“Periodic fever” without fever: Two cases of non-febrile TRAPS with mutations in the TNFRSF1A gene presenting with episodes of inflammation or monosymptomatic amyloidosis.

T. Kallinich¹, D. Haffner², B. Rudolph³, R. Schindler⁴, S. Canaan-Kühl⁴, R. Keitzer¹, G. R. Burmester⁵, A. Roesen-Wolff⁶, J. Roesler⁶

¹ Department of Pediatric Pulmonology and Immunology, Charité Campus Virchow-Klinikum, Universitaetsmedizin Berlin, Germany
² Department of Pediatrics, University Hospital Rostock, Germany
³ Department of Pathology, Charité Campus Mitte, Universitaetsmedizin Berlin, Germany
⁴ Department of Nephrology and Internal Intensive Care Medicine, Charité Campus Virchow-Klinikum, Universitaetsmedizin Berlin, Germany
⁵ Department of Rheumatology and Clinical Immunology, Charité Campus Mitte, Universitaetsmedizin Berlin, Germany
⁶ Department of Pediatrics, University Hospital Carl Gustav Carus Dresden, Germany

Corresponding author:
J. Roesler, Department of Pediatrics, University Hospital Carl Gustav Carus, Fetscherstr. 74, 01307 Dresden, Germany, e-mail: roeslerj@rcs.urz.tu-dresden.de

Key words: TRAPS, amyloidosis, hereditary periodic fever syndromes

Category of publication: Concise report
Abstract

**Background:** TNF-receptor-associated periodic syndrome (TRAPS) is caused by dominant mutations in the *TNFRSF1A* gene. In typical cases TRAPS begins early in childhood and is characterized by high and remittent fever over a period of one to four weeks or longer accompanied by systemic and local inflammation.

**Case reports:** Patient 1 presented with recurrent episodes of weakness, migrating myalgias, arthralgias, exanthema, and chest pain lasting for one to four weeks, but without any fever over an initial period of four years at least. Diagnosis of TRAPS was confirmed by heterozygous mutation Y20H in *TNFRSF1A*. The 23-year old female patient 2 never had any symptoms indicative of TRAPS. Genetic evaluation of all members of her family with a TRAPS index patient disclosed the T50M mutation in *TNFRSF1A*. A medical checkup revealed proteinuria, and renal biopsy unveiled AA-amyloidosis.

**Conclusions:** TRAPS associated mutations can induce considerable inflammation that is not necessarily accompanied by fever. Even monosymptomatic severe amyloidosis can occur in these patients. Consequences for prevention are discussed.
Introduction

Tumor necrosis factor α (TNFα) receptor-associated periodic syndrome (TRAPS) is a rare autosomal dominantly inherited autoinflammatory disease characterised by recurrent febrile episodes of variable duration (mostly between one and four weeks). In typical cases it is associated with exanthema, arthralgias, migrating muscle pain, and abdominal and/or chest pain [1][2], but symptoms in other organs have also been observed. [3][4] TRAPS is caused by missense mutations on one allele of the TNFα receptor 1 (TNFRSF1A) gene usually involving the first two cysteine rich domains of the receptor. [1] It has been shown that some mutations cause a decreased shedding of the TNFα-receptor after activation of monocytes/macrophages in vitro. [2][5] Therefore, it has been hypothesized that a conformational change of the extracellular domain of the receptor inhibits cleavage from the cell surface by a metalloprotease, thereby enhancing and prolonging pro-inflammatory TNFα signalling.

A severe long-term complication of TRAPS and other periodic syndromes is the development of secondary amyloidosis. [6] This risk partially depends on the type of mutation. Mutations affecting cysteine residues in TRAPS are generally accompanied by a higher risk than other alterations [7], but amyloidosis also occurs in patients with non-cysteine mutations. [8]

Many but not all TRAPS patients respond well to steroid medication. Application of an anti-TNFα therapy (etanercept) has favourably influenced the course of the disease in several patients [8][9] and can hopefully inhibit the emergence or the progress of amyloidosis. [10][11] The diagnosis of TRAPS is important because it dictates appropriate management and genetic counselling.

