UDC 616-003.821-053.4-056.76-07-08-036:612.59

K.Y. Pashenko[2], T.V. Frolova[1], Y.V. Karpushenko[1], G.R. Muratov[2], O.M. Savvo[2,3], T.O. Khalturina[2], O.M. Ashcheulov[1]

Clinical report of Mediterranean fever in a child in Ukraine – Don't miss it!

[1]Kharkiv National Medical University, Ukraine
[2]Regional Children's Clinical Hospital, Kharkiv, Ukraine
[3]V.N. Karazin Kharkiv National University, Ukraine

Modern Pediatrics. Ukraine. (2024). 4(140): 93-96. doi: 10.15574/SP.2024.140.93

For citation: Pashenko KY, Frolova TV, Karpushenko YV, Muratov GR, Savvo OM, Khalturina TO, Ashcheulov OM. (2024). Clinical report of Mediterranean fever in a child in Ukraine – Don't miss it! Modern Pediatrics. Ukraine. 4(140): 93-96. doi: 10.15574/SP.2024.140.93.

Introduction. Familial Mediterranean fever (FMF) is a non-infectious genetic disease caused by a mutation in the MEFV gene. This disease is more common in people of Mediterranean or Middle Eastern descent, but can occur in any ethnic group, including those living European countries. FMF has typical clinical symptoms. Its long term without appropriate treatment the disease can lead to a violation of the child's physical development and result in the development of amyloidosis.

The aim is to focus the attention of the medical community of Ukraine and inform European medical specialists on the FMF cases due to migration changes in Ukraine.

This article presents a **clinical case** of FMF in a 4-year-old child who was admitted to our hospital with complaints of fever, abdominal pain, vomiting, and stool retention. Additional examination included: laboratory tests (complete blood count, urinalysis, biochemical blood test with determination of liver and kidney tests); instrumental methods: ultrasound examination of the abdominal organs and urinary system, X-ray examination of the abdominal organs with contrast. The results of additional tests revealed the signs of inflammatory process and impaired kidney function. When clarifying the family medical history, it was revealed that the older brother suffers from FMF (a mutation of the MEFV genotype was determined) and takes specific therapy (colchicine). The final diagnosis was determined: Acute strangulated intestinal obstruction. Familial Mediterranean Fever (clinically). Peritonitis. Operative laparoscopic and conservative treatment was performed. The patient was discharged in a satisfactory condition with appropriate recommendations.

Conclusions. The number of FMF cases in children have increased due to changes in the migration process in Ukraine. The relevance of this disease has increased. Taking into consideration a significant migration of population, the likelihood of an increase in the number of cases of FMF in European countries is increasing, which requires awareness among a wide range of doctors.

In this report we have described a pediatric FMF case which was represented by recurrent episodes of fever, abdominal pain, impaired kidney function test results, and inflammatory markers. A determined mutation of the MEFV genotype in the brother of our patient makes the diagnosis of FMF unquestionable.

The research was carried out in accordance with the principles of the Helsinki Declaration. The informed consent of the patient was obtained for conducting the studies.

No conflict of interests was declared by the authors.

Keywords: Mediterranean fever, children, gene mutation MEFV.

Клінічний випадок середземноморської лихоманки у дитини в Україні — не пропустіть!

К.Ю. Пащенко[2], Т.В. Фролова[1], Ю.В. Карпушенко[1], Г.Р. Муратов[2], О.М. Савво[2,3], Т.О. Халтуріна[2], О.М. Ащеулов[1]
[1]Харківський національний медичний університет, Україна
[2]Обласна дитяча клінічна лікарня, Харків, Україна
[3]Харківський національний університет ім. В.Н. Каразіна, Україна

Сімейна середземноморська лихоманка (ССЛ) — неінфекційне генетичне захворювання, спричинене мутацією в гені MEditerranean FeVer (MEFV). Найчастіше зустрічається в осіб середземноморського або близькосхідного походження, але може вражати і будь-яку етнічну групу, зокрема жителів європейських країн. Захворювання має типову клінічну симптоматику. Його тривалий перебіг без відповідної терапії може призвести до порушення фізичного розвитку дитини та бути причиною розвитку амілоїдозу.

