**Olga V. Zhogova1, 2, Sergey V. Ivanovskiy1, 2, Natalya V. Lagunova1, Anastasia V. Tumakova3, Mikhail M. Kostik3**

1 V.I. Vernadsky Crimean Federal University, Simferopol, Russian Federation

2 Republican Children's Clinical Hospital, Simferopol, Russian Federation

3 St. Petersburg State Pediatric Medical University, Saint Petersburg, Russian Federation

**The Clinical Course and Outcomes of Familial Mediterranean Fever in Crimean Tatar Patients: Preliminary Results of Case Series**

**Corresponding author:**

*Kostik Mikhail M.*, MD, PhD, professor of hospital pediatrics department in St. Petersburg State Pediatric Medical University

**Address**: 194100, Saint Petersburg, Litovskaya Str., 2, **phone:** +7 (812) 416-52-98, **e-mail:** kost-mikhail@yandex.ru

**Article received:** May 16, 2020, **accepted for publication**: Jun 26, 2020

***Background.*** *Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease. It is more typical among Turks, Jews, Armenians, Arabs and nationalities permanently living in the Mediterranean area. Crimean Tatars were not considered as the population where FMF may occur until 2016.* ***Objective****. The aim of the study was to describe the clinical course and outcomes of familial Mediterranean fever in Crimean Tatar children.* ***Methods.*** *We have studied data from medical records of children under the age of 18 with the diagnosis of FMF verified according to the Eurofever/PRINTO 2019 criteria. The illness onset characteristics were estimated on the last admission to the hospital, as well as aspects of management.* ***Results.*** *The median age of FMF diagnosis was 9.5 (4; 14) years, time from the first clinical manifestations to diagnosis establishment was 5.5 (2; 9) years. The primary clinical manifestations of SSL were fever and arthritis (n = 16), erysipelas rashes (n = 9/16), peritonitis (n = 8/16), pleurisy (n = 1/17). All patients had knee arthritis, and 4/16 had hip arthritis. 12 children with FMF at debut were diagnosed as acute respiratory infection, 2 — as teething, 2 — as juvenile arthritis. The M694V variant of MEFV gene were revealed in 14/16 patients (3 in homozygous state), M680I and V726A variants were revealed once each. Parents of 8/16 patients were near related (cousins and second cousins). Colchicine* *intolerance was diagnosed in 2/16 patients, resistance — in 4/16 patients. Genetically engineered biologic drugs (GEBD) were prescribed for 6 patients (canakinumab in 4 cases, tocilizumab in 2 cases). Colchicine and/or GEBD therapy was effective in all patients (lesser frequency, duration and severity of episodes; improvement of laboratory signs of disease activity).* ***Conclusion.*** *Heterozygous pathological variant M694V of MEFV gene is the most common among Crimean Tatar patients with FMF, when the most frequent clinical signs are fever and arthritis. Every third patient has received GEBD therapy. This therapy was effective in all cases.*

***Key words:*** *children, familial Mediterranean fever, Crimean Tatar, periodic fever, autoinflammatory diseases.*

***For citation***: Zhogova Olga V., Ivanovskiy Sergey V., Lagunova Natalya V., Tumakova Anastasia V., Kostik Mikhail M. The Clinical Course and Outcomes of Familial Mediterranean Fever in Crimean Tatar Patients: Preliminary Results of Case Series. *Voprosy sovremennoi pediatrii — Current Pediatrics*. 2020; 19 (3): 200–206. doi: 10.15690/vsp.v19i3.2115

**RESULTS**

**Table 1**. Eurofever/PRINTO criteria for FMF diagnostics (adaptation from [18])

|  |
| --- |
| **New classification criteria** |
| Presence of confirmed *MEFV*\* genotype and at least one of the following criteria:  - episode duration 1–3 days;  - arthritis;  - thoracic pain;  - abdominal pain |
| OR |
| Presence of non-confirmed *MEFV*\*\* genotype and at least two of the following criteria:  - episode duration 1–3 days;  - arthritis;  - thoracic pain;  - abdominal pain |
| **Clinical classification criteria** |
| At least 6 of the following 9 criteria  *Presence*:  - Eastern Mediterranean ethnic group\*\*\*;  - episode duration 1–3 days;  - arthritis;  - thoracic pain;  - abdominal pain.  *Absence*:  - ulcerative stomatitis;  - urticarial rash;  - maculopapular rash;  - painful lymph nodes |

*Note.* \* — pathogenic or likely pathogenic variant (homozygous or biallelic compound heterozygous); \*\* — *MEFV* gene variant in biallelic compound heterozygous state (one allelic variant of the gene is pathogenic, another is one of undescribed significance, or both biallelic variants are of undescribed significance, or one pathogenic allelic variant in heterozygous state). \*\*\* — Turks, Armenians, non-Ashkenazi Jews, Arabs.

More information on used terms can be found in Table 7 of article annexes [18].

Diagnostic pattern of new criteria: sensibility — 0.94, specificity — 0.95, accuracy — 0.98; clinical criteria: sensibility — 0.91, specificity — 0.92 and accuracy — 0.97 respectively.

