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THE FIRST CASE OF FAMILIAL MEDITERRANEAN FEVER DIAGNOSED IN LATVIA

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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
Serum	IgG 20.8 g/l [NR 7.0–16.0] HIGH
	IgA 3.8 g/l [NR 0.7–4.0]
	IgM 1.4 g/l [NR 0.4–2.3]
Autoantibodies (ANCA, ENA, ANA)	Negative
β2 mikroglobulin	2.14 mg/l (NR <1.9) INCREASED
Serum Amiloid	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 (FMV) was suspected clinically and a DNA sample for screening of *MEFV* gene mutations was sent to the Primary Immunodeficiency Genetic Laboratory in Slovenia.
The whole coding region of *MEFV* 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 (Jews, 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 Amiloid A are noted. FMF is caused by mutations in the *MEFV* 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 *MEFV* 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 affiliation to the Mediterranean populations. Although only one mutation was found, the level of serum amiloid was elevated and we started treatment with colchicine. According to some reports FMF could be the correct diagnosis in patients with typical clinial picture and only one mutation (2). The M694V mutation is the most frequent mutation in the various ethnic groups considered, although its frequency varies from group to group. The M694V mutation is often correlated with severe phenotypes, mainly in the homozygous state. It has been specifically correlated with arthritis, pleuritis and especially amyloidosis. The most effective treatment for FMF patients is colchicine that should be taken regularly for the whole life. It decreases the frequency and severity of crises and prevents renal amyloidosis, gradually leading to life-threatening renal failure. In our case the patient takes Colchicine from July 2012 till now. Despite the Colchicine treatment the patient had one episode of fever, swelling of the leg joints again in September. Due to the last exacerbation, recombinant interleukin 1 receptor antagonist is considered as an alternative treatment in this case.

CONCLUSIONS

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.

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