Published in final edited form as:

Mod Rheumatol. 2010 June ; 20(3): 311–315. doi:10.1007/s10165-010-0273-y.

Variable intrafamilial expressivity of the rare tumor necrosis factor-receptor associated periodic syndrome-associated mutation I170N that affects the TNFR1A cleavage site

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Abstract

We report on a 33-year-old female patient with a relatively mild clinical case of TNF-receptor associated periodic syndrome (TRAPS) and her 58-year-old father in whom end-stage renal disease due to TRAPS-related AA-amyloidosis has already developed. TRAPS was caused by a I170N mutation that has previously not been associated with amyloidosis. It remains unclear if an only mildly affected patient such as ours would benefit from treatment considering her father's severe course of disease. The relevant literature on this problem is reviewed.

Keywords

Hereditary fever syndrome; Tumor necrosis factor-receptor associated periodic syndrome; Etanercept; Amyloidosis

Introduction

TNF-receptor associated periodic syndrome (TRAPS) belongs to the group of hereditary periodic fever syndromes characterized by recurrent attacks of fever, abdominal or musculoskeletal pain, and skin rash. The most serious long-term complication is amyloidosis, which is predominantly due to deposition of serum amyloid A (SAA) fragments in vital organs. We report on a 33-year-old female patient with relatively mild disease (case 1) and her 58-year old father (case 2) in whom end-stage renal disease due to AA-amyloidosis had already developed at the time of diagnosis. TRAPS was caused by the rare I170N mutation that has previously not been associated with amyloidosis.

Case 1

A 33-year-old female patient was referred to our outpatient clinic because of recurrent attacks of fever up to 39°C, fatigue, arthralgia and myalgia of the arms and back sometimes accompanied by a mild rash on her thighs. The attacks occurred about twice or thrice a year and lasted for about 3 days. Only during the third trimester of her pregnancy had she remained unaffected. The patient had been thoroughly investigated for acute or chronic infectious diseases several times. In addition, there were no confirmatory findings indicating any kind of malignant or rheumatic disease. Anti-nuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), rheumatoid factor, complement as well as phospholipid antibodies were normal, and inflammatory parameters such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were only marginally elevated (Table 1). She was a nurse and had a healthy 3-year-old son. Several treatments with paracetamol and antibiotics did not result in an improvement of her symptoms. She had never taken corticosteroids or immunosuppressant agents so far. She reported that her father had similar symptoms. The paternal grandfather had also suffered from attacks of fever and died of renal failure. Other family members were not affected at present (Fig. 1). At the time of presentation to our clinic, the physical examination revealed no pathologic findings.

Case 2

Her father, 58 years old at the time of presentation in our clinic, had been suffering from attacks of fever, arthralgia of the fingers, elbows, and shoulders, as well as abdominal, chest, and musculoskeletal pain, since early adulthood. During the attacks, he occasionally took paracetamol for pain relief. C-reactive protein was always slightly above the normal range and elevated during an attack. He had gone through several treatments for various diagnoses. Because of a high antistreptolysine titer, the patient had also received antibiotic treatment without effect. As no infectious, rheumatic, or malignant diseases could be found, he had been treated with antidepressants for several years. At the age of 52, the patient developed persistent back pain and, after an unsuccessful orthopedic work-up, he was referred to a nephrologist. A splenomegaly and a proteinuria of 2.4 g/24 h were detected, and a renal biopsy was performed that revealed AA-amyloidosis. The rheumatoid factor was elevated and, although no typical inflammatory alterations of the joints could be discovered, the patient was diagnosed with Felty's syndrome and an immunosuppressive therapy was started, first with sulfa-salazine, then with oral cyclophosphamide. No further attacks occurred during cyclophosphamide therapy, but the treatment had to be terminated because of progressive renal deterioration, and hemodialysis was required 2 years later. He also suffered from intermittent atrial fibrillation probably due to myocardial amyloidosis as cardiovascular disease could not be found.

