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**Tumor necrosis factor receptor 1-associated periodic syndrome
(TRAPS) without fever – cytokine profile before and during etanercept
treatment**

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Abstract

Objective. Autoinflammatory syndromes are usually characterized by repeated attacks of fever, especially in children. The presentation of these diseases, however, varies between entities and between patients of a particular syndrome.

Subject. We report a 16-year-old female patient, who suffered from periodic erythema and myositis/fasciitis. She experienced at least 9 attacks of dermatitis and myositis, while no fever episodes were noted over a 3-year period. A delay of puberty with amenorrhea and a short stature were also present.

Results. Laboratory investigations consistently showed markedly increased inflammatory parameters (especially a high serum amyloid A) and dysproteinemia. Because the patient's mother complained about chronic and periodic abdominal pain with also persistently elevated inflammatory parameters, the differential diagnosis included hereditary disorders resulting in chronic inflammation. The diagnosis of an inherited tumor necrosis factor receptor (TNFR) 1-associated periodic syndrome (TRAPS) was confirmed by genetic analyses. Long-term anti-inflammatory treatment with etanercept resulted in a significant clinical improvement and reduction of the inflammatory parameters ESR, CRP, interleukin-6, TNF- α , and soluble TNF- α receptor 1, but not of interleukin-12.

Conclusion: Monitoring of the cytokine profile suggested partial effectiveness of etanercept in the treatment of TRAPS. Hereditary fever syndromes have to be considered in case of chronic unexplained inflammation even if fever is no presenting symptom.

Introduction

Tumor necrosis factor receptor (TNFR) 1-associated periodic syndrome (TRAPS; OMIM 142680) is the most common autosomal dominantly inherited periodic fever syndrome (10). This disease group also includes the autosomal recessively and dominantly inherited familial Mediterranean fever (MIM 249100), the autosomal recessive hyperimmunoglobulinemia D and periodic fever syndrome (MIM 260920), and the autosomal dominantly transmitted cryopyrin-associated periodic syndromes (CAPS; MIM191900, MIM120100, and MIM607115).

TRAPS is characterized by recurrent attacks of fever, abdominal pain, synovial inflammation, migratory rash, conjunctivitis, and unilateral periorbital edema with a duration of at least 5 days up to 4 weeks. The phenotypic presentation of affected patients, however, varies considerably. TRAPS is caused by mutations in the *TNFRSF1A* gene, which encodes the TNF receptor 1 (TNFR1). This transmembrane receptor contains four cysteine-rich domains (CRDs) in the extracellular region and an intracellular death domain which can signal apoptosis via death domain proteins or activate transcription factor NF- κ B and bring forth inflammation. Mutations described in association with TRAPS are mostly missense mutations, which may involve cysteine residues that are part of structurally important disulfide bonds (18).

How TNFR1 mutations lead to the inflammatory phenotype of TRAPS is still under investigation. One early explanation was the so-called shedding hypothesis (12). After activation of the receptor, the extracellular part is normally shed from the cell surface by metalloproteases. This soluble TNFR1 (sTNFR1) is able to effectively neutralize TNF- α in the plasma. Initial observations in TRAPS patients showed increased cell surface TNFR1 and decreased plasma levels of soluble TNFR1 (sTNFR1), which resulted in increased and prolonged TNF- α signaling and decreased blocking of circulating TNF- α . However, with the number of TRAPS mutations increasing, further studies demonstrated that cleavage defects are not generally found in association with TRAPS mutations. Thus, the shedding hypothesis can't be the sole explanation for the pathogenesis of TRAPS. Recent findings strongly suggest additional signaling defects in TRAPS patients. *In vitro* experiments

performed by Rebelo et al. (14) demonstrated that the mutant TNFR1 may aggregate and be retained in the cytoplasm, resulting in defective cell surface expression and ligand-independent signaling. In a similar study by Lobito et al. (11), mutant TNFR1s showed reduced surface expression which correlated with reduced apoptosis induction and NF- κ B signaling. The structurally altered receptors failed to interact with the wild-type receptor and instead formed abnormal disulfide-linked self-aggregates which were retained intracellularly in the endoplasmatic reticulum (ER). These findings indicate that the inflammatory phenotype of TRAPS may be due to mutant receptor misfolding, and subsequent induction of cytokines like IL-1 β due to an unfolded protein response.