Мета: сфокусувати увагу медичної спільноти України та проінформувати європейських спеціалістів про випадки ССЛ через міграційні зміни в Україні.

Наведено **клінічний випадок** ССЛ у дитини 4 років, яку госпіталізували зі скаргами на лихоманку, біль у животі, блювоту, затримку стулу. Додаткове обстеження містило: лабораторні тести (клінічний аналіз крові, сечі, біохімічний аналіз крові із визначенням печінкових та ниркових проб); інструментальні методи: ультразвукове дослідження органів черевної порожнини та сечовидільної системи, рентгенологічне обстеження органів черевної порожнини з контрастом. Результати додаткових тестів виявили ознаки запального процесу та порушення функції нирок. Під час уточнення сімейного анамнезу виявлено, що старший брат страждає на ССЛ (визначена мутація MEFV генотипу), приймає специфічну терапію (колхіцин). Дитині встановлено остаточний діагноз: Заворіт тонкої кишки. Гостра странгуляційна кишкова непрохідність. Сімейна середземноморська лихоманка (клінічно). Перитоніт. Проведено оперативне лапароскопічне та консервативне лікування. Пацієнта виписано у задовільному стані із відповідними рекомендаціями.

Висновки. Через міграційні процеси на сучасному етапі в Україні почастішали випадки ССЛ у дітей та підвищилася актуальність цього захворювання. З огляду на значну міграцію населення, вірогідність збільшення кількості випадків ССЛ в європейських країнах зростає, що потребує обізнаності широкого кола лікарів.

Клінічна картина захворювання представлена рецидивуючими епізодами лихоманки, абдомінальним болем, порушеннями функції нирок і маркерами запалення, які стали підставою для клінічної діагностики ССЛ. Детермінована мутація генотипу MEFV у брата пацієнта робить діагноз ССЛ безсумнівним.

Дослідження виконано відповідно до принципів Гельсінської декларації. На проведення досліджень отримано інформовану згоду батьків дитини.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: середземноморська лихоманка, діти, мутація гену MEFV.

Introduction

Familial Mediterranean fever (FMF) is a non-infectious genetic disease caused by a mutation in the MEFV gene. This disorder is more common in people of Mediterranean or Middle Eastern origin (prevalence varies from 100–400 cases per 100,000 inhabitants among Sephardic Jews to 2.5 cases per 100,000 inhabitants in Western European countries) [3], but it can affect any ethnic group, including European countries.

FMF is one of the most common monogenic autoinflammatory diseases, which is inherited by an autosomal recessive type from one or both parents. In 90% of cases, episodes begin before the age of 20 years, about 75% of cases among them manifest before the age of 10 years [11].

Innate immunity dysregulation with the main types of cells (monocytes, macrophages and neutrophils) involvement is in the pathogenesis of the disease.

The MEFV gene, located on the short arm of the 16th chromosome, was discovered in 1997 [5,6]. It encodes the protein pyrin, which is present predominantly in neutrophils and macrophages. Pyrin is responsible for the development of cell apoptosis and inflammation [8,9]. As a result of gene mutation, complexes are formed that, due to a cascade of catalytic reactions, lead to the uncontrolled release of pro-inflammatory cytokines (interleukin-1β, interleukin-18) [7,10] with the development of autoinflammation.

