1), thus causing the activation of IL1β system [*Simon A, van der Meer J, 2007*].

The inflamed receptors irritated by mediators cause pain syndrome, and the heat-regulating center affected by a large number of endogenous pyrogens leads to fever.

So far, approximately 73 mutations in the MEFV gene have been described. The majority of researchers consider that the gene transfer occurs in accordance with the autosomal recessive type, which proves the abnormal gene carriage. However, some authors believe that the gene transfer can be considered dominant only if the family have had 4 or more affected offspring, possibly due to the presence of mutations with high penetration potential [*Heller H et al.,1958; Cozzetto F, 1961; Harpey J, 1981*]. E. Sohar (1967) suggested a heterozygous nature of inheritance. E.K. Torosyan (1996) highlights two clinical and aetio-pathogenetic forms: minor form, manifested in male heterozygotes with a mild clinical course (late symptoms, rare isolated attacks, lack of amyloidosis), overt form of the disease found in homozygotes of both sexes with severe clinical course (early symptoms, mixed attacks, development of amyloidosis). Other authors suggest the existence of two separate phenotypic clinical presentations [*Heller H et al., 1961; Pras M et al., 1981; 1982*]. According to the first phenotype, a typical periodic disease pattern is observed initially and is later complicated by amyloidosis. According to the second phenotype, however, the initial condition is presented with a picture of amyloidosis, followed by attacks in the little later stage.

There are three most common mutation types, which are present in over 90% of the periodic disease cases: the replacement of isoleucine to methionine (M680I) is mostly found in Armenians, whereas the replacement of valine to methionine (M694V) and alanine to valine (V726A) can be found in all ethnic groups. The gene expression is mainly observed in the fraction of mature stab leukocytes of peripheral blood and in the cells of human adenocarcinoma line SW-480 [*Harutyunyan V, Hakobyan G, 2000*].

Materal and methods

In the period from December 2014 to April 2016, 36 children aged from 4 to 17 years with genetically confirmed diagnosis of periodic disease were being supervised at gastroenterological department of University Children's Clinical Hospital of First Moscow State Medical University. They were 16

girls (45%) and 20 boys (55%). All the children underwent DNA molecular genetic testing .

The analysis of data obtained from genetic research showed that 7 children were heterozygotes (5 of the children with M 694V mutation, 1 child with V726A mutation and 1 child with R761H mutation). The other 29 children were divided into 2 groups: a group of children with mutations in the compound heterozygous state, which amounted to 12 people, and a group of 17 children homozygous with the same type of mutation. The most common compound heterozygous combination was M694V/V726A (in 6 children), whereas the most frequent homozygous combination was M694V/M694V (in 15 children). Among the ethnic groups of children were 26 Armenians, 5 Azeris, 2 Avars and 3 Russians.

The first symptoms of the periodic disease usually appear in childhood and in teenage years. According to E.K. Torosian (1996), the age grouping is presented as follows: from 1 up to 3 years – 16.2%, from 4 to 7 years – 23.4%, from 8 to 12 years – 38.8%, from 13 to 15 years – 21.6%. Infants rarely get sick during the first year of life. Boys suffer 1.5 times as often as girls, due to the predominance of paternal genetic transfer (from 5.0% to 23.4%), whereas the risk of genetic transfer from mother to daughter is rather low (2.2%) [*Malkoch A, 2008*].

The analysis of the clinical-anamnestic data showed that the first clinical symptoms in most children appeared under the age of five (the average age of the clinical event was 2.43±3.32). The inheritance analysis of the children with periodic disease revealed that 16 children (44%) had familial periodic disease, and 10 children were siblings. All the children were either compound heterozygous (1 child with F479L/E148Q mutation, 1 child with M694V/R761H mutation, 3 children with M694V/V726A mutations) or homozygous (1 child with M680I mutation, 9 children with M694V mutation), and 1 girl was heterozygous with M694V mutation.

RESULTS AND DISCUSSION

According to the classification suggested by Yerevan State Medical University after M. Heratsi, there are the following forms of periodic disease: abdominal syndrome, thoracic syndrome, articular syndrome, fever syndrome, mixed syndrome [*Harutyunyan V, Hakobyan G, 2000*]:

Clinically, the periodic disease occurs at regular intervals (days/weeks/months) and is characterized by common fever attacks. Fever may be accompanied by pain episodes caused by non-specific inflammation in serous and synovial membranes. Any attack is accompanied by laboratory signs of inflammation: leukocytosis, increased erythrocyte sedimentation rate and other inflammatory proteins, increased α- and β-globulin fractions, decreased neutrophil myeloperoxidase activity. Outside the attack the patients are symptom-free and the laboratory values gradually come to the norm.

The most common and persistent symptom of periodic disease is fever, which occurs in 96-100% of cases. Abdominal syndrome (aseptic peritonitis) occurs in 91% of cases, having isolated form in 55% [*Brik R at al., 1999*]. The length of the abdominal syndrome of periodic disease usually ranges from 1 to 3 days, though sometimes extended up to 1-2 weeks. Additional signs can include gastrointestinal disorders, such as delayed stool and gases, loss of appetite, nausea, vomiting in early attack or at the height of the attack, whereas liquid and abundant stools or diarrhea may be observed during the symptom resolution stage. Articular syndrome can manifest itself as arthralgia with underlying fever and inflammation of major joints. According to various sources, arthritis and arthralgia are observed in 35-80% of cases. The length of the articular syndrome in periodic disease attack is about 4-7 days, sometimes extended up to 1 month. Thoracic syndrome occurs in isolated form in 8% and combined with abdominal syndrome in 30% of cases. Skin changes during periodic disease attack occur in 20-30% of cases [*Lidar M, Livneh A, 2007*].