Corticosteroids are generally effective in reducing inflammation in TRAPS, but high doses are often required. When the genetic basis of TRAPS was identified, great hope was placed on an anti-TNF- α therapy, with etanercept being the most commonly used anti-TNF- α agent in TRAPS today. Various publications about the effect of etanercept are available, but results are mixed. It seems that etanercept is of use in replacing or reducing steroids, but the response can also be only a partial one or even be absent in some cases. The long-term benefit and potential adverse effects of etanercept in TRAPS are unknown. Recently, successful IL-1 blockade has been described in patients refractory to an etanercept therapy (6) (15).

Clinical Report

The 16-year-old girl initially presented with the incidental finding of a high CRP of 7.6 mg/dl and of an increased ESR of 93 mm/hour. She mentioned recurrent attacks of localized pain and redness of her extremities at varying locations since she was 13 (Figure 1). These symptoms were mostly affecting her thighs or upper arms and were sometimes associated with mild swelling of the joints, lasting for several days up to one week. Up to 10 episodes per year were noted. Fever had never occurred during these episodes. She also reported occasional conjunctivitis and swelling of one of her eyelids. Her skin showed a slightly greyish complexion. She didn't have her menarche yet and her pubertal development was delayed (Tanner stage BII, PHI). She was of short stature (20th percentile) and her weight had been persistently low (2 kg below 3rd percentile). Microcytic anemia was noted (Hb 10.4 g/dl, MCH 20.3 pg, MCV 67 fl, reticulocytes 1.9 %). Leukocytes (14570/ μ l (63% granulocytes, no blasts) and platelets (732000/ μ l) were elevated. Inflammatory parameters were significantly increased: ESR 93 mm/h, CRP 7.6 mg/dl, serum amyloid A (SAA) 736 mg/dl (normal range < 10 mg/dl), serum IgG (polyclonal rise to 2410 mg/dl, normal range 770–1510 mg/dl). Iron metabolism showed a serum iron of 18 μ g/dl and a ferritine of 70 μ g/l (normal range: 9.3-59 μ g/l). Further analyses including IgD, IgA, IgM, thyroid and growth hormones as well as autoimmune antibodies (ANA, ENA, ANCA, dsDNA) and a tuberculin skin test were unremarkable. A bone marrow examination showed unspecific inflammatory changes. The constellation of increased acute phase reactants associated with recurrent episodes of localized myositis supported the diagnosis of an autoinflammatory syndrome. Subsequent evaluation of the family's history revealed that the patient's mother had suffered from episodes of severe stomach pain related to cholecystitis associated with a high ESR of 85 mm/hour. Therefore - despite the fact that no fever was ever present - further diagnostic analyses of our patient were initiated, targeting hereditary fever syndromes. DNA sequence analysis of exons 2, 3, 4, and 6 of the *TNFRSF1A* gene (16), encoding the 55-kDa receptor for TNF- α , revealed a T→C nucleotide substitution in exon 2 which leads to the replacement of

tyrosine (TAT) by histidine (CAT) at amino acid position 20 (Y20H). Genetic analysis of the mother revealed the presence of the identical mutation.

After the diagnosis of TRAPS was made, treatment with etanercept, a dimeric molecule joining the 75-kDa TNF- α receptor with the Fc portion of a human IgG1 antibody, was initiated (0.4 mg/kg subcutaneously twice a week). The patient responded promptly with an improved physical condition. In the following months, a gain of weight and a rapid development of puberty (onset of menstrual bleeding, rapidly advancing breast and pubic hair growth) were noted. Episodes of focal myositis and erythema decreased in intensity and in frequency to about one to two per year. Attacks responded promptly to an additional naproxen or oral glucocorticoid therapy (0.2 mg/kg prednisone for two days). ESR, CRP, and serum amyloid A were within the normal range, except during attacks (Figure 2a). Anemia improved to 11.5 g/dl. IgG titers remained elevated (1600 - 2140 mg/dl).

The peripheral blood cytokine pattern of the TRAPS patient before and during TNF- α blockade with etanercept was analyzed by ELISA technique (Bender Med Systems, Vienna, Austria). Serum concentrations of IL-6, IL-12p70, TNF- α , and the sTNFR1 were determined during a 2-year period. IL-6, TNF- α , and sTNFR1 serum levels correlated well with markers of inflammation (ESR, CRP) (Figures 2b, c, d) as well as with clinical symptoms. IL-12, in contrast, remained elevated. After etanercept treatment, IL-6 serum levels decreased, whereas IL-12 concentrations increased (Figure 2e).