The typical clinical manifestations of FMF are irregular recurrent attacks of fever above 38°C, which are usually accompanied by pain in the abdomen, less commonly in the joints or chest, and also a skin rash. Episodes usually last one to three days and then disappear. The relapse incidence ranges from once a week to once a decade [4]. Children under five years of age may only have a high fever. Severe abdominal pain often requires a surgical consultation, and chest pain can cause difficulty breathing. Joint syndrome is characterized by extensive damage to the joints, accompanied by pain and swelling. Swelling disappears in 1–2 weeks. Another typical pediatric symptom is the appearance of a rash, which in a third of patients is localized on the lower extremities. Some children experience pain in the leg muscles that occurs after physical activity. Inflammatory lesions of the heart (pericarditis), lining of the brain and spinal cord (meningitis), skeletal muscles (myositis) or testicles (orchitis) are rare complications. A long-term illness without appropriate treatment can lead to disturbances in the physical development of the child and cause the development of amyloidosis (in the ICD-10, the disease is classified under heading E 85.0 Hereditary familial amyloidosis without neuropathy).

The establishment of diagnosis is based on the clinical manifestations and confirmed by a positive test for the MEFV gene mutation.

Lifelong treatment to control inflammation can prevent organ damage and disease progression. The main treatment for FMF is colchicine, which is taken by mouth once or twice a day for life. It helps to control symptoms of the disease by preventing episodes, but is not a therapeutic agent in the acute phase. In view of the pathogenesis of the disease, interleukin-1 blockers, such as rilonacept, anakinra or canakinumab are considered as alternatives to colchicine as prophylactic agents that lead to a sustained reduction in disease severity [2].

The aim is to focus the attention of the medical community of Ukraine and inform European medical specialists on the FMF cases due to migration changes in Ukraine.

The research was carried out in accordance with the principles of the Helsinki Declaration. The informed consent of the patient was obtained for conducting the studies.

Clinical case

A 4-year-old boy was admitted to the children's hospital by the ambulance with complaints of abdominal pain, repeated vomiting up to 5 times, subfebrile fever, and stool retention.

From the medical history, it is known that the child has been ill for 2 days and has not had contact with infectious patients. Periodically, note an increase in body temperature up to 38.0°C, which is accompanied by the retention of intestinal gases, bowel movements, and bloating. Early medical history – without features, heredity, and allergy — is not burdened. Family medical history: a sibling suffers from FMF, which was confirmed by genetic tests, and takes specific therapy (colchicine). The patient's condition on admission was moderate, caused by pain syndrome. A boy has a normosthenic body type. Physical development is harmonious and average. The skin and mucous membranes are pink and clean. There were no physical

changes in the respiratory, cardiovascular, urinary, skeletal, or endocrine systems. Moderate pain was noted in the periumbilical region without a clear localization on abdominal palpation. The liver and spleen are not enlarged. Peripheral lymph nodes are not enlarged and painless. Urinary excretion — without features. The child was examined by a surgeon, the preliminary diagnosis was: intestinal obstruction.

An additional examination was conducted. The data is presented in the dynamics of observation.

Pathological formations, fluids, and X-ray-contrast foreign bodies were not detected in the abdominal cavity on the initial X-ray examination of the abdominal cavity organs. The next X-ray of the abdominal organs with contrast revealed signs of small intestinal obstruction, and the examination in a few days against the background of therapy revealed functional intestinal disorder signs with hypotonus.

On the ultrasound examination of the abdominal organs, enlarged abdominal lymph nodes, local dilatation of the intestine with hyperpneumatosis, as well as the absence of peristalsis in the periumbilical region and a small amount of fluid were visualized. This did not exclude the presence of Meckel's diverticulum. In dynamics, the previous dilatation of intestinal loops acquired a diffuse character. The result was interpreted as intestinal obstruction; signs of peritonitis appeared. The identified changes during further observation showed positive dynamics.

Laboratory tests detected inflammatory markers and impaired kidney function.

A complete blood count showed: upon admission, neutrophilic leukocytosis with a shift of the leukocyte formula to the left, increased erythrocyte sedimentation rate (ESR) with gradual normalization of values in the dynamics of observation.

Biochemical blood tests revealed a moderate increase in creatinine level (up to 0.140 mmol/l), residual nitrogen – 178 mmol/l, C-reactive protein — 12 mg/l. Liver function tests were without pathological changes.