Familial Mediterranean fever (FMF) had been suspected once but treatment with colchicine could not prevent further attacks and progression of proteinuria. Primary genetic testing for an (MEFV)-gene mutation was negative in both father and daughter. Nevertheless, the

course of disease affecting family members in different generations suggested the diagnosis of a hereditary periodic fever syndrome based on a hitherto undetected mutation within the family. The symptoms described by both patients were most suggestive for TRAPS. Therefore, both patients and other family members were tested after obtaining oral informed consent for gene analysis for a mutation in the TNF-alpha receptor 1 gene. In both father and daughter, a tumor necrosis factor associated periodic syndrome due to an I170N mutation could be diagnosed. All other family members tested were negative for the TNFR1 gene mutation. Analysis of blood samples showed a soluble TNFR1 level below the normal range; TNFR2 levels were normal. CRP and SAA levels were markedly elevated during the attacks and also did not return within the normal range between the attacks (Table 1). Evaluation of the daughter's urine and kidney function did not reveal any pathologic findings. The daughter was treated symptomatically with steroids as she felt severely physically impaired during the attacks. An initial dose of 60 mg for 2 days was needed to gain partial relief of the symptoms. Afterwards, the steroids were tapered down quickly over 4 days. Over the last year, she also has experienced a gradual deterioration of the course of the disease with more frequent attacks and extension of attacks up to 5–7 days. Etanercept was discussed, but the patient is reluctant to undergo the treatment.

Discussion

The TNF-receptor associated periodic syndrome (TRAPS) belongs to the entity of hereditary periodic fever syndromes characterized by recurrent attacks of fever and systemic inflammation. Progress in genetics facilitated the specification of the clinical subgroups by determining the underlying genetic defect. At present, seven inflammatory disorders and corresponding genetic defects have been identified [1]. The affected genes are known to play a role in regulation of the innate immune system. To date more than 50 disease-associated mutations of the *TNFRSF1A* gene are listed for TRAPS in the INFEVERS database (<http://fmf.igh.cnrs.fr/ISSAID/infevers/>).

TNFR1A is a transmembrane receptor on immunocompetent cells. Binding of TNF-alpha leads to activation of intracellular pathways but also to cleavage and shedding of soluble TNFR1 (sTNFR1), which is able to neutralize TNF-alpha and so control systemic inflammation [2]. Mutated TNFR1 can lead to defective signaling in the immune system by decreased shedding of sTNFR1 [3] and, indeed, most TRAPS patients have sTNFR1 levels below the normal range, which was also the case in our patients. The fact that the I170N mutation lies near the cleavage site supports this theory.

In our family, genetic analysis revealed a mutation with exchange of isoleucine for asparagine (I170N). It has already been described in two members of another German family but was not associated with amyloidosis in these cases [4]. The authors of this publication have also screened 192 ethnically matched control chromosomes of 96 patients for the mutation, but found no other carriers. Also, all noncarriers in both families were healthy.

TRAPS is a dominantly inherited genetic disorder that was first described in an Irish/Scottish family in 1998 [2]. Characteristic features are recurrent fever, musculoskeletal and abdominal pain and skin rash due to sterile synovial, pleuritic, peritonitic, fascial or ocular inflammation. Other symptoms such as conjunctivitis, scrotal pain, and myo-cardiopathy [5] have been described. Histology usually shows monocytic infiltration of the affected sites [6–8]. The severity of symptoms differs strongly, ranging from asymptomatic patients [9,10] to severe clinical impairment or even intestinal pseudo-obstruction [11]. Some patients present with nonfebrile attacks [8,9]. In rare cases, the CNS can be affected. There are reports of psychosis, depression, and flares mimicking multiple sclerosis in clinical, radiological, and

laboratory findings with proof of missense mutations in TNFR1A and an excellent clinical response to etanercept [8,12]. The disease usually manifests in young adults, but later onsets or symptomatic infants have been described [13,14]. The most common indicator symptoms of TRAPS are summarized by Hull et al. [3] and are also depicted in Table 2, where the symptoms of the members of both TRAPS families with the I170N mutations are listed.