**Table 2**. Characteristics of enrolled patients with FMF (*n* = 16)

|  |  |
| --- | --- |
| **Characteristics** | **Value** |
| Gender (male), abs. (%) | 6 (38) |
| Age (when included into the study), years | 11,3 (6,8; 14,9) |
| Age at FMF debut, years | 2,0 (0,3; 4,9) |
| Age at FMF diagnosis, years | 9,5 (4,0; 14,2) |
| Time before FMF diagnosis, years | 5,5 (2,0; 9,3) |
| Children from related couple, abs. (%) | 8 (50) |
| Body weight, kg | 41 (31; 48) |
| *MEFV* variants (exon 10), abs. (%)  *- M694V*  *- M680I*  *- V726A*  - homozygotes *М694М*  - heterozygotes | 14 (88)  1 (6)  1 (6)  3 (19)  13 (81) |
| Colchicine, abs. (%)  - median dose, mg  - median dose, mg/kg | 16 (100)  1,5 (1,0; 1,5)  0,03 (0,02; 0,05) |
| Resistance to colchicine, abs. (%) | 4 (25) |
| Intolerance to colchicine, abs. (%) | 2 (13) |
| Genetically engineered biologic drugs, abs. (%)  - canakinumab  - tocilizumab | 4 (25)  2 (13) |

*Note (here and in Tables. 3, 4)*. FMF — familial Mediterranean fever.

**Table 3**. Dynamics of clinical laboratory characteristics of Crimean Tatar patients with FMF

|  |  |  |  |
| --- | --- | --- | --- |
| **FMF characteristics** | **At debut** | **Last admission** | ***р*** |
| **FMF clinical signs** | | | |
| Episode duration, hours | 90 (84; 144) | 0 (0; 2) | <0,001 |
| Fever, abs. (%) | 16 (100) | 5 (31) | <0,001 |
| Arthritis, abs. (%) | 16 (100) | 5 (31) | <0,001 |
| Arthralgia, abs. (%) | 16 (100) | 6 (38) | 0,002 |
| Monoarthritis, abs. (%) | 14 (87) | 5 (31) | 0,013 |
| Oligoarthritis, abs. (%) | 2 (13) | 0 (0) | 0,716 |
| Affected joints, abs. (%)   * knee joint * hip joint | 16 (100)  4 (25) | 5 (31)  0 (0) | <0,001  0,450 |
| Thoracic pain, abs. (%) | 1 (7) | 0 (0) | 0,858 |
| Abdominal pain, abs. (%)   * > 3 h | 8 (50)  8 (50) | 2 (13)  1 (6) | 0,201  0,145 |
| Erysipelas rashes, abs. (%) | 9 (57) | 0 (0) | 0,061 |
| **FMF laboratory signs** | | | |
| Hemoglobin, g/l | 104 (98; 111) | 121 (111; 131) | 0,003 |
| WBC, × 109/l | 20,0 (14,0; 29,0) | 9,7 (8,3; 12,0) | 0,002 |
| PLT, × 109/l | 400 (340; 468) | 289 (224; 329) | 0,005 |
| Erythrocyte sedimentation rate, mm/h | 51 (25; 95) | 8 (5; 12) | <0,001 |
| C-reactive protein, mg/l | 52,5 (31,0; 98,0) | 5,5 (1,2; 12,0) | <0,001 |

**Table 4**. Clinical course of FMF in patients with tolerance and intolerance to colchicine

|  |  |  |  |
| --- | --- | --- | --- |
| **FMF characteristics** | **Colchicine tolerance (*n* = 10)** | **Colchicine intolerance/ resistance (*n* = 6)** | ***p*** |
| Time before FMF diagnosis, years | 8,5 (7,0; 12,0) | 2,3 (2,0; 4,0) | 0,026 |
| Episode duration (last admission), hours | 0 (0; 0) | 2 (0; 4) | 0,04 |
| C-reactive protein, mg/l (last admission) | 2,5 (0,3; 8,0) | 4,5 (5,0; 17,0) | 0,026 |

**STUDY LIMITATIONS**

The limitations are associated with small sample size and relatively short follow-up period (median was 2.6 years). Low awareness of doctors about the FMF prevalence in Crimean Tatar population presumably leads to diagnosis primarily patients with more severe clinical course. Thus, it can overestimate the severity and activity of the disease in patients whose data were analysed in the present study. The estimated FMF incidence is 5.7 cases per 100 thousand population or 22 cases per 100 thousand children (for population living in Crimea). Whereas most of the Crimean Tatars live outside the territory of Crimea, we can assume that the total number of patients exceed manifold the number revealed in our study.

**FINANCING SOURCE**

The article has been funded by Novartis.

Company employees did not participate in planning, conducting and discussing of the results of this study.

**CONFLICT OF INTERESTS**

**Mikhail M. Kostik** ― receives fees for lecturing from Pfizer, Novartis, Sanofi companies.

Other authors confirmed the absence of a reportable conflict of interests.