CASE REPORT

First Case of TNF-Receptor-Associated Autoinflammatory Syndrome (TRAPS) in Bulgaria

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TRAPS is a very rare disease with an estimated prevalence of about one per million.

We present a 53-year-old patient from Bulgaria.

The clinical features of the disease are periodic fever, arthralgia, myalgia, rash, abdominal pain and hepatosplenomegaly. Laboratory studies yield leukocytosis, highly elevated levels of CRP, significantly high ESR. Secondary amyloidosis AA is determined.

The genetic analysis found a heterozygous T>C nucleotide substance (c.250T>C) in exon 3 of TNFRSF1A gene which is associated with TRAPS (MIM*191190).

The presented case of genetic changes and clinical manifestations in the autoinflammatory syndrome TRAPS due to a mutation in the gene encoding the receptor for tumour necrosis factor alpha (TNFRSF1A) is the first documented case of the disease reported in Bulgaria.

INTRODUCTION

TRAPS is considered to be the second most common inherited recurrent fever syndrome after a similar condition called familial Mediterranean fever. The disease is very rare with an estimated prevalence of approximately one per million.^{1,2} More than 1000 people have been diagnosed with TRAPS worldwide, but it is believed that there are less than 200 confirmed cases.³ However, true prevalence is currently unknown. (EUROTRAPS international). Mutation in TNFRSF1A gene cause TRAPS. This gene provides instructions for making a protein TNFR1. This protein is found within the membrane of cells where it binds TNF. However, some people who inherit the altered gene never develop TRAPS (reduced penetrance). TRAPS has been discovered, since the gene defect was diagnosed. TRAPS is a specific syndrome of dominant mode of inheritance which refers to the potency affected TNF receptor superfamily type 1A (TNFRSF1A protein).

EUROTRAPS international¹ describe 158 patient with clinical manifestation of TRAPS; of these, 53 are children and 105 adults. The annual incidence of the disease has been estimated to be 1/1,785,000 children under 16. The median age of onset is 3 years, but cases of later onset have also been described.

CASE REPORT

We report a 53-year-old woman from Bulgaria of Mediterranean origin. Her history dates back to childhood or adolescence. The symptoms seemed to have developed between the ages of 7 and 15. At the age of seven she had a laparotomy and appendectomy for what was thought to be an acute abdomen, but her mother was told at surgery that nothing abnormal was found. She remembers from the age of 15 or 16 episodes of fever accompanied by pain in her joints, particularly her wrists and knees. These initially occurred perhaps once a

year and lasted for about a week and responded to painkillers. As she got older they became more frequent and now she has attacks perhaps every 20 to 15 days lasting up to seven days with very significant myalgia accompanied by fevers up to 38.7 degrees with occasional rigours. Fever episodes usually occur spontaneously but sometime they are caused by infection, stress, physical exercise or hormonal changes. She was previously thought to have rheumatoid arthritis and was treated with a variety of agents without much benefit, the drugs including rituximab and adalimumab. She did not derive any benefit from adalimumab, but it did not appear to have worsened her TRAPS symptoms either. She was found to have hyperprolactinaemia and her MRI scans were a little ambiguous as to whether or not she had a pituitary microadenoma, so she was placed on a lifelong treatment. She is also known to be osteoporotic secondary to corticosteroid therapy.

ECG AND ECHOCARDIOGRAM WERE NORMAL STUDIES.

She has a dizygotic twin sister who is well. The patient has no family history of TRAPS-like symptoms or of any similar disease. Her mother is well at the age of 82 and her father died at 70 with what was thought to be osteoarthritis. She is an accountant and a lifelong non-smoker. She has no children.

LABORATORY INVESTIGATIONS

Investigations here were as follows: proteinuria 0.2 g/24h (with very low grade proteinuria), ESR 90-98 mm, CRP 92 mg/l, HGB 78-90 g/l, RBC 4.1-5.05 T/l, white blood cells 9.9-8.7 G/L, neutrophils 76.8%, lymphocytes 14.8%, monocytes 7%, platelets 347 G/L, glucose 5.4 mmol/L, urea 6.7 mmol/L, creatinine 83 μ mol/L, total calcium 2.8 mmol/L, potassium 3.8 mmol/L, serum proteins 7.0 g/L, albumin 34 g/L, total cholesterol 3.73 mmol/L, aspartate aminotransferase 8.0 U/L, alanine aminotransferase 19 U/L, gamma-glutamyl transferase 147 U/L, p-ANCA-negative, c-ANCA-negative, alkaline phosphatase 375 U/L.