In some TRAPS patients a decline in severity and frequency of fever in the long-term has been reported. Short febrile attacks (as short as 1 day) have been detailed in such patients and symptoms typical for TRAPS have continued thereafter in the absence of fever. [12] Healthy individuals with mutations that are associated with TRAPS have also been reported. However, patients with such mutations and severe disease without fever have not been previously described. Here we report on two adult patients suffering from TRAPS who have never shown typical recurrent febrile episodes. In one case renal amyloidosis is almost the only manifestation.

Case reports

Case 1

The now 34 year-old patient (III/1 in Fig. 1 A) was completely healthy until the age of 28 years. Thereafter, he showed episodes characterized by general weakness, chest pain, migrating pain in the limbs, neck and shoulders, arthralgias, arthritis, and exanthema, but he had no fever. The episodes were sometimes triggered by physical strain or stress and respiratory infections. Laboratory parameters for inflammation, such as C-reactive-protein (CRP: 300-350 mg/L, normal <6 mg/L) and erythrocyte sedimentation rate, were considerably elevated. Autoantibodies were never detected. These episodes lasted for one to four weeks and occurred three to five times a year for four or five years. Thereafter, some of the episodes started with fever lasting for half a day, but continued without fever. The patient could not remember any fever lasting longer than half a day. No signs of amyloidosis have been revealed so far. Since fever was absent during the first four or five years after the onset of TRAPS and infrequent and short thereafter, it took
several years until the correct diagnosis was found and confirmed by molecular analysis (Y20H in the \(TNFRSF1A\) gene, Fig. 1C).

The maternal grandfather of the patient was assumed to suffer from a war-acquired yet unknown chronic infection with recurrent episodes. The patient’s 38 year-old brother (III/4 in Fig. 1 A) had typical but undiagnosed TRAPS with febrile attacks three to five times per year since he was a little boy. These attacks were accompanied by fever, colicky abdominal pain, muscle pain and red or livid spots of the skin slowly migrating from the upper arms to the hands lasting for approximately two weeks. Stiffness of the neck, but no arthralgias or headache was reported. The attacks could be triggered by heavy exercise or emotional stress. The clinical symptoms of the brother improved, but did not disappear. They responded well to steroids. Two more brothers and the parents never had symptoms suggestive of TRAPS, but molecular analysis disclosed the Y20H mutation in \(TNFRSF1A\) in the mother (II/1 in Fig. 1 A).

Case 2

This female patient aged 23 years presented with a family history of TRAPS (III/2 in Fig. 1B). [8] Her father and brother suffered from recurrent febrile attacks associated with general weakness and arthralgias/arthritis since childhood. Both developed multisystemic amyloidosis with depositions in several organs including renal transplants. The father died at age 56 years. Molecular analysis of the \(TNFRSF1A\) gene revealed a heterozygous T50M mutation in both family members. [8]

The patient had been interviewed several times for symptoms similar to the affected family members before their diagnosis of TRAPS was confirmed by genetic analysis. At that time she had denied any symptoms such as recurrent febrile episodes, arthralgias/arthritis, erythemas, edemas or myalgias. Genetic evaluation of the whole family revealed the T50M mutation in \(TNFRSF1A\) in her case, too (Fig. 1E). After receiving this information, she admitted retrospectively recurrent sore muscles, which she had not taken seriously and referred to the impact of hard work. During follow-up she developed marked proteinuria (3 to 4 g/day, mainly albumin) and a kidney biopsy revealed considerable AA-amyloid deposition (Fig. 2). At this time markers of acute phase reaction (e.g. CRP 360 mg/L) were elevated. Complement C3 and C4 was normal as well as glomerular filtration rate (118 - 140 ml/min). Treatment with etanercept was started, which had previously been shown to be successful in her brother with respect to kidney function and clinical symptoms.

