CONCISE REPORT

"Periodic fever" without fever: two cases of non-febrile TRAPS with mutations in the *TNFRSF1A* gene presenting with episodes of inflammation or monosymptomatic amyloidosis

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Background: Tumour necrosis factor (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 characterised by high and remittent fever over a period of 1–4 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 1–4 weeks, but without any fever over an initial period of 4 years at least. Diagnosis of TRAPS was confirmed by the heterozygous mutation Y20H in *TNFRSF1A*. Patient 2, a 23 year old woman 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 check up showed proteinuria, and renal biopsy disclosed 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. Genetic counselling and appropriate management to prevent or mitigate amyloidosis may be necessary.

Many but not all patients with TRAPS respond well to steroid treatment. Use of anti-TNF α 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 patients with TRAPS a decline in the 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 people 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 with TRAPS who have never shown typical recurrent febrile episodes. In one case renal amyloidosis was almost the only manifestation.

CASE REPORTS

Case 1

Patient 1 (III/1 in fig 1 A), now aged 34 years, was completely healthy until the age of 28. Thereafter, he showed episodes characterised 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 measures for inflammation, such as C reactive protein (300–350 mg/l, normal <6 mg/l) and erythrocyte sedimentation rate, were considerably raised. Autoantibodies were never detected. These episodes lasted for 1–4 weeks and occurred three to five times a year for 4 or 5 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 seen so far. Because fever was absent during the first 4 or 5 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 have a war-acquired yet unknown chronic infection with recurrent episodes. The patient's 38 year old brother (III/4 in fig 1 A) had had typical but undiagnosed TRAPS with febrile attacks three to five times a year since he was a little boy. These attacks were accompanied by fever, colicky abdominal

Tumour necrosis factor α (TNF α) receptor associated periodic syndrome (TRAPS) is a rare autosomal dominantly inherited autoinflammatory disease characterised by recurrent febrile episodes of variable duration (mostly between 1 and 4 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 seen.^{3–4} TRAPS is caused by missense mutations on one allele of the TNF α receptor 1 (*TNFRSF1A*) gene, usually affecting the first two cysteine rich domains of the receptor.¹ It has been shown that some mutations cause a decreased shedding of the TNF α receptor after activation of monocytes/macrophages in vitro.^{2–5} Therefore, it has been suggested that a conformational change of the extracellular domain of the receptor inhibits cleavage from the cell surface by a metalloproteinase, thereby enhancing and prolonging pro-inflammatory TNF α 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

Abbreviations: TNF, tumour necrosis factor; TRAPS, tumour necrosis factor receptor associated periodic syndrome

Figure 1 (A, B) Pedigrees of the patients (A, patient 1, III/1; B, patient 2, III/2). Filled black symbols, TRAPS and family-specific mutation; filled grey symbol, Y20H mutation, but clinically unaffected; #, analysed for respective family-specific mutation; n.a., not available for molecular analysis. (C–F) 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 sequencing⁴; numbering according to www.ensembl.org (accessed 31 March 2006), *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.

pain, muscle pain, and red or livid spots of the skin slowly migrating from the upper arms to the hands lasting for about 2 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).

Figure 2 Amyloid deposits in the kidney of patient 2. An alkaline phosphatase-anti-alkaline phosphatase staining technique was performed according to standard protocols. The antibody against serum amyloid A (clone mc1, mouse IgG2a, DAKO, Germany) strongly stains deposits in the glomerular mesangium.

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 had had 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 showed a heterozygous T50M mutation in both family members.⁸

The patient had been interviewed several times for symptoms similar to those of 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, oedemas or myalgias. Genetic evaluation of the whole family showed 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 (3–4 g/day, mainly albumin), and a kidney biopsy showed considerable AA amyloid deposition (fig 2). At this time markers of

acute phase reaction (for example, C reactive protein 360 mg/l) were raised. 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 for kidney function and clinical symptoms.

DISCUSSION

The mutations found in the patients' families (Y20H, fig 1C; and T50M fig 1E,⁸) have been previously described as causing TRAPS.^{4 8 13 14} Accordingly, in both families some members with the respective mutations had typical TRAPS. However, as emphasised 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-specialised 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 shown in patient 1. Therefore he is certainly at some risk of developing amyloidosis. Case 2 demonstrates that amyloid deposition can occur in otherwise asymptomatic carriers of TRAPS causing mutations. Similarly, in familial Mediterranean fever, 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: (a) 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 familial Mediterranean fever.) The search for such syndromes has of course a high priority if family members are affected by suspicious symptoms. (b) 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 mutation causing TRAPS should be carefully monitored for systemic inflammatory activity and signs of amyloidosis. Treatment with anti-TNF α 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—for example, serum amyloid A polymorphisms, when available. Such treatment has a high priority and is probably indicated if signs of amyloidosis have already manifested.

In conclusion, knowledge of the full range of TRAPS manifestations is important because the diagnosis enables genetic counselling and appropriate management to prevent or mitigate amyloidosis.

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