Urinalysis showed ketonuria (+++), slightly alkaline pH, proteinuria — protein 0.005 g/l, hematuria — unchanged erythrocytes 30–40 in the field of view.

Thus, the patient was given a final diagnosis: Small bowel volvulus. Acute strangulated intestinal obstruction. Familial Mediterranean fever (clinically). Peritonitis.

Surgical treatment to eliminate small intestinal volvulus and appendectomy was performed laparoscopically. Further conservative therapy included antibacterial, anti-inflammatory (dexamethasone, methylprednisolone), analgesics, and symptomatic agents. Colchicine was prescribed after the patient's condition normalized.

The patient was discharged in a satisfactory condition with recommendations to take colchicine at a dose of 1 mg per day once, for life; genetic testing for MEFV mutation is planned.

In the presented clinical case, the patient was a 4-year-old child whose age-related onset of the FMF disease corresponds to the average statistical frequency. Clinical manifestations are typical for this age: episodes of fever accompanied by abdominal pain syndrome. However, the severity of abdominal pain required the exclusion of acute surgical pathology, which was done. Instrumental and laboratory research methods confirmed the presence of intestinal obstruction and peritonitis against the background of the inflammatory process requiring surgical treatment. At the same time, the patient was diagnosed with impaired kidney function, which was reversible, but required further monitoring, as it is typical for FMF. The difficulty in diagnosing of this clinical case lies in the presence of acute surgical pathology. It is also possible that primary uncontrolled autoinflammation against the background of the child's anatomical and physiological features became the cause of the development of intestinal obstruction and peritonitis. An existing family medical history with a diagnosed MEFV gene mutation in a sibling allowed us to correctly determine the diagnosis. According to the existing classification criteria, a diagnosis of FMF can be made both in the presence and absence of MEFV genotype test results. Genetic analysis is not mandatory in cases of typical clinical manifestations, since a MEFV gene mutation may be absent, as confirmed by the data of the study of I. Ben-Zvi at al. [1], in which 10–20% of patients with typical clinical manifestations of FMF did not have MEFV gene mutations.

Conclusions

Taking into account a wide migration of population, the probability of meeting FMF in European countries is increasing that requires the awareness of this disease among a range of doctors. FMF is the most common autoinflammatory disease, which is often associated with

a MEFV gene mutation and manifests in childhood or adolescence. The characteristic clinical picture is represented by recurrent episodes of fever, abdominal pain, abnormal renal function tests, and inflammatory markers, which are the basis of the clinical diagnosis of FMF. A determined mutation in the brother's MEFV genotype makes the diagnosis of FMF undoubted.

No conflict of interests was declared by the authors.