Discussion

The mutations found in the patients’ families (Y20H, Fig.1 C; and T50M Fig.1 E, [8]) had been previously described as causing TRAPS. [4][8][13][14] Accordingly, in both families some members with the respective mutations suffered from typical TRAPS. However, as emphasized above the clinical course of both patients was rather unusual because their illness was not accompanied by fever (at least for several years in patient 1).

In general, it is very difficult for non-specialized physicians to find the right diagnosis in patients with a non-typical clinical course of a rare disease. Therefore, our observations showing extremes of the clinical spectrum of TRAPS seem to be of special interest. In the first case the lack of fever was a diagnostic hurdle and in the second case the diagnosis could not be made without genomic sequencing.
Despite the lack of recurrent febrile episodes considerable persistent systemic inflammatory activity was revealed in patient 1. Therefore he is certainly at some risk to develop amyloidosis. Case 2 demonstrates that amyloid deposition can occur in otherwise asymptomatic carriers of TRAPS causing mutations. Similarly, in Familial Mediterranean fever (FMF), another hereditary autoinflammatory disease, amyloidosis can occur as the sole and first manifestation and is defined as phenotype II. [15]

We suggest the following approach: I. Patients with signs of severe recurrent or chronic inflammation should be analysed for TNFRSF1A mutations when another diagnosis has not been established and when one or more symptoms such as myalgia, abdominal pain, conjunctivitis, or exanthem match TRAPS even if fever is scarce or absent. (An analogous approach may be appropriate for other hereditary periodic fever syndromes, especially FMF). The search for such syndromes has of course a high priority if family members are affected by suspicious symptoms. II. In families with TRAPS index patients as in case 2, genetic analysis and subsequent counselling should be offered even to asymptomatic family members. Every carrier of a TRAPS causing mutation should be carefully monitored for systemic inflammatory activity and signs of amyloidosis. Treatment with anti-TNFα agents and corticosteroids should be considered based on inflammatory activity, type of TRAPS mutation, amyloidosis in other family members, and the involvement of modifying genes, e.g. SAA polymorphisms, when available. Such treatment has a high priority and is probably indicated if signs of amyloidosis have already manifested.

In conclusion, the knowledge of the full range of TRAPS manifestations is important because the diagnosis enables genetic counselling and appropriate management to prevent or mitigate amyloidosis.
Conflict of interest: We have no conflict of interest to declare

Copyright: The corresponding author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence on a worldwide basis to the BMJ Publishing Group Ltd to permit this article (if accepted) to be published in ARD and any other BMJ products and sublicences such use and exploit all subsidiary rights, as set out in the licence (http://ard.bmjournals.com/misc/ifora/licenceform.shtml).
Figure legends

Fig.1: Pedigrees of the patients (A, patient 1, III/1; B, patient 2, III/2). Filled black symbols: TRAPS and family specific mutation; filled gray symbol: Y20H mutation, but clinically unaffected; #, analysed for respective family specific mutation; n.a., not available for molecular analysis. Bottom: The Y20H and the T50M mutation on one allele of the TNFRSF1A gene in the patients (C, patient 1; E, patient 2; D and F, healthy DNA donors). Genomic sequencing [4]; numbering according to www.ENSEMBL.org, TNFRSF1A precursor, ENSG00000067182: 426T->C, Y49H and 517C->T, T79M. All patients and healthy family members gave written consent for genetic analysis and anonymous publication.

Fig. 2: Amyloid deposits in the kidney of patient 2. APAAP staining technique was performed according to standard protocols. The antibody against SAA (clone mc1, mouse IgG2a, DAKO, Germany) strongly stains deposits in the glomerular mesangium.
Reference list


(10) Dode C, Hazenberg BP, Pecheux C, Cattan D, Moulin B, Barthelemy A et al. Mutational spectrum in the MEFV and TNFRSF1A genes in patients suffering


