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Skin manifestations in tumor necrosis factor receptor-associated periodic syndrome (TRAPS)

Rebecca Schmaltz,* Thomas Vogt and Jörg Reichrath

Klinik für Dermatologie, Venerologie und Allergologie; Universitätsklinikum des Saarlandes; Homburg/Saar; Germany

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Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is a rare autosomal dominant inherited disease that belongs to the group of hereditary fever syndromes, that are also named hereditary auto-inflammatory syndromes. TRAPS is characterized by a variety of naturally occurring mutations in a TNF receptor (TNFR), that affect the soluble TNFRSF1A gene in the 12p13 region. In some patients, the pathogenesis of TRAPS involves defective TNFRSF1A shedding from cell membranes in response to varying stimuli. TRAPS is characterized by the periodic occurrence of a broad variety of different clinical symptoms that represent an acute-phase response, including fever and pain in the joints, abdomen, muscles, skin or eyes, with broad variations across patients. In many cases, skin involvement is present that may include migratory patches, skin rashes, erysepela-like erythema, edematous plaques, urticaria, periorbital edema and/or conjunctivitis. The histology of skin lesions in TRAPS is nonspecific, in general a perivascular dermal infiltrate of lymphocytes and monocytes can be found. Cutaneous findings are of particular importance in TRAPS: they have been shown to give direction to the diagnosis of TRAPS and in most cases their treatment is challenging. As the incidence of TRAPS is very low, no prospective randomized controlled trials and only a few studies with case numbers up to twenty-five patients have been published. No guidelines for TRAPS treatment have been established so far. This review summarizes our present knowledge about pathogenesis, clinical outcome and treatment options of skin manifestations in TRAPS.

Introduction

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is a rare autosomal dominant inherited inflammatory disease of periodic fever and pain.[1-3] It has been reported that most patients are of northern European descent. TRAPS seems to be the most common hereditary periodic fever (HPF) syndrome in some western populations, and the second most prevalent HPF worldwide, behind familial mediterranean fever (FMF).[4] The inflammatory attacks manifest as fever and pain in the joints, abdomen, muscles, skin or eyes, with variations across patients.[1,5]

*Correspondence to: Rebecca Schmaltz; Email: rebecca.schmaltz@uks.eu
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An acute-phase response occurs during the attacks.[6] Patients with TRAPS are at risk for AA amyloidosis, the most common targets being the kidneys and liver.[7] Soluble TNFRSF1A is usually low between the attacks and may be normal during the attacks, when TNF levels are high. TNFRSF1A is found in abnormally high numbers on leukocyte cell membranes. TRAPS is the first condition for which naturally occurring mutations in a TNF receptor were found; the mutations affect the soluble TNFRSF1A gene in the 12p13 region. In some patients, the pathogenesis involves defective TNFRSF1A shedding from cell membranes in response to varying stimuli. Thus, TRAPS represents a model for a pathogenic concept characterized by failure to shed a cytokine receptor. Cutaneous findings are of particular importance in TRAPS: they have been shown to give direction to the diagnosis of TRAPS and in most cases their treatment is challenging. As the incidence of TRAPS is very low, no prospective randomized controlled trials and only a few studies with case numbers up to seven patients have been published. No guidelines for TRAPS treatment have been established so far. This review summarizes our present knowledge about pathogenesis, clinical outcome and treatment options of skin manifestations in TRAPS.

Pathogenesis of TRAPS

The proteins involved in TRAPS (TNFRsf1a) and FMF (pyrin) are both members of the death-domain-fold superfamily.[4] Mutations affecting these proteins cause dysregulation of innate immune responses, with a propensity to autoinflammation.[4] Most traps patients have reduced blood levels of soluble TNFRSF1a between attacks, with an inappropriately small increase during bouts of fever.[4] The pathogenesis of the 'hyperinflammatory state' in TRAPS has been variously described to a shedding defect of TNFRsf1a from the cell surface resulting in increased TNF inflammatory signalling or impaired TNF apoptotic signalling.[4] Some low-penetrance TNFRsf1a variants also contribute to the clinical phenotype in individuals carrying other HPF-associated mutations, and have been reported in several disorders such as Behcet disease and systemic lupus erythematosus.[4] Tumor necrosis factors (TNF) are important inflammatory cytokines that exert a wide range of effects on tissues throughout the body by interacting with two cell-surface receptors: TNF receptor I (TNFRSF1A, TNFR1, p55/p60-TNFR, CD120a) and TNF receptor II (TNFRSF1B, TNFR2, p75/p80-TNFR, CD120b) (reviewed in refs. 6 and 8). TNF-receptor-associated periodic