During 5 years of further follow-up, a streptococcal skin infection of the face and a one-sided superficial keratitis were noted as potentially therapy-associated side effects. Up to this point, fever associated with a flare has never occurred. Also, no clinical signs of amyloidosis have been found yet.

Discussion

TRAPS usually presents before the age of 20 years with prolonged febrile episodes of at least 7 days up to several weeks (9). In our patient, however, fever was never present, thus challenging the diagnosis of a recurrent fever syndrome.

The Y20H amino acid substitution detected in our patient has been described so far in two other patients and one asymptomatic carrier, thus suggesting a variable penetrance of this mutation (2). Disease onset (13 years of age) and duration of attacks (several days) in our patient corresponded to some extent with the data in the literature which described an average age of onset of 14 years and a fever duration of 2–4 days. Interestingly, a different amino acid substitution at the same position (Y20D) was reported to be associated with a very early disease onset at 1 year of age, prolonged febrile episodes, and severe abdominal pain, but no myositis and accompanying erythema (17). Whether this is indicative of the phenotypic heterogeneity or due to the heterozygous presence of another proinflammatory mutation (*MEFV* E148Q) in that proband, remains to be elucidated.

Usually TRAPS responds to high doses of oral corticosteroids. However, considering the underlying pathophysiology, etanercept seems to be the treatment of choice. It is considered safe in children (8) and has been successfully applied to a series of TRAPS patients (4; 5). Long-term anti-inflammatory treatment with etanercept resulted in a dramatic clinical improvement and in a reduction of inflammatory parameters, thereby demonstrating its efficacy. Amyloidosis is the most severe complication of the disease and seems to occur more commonly in patients with cysteine mutations (7) (9) (3). Our patient so far did not show any signs of amyloidosis. Whether this is due to the non-cysteine Y20H mutation, the relative short disease course of less than 10 years, or the partially effective treatment with etanercept, which has been shown to slow down or even reverse organ manifestation of amyloidosis in TRAPS (4), can actually not be decided.

Nowlan et al. (12) studied systemic pro-inflammatory cytokine levels in TRAPS patients affected by the C33Y mutation with and without etanercept treatment. They found that IL-6 concentrations were significantly increased

and correlated with CRP levels in some of the affected patients. IL-8 was elevated as well. Neither TNF- α nor IL-1 β demonstrated a similar increase. Etanercept appeared to induce an increased plasma concentration of TNF- α , potentially by increasing TNF- α stability. Overall, the cytokine profile of TRAPS patients differed from the generalized elevation of pro-inflammatory cytokines typically observed in autoimmune or infectious inflammatory diseases (13)..

In our patient, we found that TNF- α , TNFR1, and IL-6 were downregulated concordantly along with conventional markers of inflammation by etanercept. This resulted in a notable clinical improvement. IL-12 showed an opposite dynamic, as it increased under anti-TNF- α therapy. IL-12 is produced mainly by activated antigen presenting cells and has been shown to play a pivotal role in chronic inflammation (1).

We therefore hypothesize that cytokine production is disturbed in TRAPS patients receiving etanercept. Different proinflammatory cytokines seem to be differentially regulated during states of high and low amounts of free TNF- α molecules.

Conclusion

Especially in children, the presence of fever is an important clinical feature to establish the diagnosis of TRAPS. However, fever may not be present in every patient. Etanercept significantly improves the clinical status, although different proinflammatory cytokines seem to react differently once TNF-blocking therapy is instituted.

Figure legends

Figure 1: Dermatitis and myositis of the thigh of the 16-year-old TRAPS patient during a flare.

Localized pain, erythema, and soft tissue induration of the right thigh were noted during inflammatory attacks. These localized symptoms sometimes migrated on the affected extremity. Lesions in proximity to joints were associated with mild joint swelling and effusions and lasted for several days up to one week.

Figure 2: Inflammatory parameters during the course of the disease of the 16-year-old TRAPS patient.

Serial measurements of ESR, CRP, and serum amyloid A concentrations over a period of 22 months are shown (figure 2a). Etanercept treatment was started at the 3rd time point shown (13.10.03), when a typical attack just had become clinically evident. Figure 2b shows the measurement of TNF- α , figure 2c of the soluble 60 kd subunit of the TNF receptor 1, figure 2d of IL-6, and figure 2e of IL-12p70 in the patient's serum by using the ELISA technique. Please note the subsequent and non-linear time points of the figures.

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