Histopathology bone marrow report: sections show a suboptimal bone marrow trephine biopsy with maturing trilineage hematopoiesis. The cellularity is difficult to assess. CD138+ plasma cells account for tall cell 5-10% of total cell population and show lambda light chain restriction; no amyloid is seen on congo red staining. Conclusion: bone marrow trephine biopsy – neoplastic plasma cell infiltrate 5-10%, and no amyloid is seen.

Our case is complicated with amyloidosis AA.

Figure 1. (A), (B). Duodenal mucosa amyloid deposition in a patient with AA amyloidosis secondary to TRAPS.

The patient have accordingly positive SAP scanning systemic amyloidosis with massive hepatosplenomegaly and cholestatic liver function tests, with very minor renal involvement. She has amyloid in duodenal mucosa, but no evidence of amyloid on abdominal fat aspirate and rectal biopsy (**Fig. 1**).

GENETIC ANALYSIS

DNA extraction from venous blood was performed using QIAamp DNA Blood Kit (Qiagen) following the manufacturer's protocol.

We performed Sanger sequencing (BigDye Terminator v3.1 Cycle Sequencing Kit, ThermoFisher) of the exons 2-4 of the TNFRSF1A gene, containing most of the previously reported mutations in the gene. The molecular-genetic testing detected heterozygous missense mutation NM_001065.3:c.250T>C, (p.Cys84Arg) in exon 3 of the TNFRSF1A gene (**Fig. 2**). The mutation was previously reported as pathogenic (ClinVar Variation ID 97672).

Figure 2. Sequencing profile of mutation NM_001065.3:c.250>C, (p.Cys84Arg) in exon 3 of the TNFRSF1A gene.

DISCUSSION

The tumor necrosis factor receptor-associated periodic fever syndrome is recognized in the hereditary syndromes, a group of autoinflammatory diseases caused by inappropriate activity of the innate activity syndrome.⁴ It is associated with TNFRSF1A. Most sequence variants underlying TRAPS lie within exons 2 to 4, just like it is in our case in exon 3.

Occasionally people with TRAPS develop AA amyloidosis, usually in abdominal organs and kidneys. It is estimates that 10% to 15% (or 20%) of people with TRAPS develop amyloidosis.²⁻⁴

The disease feature in our TRAPS patient is specific with restrict hepatosplenomegaly AA amyloidosis without kidney damage.

Our patient has TRAPS with a history of persistent high levels of chronic inflammation and systemic AA amyloidosis with massive hepatosplenomegaly and very minor renal involvement. Without the renal damage it would be unusual for AA type amyloidosis. SAP scan is very significant in establishing the amyloid deposits.

IgA lambda light chain secreting plasma cell dyscrasia: 10 g/L. IgA lambda paraproteins on a polyclonal background, mild lambda FLC excess with lambda Bence Jones proteinuria.

Autoimmune and infectious diseases were excluded.

CONCLUSIONS

TRAPS is pleomorphic condition characterized by attacks of fever accompanied with diffuse limb pain, abdominal pain and rash in >83% of patients.¹ In

many respects our patient confirms the clinical case descriptions of early publications.

The diagnosis of TRAPS is often delayed because the signs and symptoms are not specific and readily recognizable. Specific blood tests can support a probable diagnosis. The blood tests suggesting inflammation are high cell count, high CRP, high serum amyloid A protein and high ESR plus abnormal genetic result (mutation in the TNFRSF1A gene).

The combined EUROPEAN Union-funded projects of Eurofever and EUTRANS consist of collected data for international registry. In Bulgaria there has been no previously documented case of TRAPS.

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Первый случай фактора некроза опухоли (TNF) с аутовоспалительным синдромом, ассоциированным с рецептором фактора некроза опухоли (TRAPS), в Болгарии

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TRAPS является редко встречающимся заболеванием, частота которого среди населения составляет один случай на миллион человек.

Представляем в качестве примера пациента из Болгарии, возраст которого составляет 53 года.

Клинические проявления: периодическое повышение температуры, артралгия, миалгия, кожные высыпания, боли в животе и гепатоспленомегалия. При проведении лабораторных исследований установлено наличие лейкоцитоза, сильно повышенных показателей CRP, значительно ускоренной СОЭ (ESR). Выявлен вторичный амилоидоз AA.

При проведении генетического анализа установлено наличие гетерозиготной T > C нуклеотидной субституции (с.250T>C) в экзоне 3 гена TNFRSF1A, которая ассоциируется с TRAPS (MIM*191190).

Представленный случай генетических изменений и клинических проявлений при наличии аутовоспалительного синдрома TRAPS, причина которого связана с мутацией гена, кодирующего рецептор альфа фактора некроза опухоли (TNFRSF1A), является первым зарегистрированным случаем в Болгарии.