THE FIRST CASE OF FAMILIAL MEDITERRANEAN FEVER DIAGNOSED IN LATVIA

Natalja Kurjane1,2, Jelena Eglite2, Natasa Tolpak3, Marusa Debeljak4, Tadej Avcin3

1 Riga Stradiņš University, Department of Biology and Microbiology, Riga, Latvia
2 Paul Stradiņš Clinical University Hospital, Centre of Clinical Immunology, Riga, Latvia
3 Riga Stradiņš University, Laboratory of Clinical Immunology and Genetics, Riga, Latvia
4 Department of Allergology, Rheumatology and Clinical Immunology, University Children’s Hospital, University Medical Centre Ljubljana, Slovenia
5 Molecular Genetic Laboratory, University Children’s Hospital Ljubljana, University Medical Centre Ljubljana, Slovenia

A 42 year-old man was referred to the Immunology Clinic at the Stradiņš Clinical University Hospital, Riga, Latvia with a six year history of recurrent episodes of fever associated with general fatigue, non-specific bone aches, abdominal pain and headache. The attacks occurred every three to four months and would settle with no specific treatment after 48 to 96 hours. He remained entirely well in between the attacks.

THE CASE INVESTIGATION

Blood samples collected during one of the attacks showed mild leucocytosis, mild anaemia and raised erythrocyte sedimentation rate, C-reactive protein and serum amyloid A levels. Subsequent investigations revealed polyclonally raised major immunoglobulin classes. Bone marrow examination, lymph node biopsy, colonoscopy, computed tomography and magnetic resonance imaging of his chest and abdomen showed no specific pathology. Common infections including HIV were excluded. Autoantibody screen was negative.

BLOOD TESTS:

- Haemoglobin: 11.1 g/dl (NR 11.3–17.5)
- Leucocytes: 11.200 (NR 4.000–10.000)
- Lymphocyte, platelet & neutrophil counts: Normal
- ESR: 27 mm/h (NR <20) INCREASED
- IgG: 20.8 g/l [NR 7.0–16.0] HIGH
- IgA: 3.8 g/l [NR 0.7–4.0] HIGH
- IgM: 1.4 g/l [NR 0.4–2.3]
- Autoantibodies (ANCA, ENA, ANA): Negative
- α2 microglobulin: 2.14 mg/l (NR <1.9) INCREASED
- Serum Amyloid A: 13.5 mg/l (NR <6.4)

PROTEIN ELECTROPHORESIS:

- Albumin: 51.9% (NR 53.2–71.2)
- α1 globulin: 4.1% (NR 1.8–5.0)
- α2 globulin: 8.5% (NR 6.4–12.8)
- β globulin: 12.0 (NR 7.7–15.7)
- γ globulin: 23.4 (NR 6.9–19.3) HIGH
- C3 1.56 g/l (NR 0.9–1.8)
- C4 0.21 g/l (0.1–0.4)
- Serum reactive protein: 22.3 mg/l (NR 0–5 mg/l) HIGH

The diagnosis of Familial Mediterranean Fever (FMF) was suspected clinically and a DNA sample for screening of MEVF gene mutations was sent to the Primary Immunodeficiency Genetic Laboratory in Slovenia. The whole coding region of MEVF gene was sequenced and identified a common mutation (M694V) in heterozygous state in exon 10, at position 694 amino acid methionine changes into valine.

DISCUSSION

Familial Mediterranean Fever (FMF) is an autosomal recessive disease affecting mainly Mediterranean populations (Ievreans, Armenians, Arabs, Turks) (1). It is not common in the Baltic countries. FMF is characterised by recurrent episodes of fever and serosal inflammation, leading to abdominal, thoracic or articular pain. Although Familial Mediterranean Fever can have nonspecific manifestations that mimic many common acquired disorders such as infections, acute appendicitis, cholecystitis, and arthritis which can delay diagnosis for many years and subject patients to extensive evaluations and even unnecessary surgery. The major complication of FMF is the development of renal amyloidosis. Usually standard laboratory tests of FMF patients are non-informative. But the high sedimentation rate and elevated fibrinogen, C-reactive protein, Serum Amyloid A are noted. FMF is caused by mutations in the MEVF gene which encodes the pyrin protein. Pyrin protein is associated with the interleukin (IL)-1-related inflammation cascade and involved in the regulation of apoptosis and inflammation. Although over 80 mutations in the MEVF gene have been reported, the majority of cases are caused by four mutations in exon 10: M694V, M694I, V726A, and M680I. In our case we identified a common mutation (M694V) in heterozygous state in exon 10, too. The patient, an inhabitant of Latvia (Caucasian), rejected anti-inflammatory treatment after 48 to 96 hours. He remained entirely well in between the attacks.

REFERENCES


The case highlights the importance of recognizing characteristic signs of rare geographically specific primary immunodeficiency disorders such as FMF in low prevalence areas. The case also serves as an example of how an efficient cooperation between centres and laboratories located in different countries can contribute to the improved care of patients with primary immunodeficiencies.