The most common symptom is erysipelas-like rash, as well as purple rashes, vesicles, nodules, angio-neurotic and allergic reactions, even angioedema and hives. Other signs of periodic disease can be a headache, which is often a warning signal of a coming attack, aseptic meningitis, pericardi-

tis, myalgia, hepatolienal syndrome, acute orchitis. The frequency of attacks can be variable in different patients widely ranging from a few times a week to 1-2 times per several years.

Among the clinical forms of periodic disease in children, the abdominal form is dominant and is found in 43.1% of cases, whereas the mixed form occurs in 50.3% of the children [*Astvatsatryan V, Torosyan E, 1989*].

The main symptoms of the disease according to the data were fever in 36 patients (100.0%), abdominal pain episodes in 34 children (94.4%), accompanied by vomiting in 7 patients (9.4%) and diarrhea in 4 patients (1.1%). Thoracic signs occurred in 19 children (52.8%), arthralgia – in 22 (61.1%). Six children (6.6%) underwent "acute abdomen" surgery, 32 children (89%) were diagnosed with mixed form of periodic disease for the time of the examination, and 4 children (11%) had abdominal syndrome.

The comparative analysis of the molecular genetic testing and clinical anamnestic data showed that the first clinical symptoms in the majority of homozygous children with M694V mutation occurred during the 1st year of life. The treatment required repeated increase of colchicine dose to reduce the frequency and relieve the severity of attacks. One child was diagnosed with renal amyloidosis.

According to various sources, amyloidosis occurs in periodic disease in 10-40% of patients [*Malkoch A, 2008*]. Some patients, however, do not develop amyloidosis despite the relatively frequent attacks. The main reason of amyloidosis is the overproduction of serum amyloid A precursor protein. The greatest accumulation of amyloid in periodic disease can be found in the organs, where the macrophages take up a fixed position: kidneys, liver, spleen. Gradually increasing amyloid sediments lead to pressure and atrophy of parenchymal cells, sclerosis and organ failure. Although amyloidosis can develop in any organ and tissue, amyloid depostition of kidney plays a crucial role for prognosis and life expectancy of a patient with periodic disease.

According to the morphological study of the rectal mucosa, amyloid was detected in 1 patient with M694V mutation in homozygous condition.

The mainstay of therapy in periodic disease is the prescription of colchicine. This medication has an antimitotic effect against amyloidoblasts and macrophages in periodic disease and stabilizes the neutrophil membrane, preventing the pyrin release. Colchicine is prescribed as life-long treatment at a dose of 3 *mg*/*kg*/*day*, normally 1-2 *mg*/*day*. The drug is well tolerated though sometimes with dyspeptic symptoms (nausea, vomiting, abdominal pain and diarrhea), which do not require a complete cancellation of the drug. In most cases colchicine completely prevents periodic disease attacks or significantly reduces relapse and severity, prevents the renal amyloidosis, reduces the severity of the symptoms. In renal failure the dosage is reduced depending on the degree of glomerular filtration decrease. The drug can be suspended in case of acute infections in children.

All patients received colchicine or colchicum-dispert® at a dose of 0.25-2.0 *mg*/*day*, no child had drug cancellation due to side effects. With the development of biological therapy medications, doctors began to use drugs that block the function of IL-1 (Anakinrum), TNFα (Infliximab) and IL1β (Canakinumab) in periodic disease treatment [*Koga T et al., 2016; van der Hilst J et al., 2016*]. It should be noted that all of the newly proposed medications do not replace, but suppley Colchicine therapy and are used in case of intolerance.

In the absence of therapy, the greatest danger is the development of renal amyloidosis, which is the only cause of death in patients with periodic disease. Analysis of morbidity among adults and children shows that in the natural course of periodic disease approximately 50% of patients develop end-stage renal disease within 5 years after the onset of proteinuria, and 75% – within 10 years [*Kallinich T et al, 2007*].

For the successful treatment of periodic disease in children, it is highly essential to rapidly relieve the abdominal pain, which is an important sign of abdominal syndrome and determines the life quality of patients with periodic disease. For these purposes, selective anticholinergics are used in gastroenterology [*Kornienko E, 2005; Shcherbakov P, Kharitonova A, 2007*].

One of the drugs from this group is Hyoscine

Butylbromide (Buscopan), which is highly affinitive especially to the M3-receptors located in the smooth muscle cells of the gastrointestinal tract, pancreas and bladder. The drug is poorly absorbed in the gastrointestinal tract and has a low bioavailability (less than 1%), which reduces the risk of systemic anticholinergic side effects to a minimum. Buscopan has local antispasmodic effect by blocking the M3-receptors and provides ganglion-blocking action by binding to nicotinic receptors.

The efficacy against abdominal pain symptoms is observed within 15 minutes after the drug intake in most patients (72%) and within 40 minutes in 16% of patients. Approximately 50% of the patients reported a significant relief of symptoms within 30 minutes [*Tytgat G, 2007; Mueller-Lissner S et al., 2010*].

Thus, periodic disease is a hereditary monogenic autosomal recessive disease characterized by recurrent serositis and frequent amyloidosis development. According to obtained data, the main symptoms are fever, abdominal pain, and arthralgia. The mainstay of periodic disease treatment is the lifetime prescription of colchicine at the dose of 0.02-0.03 *mg/kg* per day, which significantly reduces both the occurrence and severity of attacks. Also, in combination with Colchicine basic therapy, children older than 6 years may be recommended to take Buscopan at the dose of 10 *mg* three times a day in the form of suppositories or tablets for a more successful treatment of abdominal syndrome.

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