Amyloidosis, especially renal amyloidosis caused by SAA deposits, is a serious complication in TRAPS usually leading to nephrotic syndrome [15]. The activity of disease does not seem to be correlated with incidence of renal failure, as there are oligosymptomatic and even asymptomatic patients diagnosed with amyloidosis. Systemic inflammation and clinical attacks do not always correlate. Symptoms due to localized inflammation can be severe without elevation of systemic inflammatory markers, whereas high levels of inflammatory markers can be asymptomatic [16]. Mutations leading to a cysteine substitution are associated with a higher risk for amyloidosis (24 vs. 2%) [3]. As this is not the case in our family, patient 2 and the possibly affected grandfather might have an additional risk factor for amyloidosis such as an SAA polymorphism. Specific tests on this matter were not done.

Treating TRAPS targets the amelioration of symptoms and improving or avoiding complications, namely amyloidosis and consecutive renal failure. Therefore, localized and systemic inflammation has to be controlled. Corticosteroids are effective in reducing the duration and severity of attacks but cannot prevent amyloidosis. Colchicine and immunosuppressants such as cyclosporine or azathioprine are usually not effective and are not able to delay progression to amyloidosis [13,15]. The recombinant, soluble human tumor necrosis factor receptor super family fusion protein TNFRSF1B, etanercept, has been shown to ameliorate clinical symptoms. Although there are reports of primary and secondary therapeutic failure [17,18], most patients benefit clinically and experience attenuation of severity and frequency of their symptoms, some even achieve complete remission [5,8,9,12,13,15,19–24]. Whether etanercept can prevent progression to amyloidosis is yet unclear, but there are favorable clinical reports [15,25]. At present, there exists only one prospective study with seven patients treated with etanercept over 24 weeks [13]. Here, a positive effect on symptoms, corticosteroid use, and inflammatory markers could be demonstrated.

In the case of our young female patient, symptoms are well controlled by occasional intake of steroids, and renal function is not affected so far. However, SAA levels are far above the normal range during attacks and slightly elevated in clinically healthy periods. Therefore, and with regard to the history of her father and grandfather, treatment with etanercept was discussed but rejected as it remains unclear if she would benefit from a regular treatment with regard to renal failure. Renal function is closely monitored.

In summary, TRAPS is a chronic inflammatory condition that is often not easy to recognize. However, making the diagnosis is important, as its complication can lead to impairment of vital organ functions. Patients with severe or frequent attacks can be treated with immunosuppressive agents, but the effect of therapy on progression of amyloidosis has not yet been determined. It remains unclear whether patients suffering from a mild form of the disease would benefit from a regular treatment.

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Fig. 1. Patients' family tree. Affected family members are depicted in *black*, including the grandfather with suspected TRAPS who died before the diagnosis. Family members who tested negative for the I170N mutation are marked *gray*

Table 1

Levels of soluble TNFR1 and inflammatory markers of patient 1 as measured during and between attacks

	Patient 1 (daughter)	
	No symptoms	TRAPS attack
C-reactive protein (mg/l, normal < 5)	6–8	67–114
Interleukin-6 (pg/ml, normal < 6)	Not measured	9
Serum amyloid-A (mg/l, normal < 6)	13–20	139–206
Soluble TNFR1 (pg/ml, normal 1,000–4,000)	524	Not measured

Comparison of clinical features of our patients and patients described by Kriegel et al. [4] with typical indicator symptoms of TRAPS [3]

Table 2

Patient	Fever	Rash	Pleuritis	Abdominal pain	Myalgia/arthralgia	Ocular involvement	Amyloidosis
Case 1 (daughter)	Yes	Yes	No	No	Yes	No	No
Case 2 (father)	Yes	Yes	Yes	Yes	Yes	No	Yes
Case III-2 (Kriegel et al.)	Yes	No	No	No	Yes	No	No
Case II-2 (Kriegel et al.)	Yes	No	No	No	Yes	No	No
Case I-1 (Kriegel et al.)	Yes	No	No	No	No	No	No

Case III-2 and case II-2 also suffered from pharyngitis