REFERENCES/ЛІТЕРАТУРА

1. Ben–Zvi I, Herskovizh C, Kukuy O, Kassel Y, Grossman C, Livneh A. (2015, Mar 25). Familial Mediterranean fever without MEFV mutations: a case-control study. Orphanet journal of rare diseases. 10: 34. https://doi.org/10.1186/s13023-015-0252-7.
2. Bettiol A, Lopalco G, Emmi G, Cantarini L, Urban ML, Vitale A et al. (2019, Apr 17). Unveiling the Efficacy, Safety, and Tolerability of Anti-Interleukin-1 Treatment in Monogenic and Multifactorial Autoinflammatory Diseases. International journal of molecular sciences. 20(8): 1898. https://doi.org/10.3390/ijms20081898.
3. De Sanctis S, Nozzi M, Del Torto M et al. (2010, Sep 3). Autoinflammatory syndromes: diagnosis and management. Italian Journal of Pediatric. 36(1): 57. https://doi.org/10.1186/1824-7288-36-57
4. Maggio MC, Corsello G. (2020). FMF is not always «fever»: from clinical presentation to «treat to target». Italian journal of pediatrics. 46(1): 7. https://doi.org/10.1186/s13052-019-0766-z.
5. Manna R, Rigante D. (2019, May 1). Familial Mediterranean Fever: Assessing the Overall Clinical Impact and Formulating Treatment Plans. Mediterranean journal of hematology and infectious diseases. 11(1): e2019027. https://doi.org/10.4084/MJHID.2019.027.
6. Migita K, Asano T, Sato S, Koga T, Fujita Y, Kawakami A. (2018). Familial Mediterranean fever: overview of pathogenesis, clinical features and management. Immunological medicine. 41(2): 55–61. https://doi.org/10.1080/13497413.2018.1481579.
7. Orning P, Lien E, Fitzgerald KA. (2019, Nov 4). Gasdermins and their role in immunity and inflammation. The Journal of experimental medicine. 216(11): 2453–2465. https://doi.org/10.1084/jem.20190545.
8. Ozdogan H, Ugurlu S. (2019). Familial Mediterranean Fever. Presse medicale (Paris, France: 1983). 48; 1 Pt 2: e61–e76. https://doi.org/10.1016/j.lpm.2018.08.014.
9. Özen S, Batu ED, Demir S. (2017, Mar 23). Familial Mediterranean Fever: Recent Developments in Pathogenesis and New Recommendations for Management. Frontiers in immunology. 8: 253. https://doi.org/10.3389/fimmu.2017.00253.
10. Schnappauf O, Chae JJ, Kastner DL, Aksentijevich I. (2019). The Pyrin Inflammasome in Health and Disease. Frontiers in immunology. 10: 1745.
11. Yaremenko OB, Sydorova AO. (2020). Simeina serezemnomorska lykhomanka: ohliad suchasnoho stanu problemy ta opysannia klinichnoho vypadku. Revmatolohichnyi zhurnal. 81(3). [Яременко ОБ, Сидорова АО. (2020). Сімейна середземноморська лихоманка: огляд сучасного стану проблеми та описання клінічного випадку. Ревматологічний журнал. 81(3)]. doi: 10.32471/rheumatology.2707-6970.81.15575.

Відомості про авторів:
Пащенко Костянтин Юрійович — к.мед.н., лікар-хірург дитячий, зав. 1 хірургічного відділення КНП ХОР ОДКЛ. Адреса: м. Харків, вул. Клочківська, 337а. https://orcid.org/0000-0003-3855-6787.
Фролова Тетяна Володимирівна — д.мед.н, проф., зав. каф. пропедевтики педіатрії ХНМУ. Адреса: м. Харків, пр. Науки, 4; тел.: +38 (057) 341-60-05. https://orcid.org/0000-0002-6861-8902.
Карпушенко Юлія Валентинівна — к.мед.н., доц. каф. пропедевтики педіатрії ХНМУ. Адреса: м. Харків, пр. Науки, 4. https://orcid.org/0000-0002-2196-8817.
Муратов Георгій Рафикович — к.мед.н., доц., директор КНП ХОР ОДКЛ, Засл. лікар України. Адреса: м. Харків, вул. Озерянська, 5; тел.: +38 (057) 725-82-82.
Савво Олексій Миколайович — к.мед.н, доц. каф. інфекційних хвороб та клінічної імунології ХНУ ім. В.Н. Каразіна, заст. директора з поліклінічної роботи КНП ХОР ОДКЛ. Адреса: м. Харків, вул. Клочківська, 337а; тел.: +38 (057) 725-10-37. https://orcid.org/0000-0002-8584-3749.
Халтуріна Тетяна Олександрівна — заст. директора з медичної роботи КНП ХОР ОДКЛ. Адреса: м. Харків, вул. Клочківська, 337а; тел.: +38 (057) 725-10-37.
Ащеулов Олександр Михайлович — к.мед.н., доц. каф. пропедевтики педіатрії ХНМУ. Адреса: м. Харків, пр. Науки, 4; тел.: +38 (057) 341-60-05. https://orcid.org/0000-0001-7454-288X.
Стаття надійшла до редакції 04.03.2024 р., прийнята до друку 14.05.2024 р.