syndrome (TRAPS; MIM no. 142680), originally termed familial hibernian fever in the prototype family, is a hereditary autoinflammatory disorder recently shown to involve autosomal-dominant missense mutations in the *TNFRSF1A* gene (reviewed in refs. 6 and 8). Both the clinical and the genetic features of TRAPS are distinct from those of familial mediterranean fever (FMF), hyperimmunoglobulinaemia D syndrome (HIDS) and other periodic fever syndromes (reviewed in refs. 6 and 8). The cell-surface TNFRSF1A protein is a single polypeptide consisting of four cysteine-rich ectodomains (CRD1-4), each of which contains three cysteinecysteine disulphide bonds, a transmembrane region and a large intracellular region that interacts with signalling molecules (reviewed in refs. 6 and 8). The intracellular region includes a death domain (DD) that can initiate signalling cascades for both apoptosis (via caspase activation), and cytokine production and other inflammatory effects (via nuclear factor-B activation). The membrane distal CRD1, also known as the preligand assembly domain (PLAD), is thought to undergo homologous interactions to form TNFRSF1A homotrimers; CRD2 and CRD3 interact with homotrimers of TNF. Over 30 different single nucleotide mutations of the *TNFRSF1A* gene have been identified in patients with TRAPS, which cause single amino acid substitutions mainly in CRD1, CRD2 or CRD3. About half of these mutations affect the highly conserved cysteine residues that are involved in disulphide bond formation, and one splice mutation has been identified that results in the insertion of four amino acids in CRD2 (reviewed in refs. 6 and 8). A TRAPS-associated missense mutation has also been described that involves an amino acid mutation at the base of the extracellular region of TNFRSF1A (I199N), proximal to the transmembrane region and close to the cleavage site for induced receptor shedding (reviewed in refs. 6 and 8). Patients with TRAPS have low blood levels of soluble TNFRSF1A (sTNFRSF1A) that do not increase above the normal range during inflammatory attacks (in contrast to with rheumatoid arthritis, where sTNFRSF1A levels start in the normal range and can increase twenty-fold). Also, the leucocytes of some patients show reduced shedding of TNFRSF1A upon stimulation. These findings have led to the hypothesis that TNF is not adequately neutralized by the low levels of sTNFRSF1A in TRAPS, resulting in exaggerated inflammatory effects. However, not all the TRAPS-related TNFRSF1A mutations result in defective receptor shedding by leucocytes, indicating that other pathophysiological mechanisms may also be involved. The importance of understanding these mechanisms extends beyond TRAPS, as there is evidence that certain of the TNFRSF1A mutations (e.g., R92Q) are also associated with much more common inflammatory diseases, such as rheumatoid arthritis and systemic lupus erythematosus.[8,9] It is possible that some of the TRAPS-related mutations have significant structural effects on TNFRSF1A conformation that may affect the subcellular distribution and/or functional properties of the receptor. Indeed, a growing number of diseases are now understood to result from the pathological effects of misfolded proteins. These 'protein conformational disorders' include Alzheimer disease, Huntington disease and Parkinson disease (that affect the central nervous system), and alpha1-antitrypsin deficiency (affecting the liver). Recently, it has been shown that reduced NFκB signalling is a feature of four TRAPS mutations.[10] It has been demonstrated that the he T50K TRAPS-related variant is capable of sustaining inappropriate NFκB activation, resulting in persistent auto-inflammation in target organs such as skin, synovial membrane and the central nervous system.[11] It has been concluded that some of the inflammatory processes seen in TRAPS do not involve direct interaction of TNF with its receptors, but that other proinflammatory mechanisms capable of upregulating TNFRI expression may cause cellular activation through the NFκB signaling pathway.[11]

Skin Lesions and other Clinial Findings in TRAPS

In most cases reported in the literature, TRAPS acute inflammatory phases have a duration of 1 to 3 weeks. They are characterised by the presence of fever, abdominal pain, myalgias and various types of skin lesions including migratory patches, skin rashes, erysepela-like erythema, edematous plaques, urticaria, periorbital edema, aphthous stomatitis and/or conjunctivitis.[1,3,5,12] Histologically, skin lesions in TRAPS are characterized by a perivascular dermal infiltrate of lymphocytes and monocytes.[3] Other clinical symptoms that may be present in TRAPS include ptosis, calf pain, testicular pain, arthralgias, rigors, breathnesless, fatigue and lymphadenopathy.[5] Additionally, it has been shown that long term inflammatory response can lead to AA amyloidosis, the most common targets being the kidneys and liver. As the incidence of TRAPS is very low, there are only a few reports in the literature about its cutaneous manifestations. In the original article of Williamson et al.[13] "painful erythemas" were described in 11 patients, mostly affecting the arms, partly associated with underlying myalgia. In 1997, McDermott et al.[14] reported skin eruptions in 11 (69%) of 16 individuals with TRAPS. While nine individuals exhibited red patches, eight had indurated lesions. It has been reported that cutaneous lesions were commonly associated with underlying myalgia.[3] In many cases, the myalgia moves down the extremity in conjunction with the skin lesions, affecting different muscle groups and limiting joint movement during the progression of the attack. In some cases, the evolution of cutaneous lesions has been observed and described.[3] Early lesions consisted of solitary or groups of erythematous macules and papules. As these lesions progressed, they expanded at the periphery, coalescing into large patches or plaques. This finding of migrating large patches and plaques associated with underlying myalgia differs from the hyperimmunoglobulinemia D syndrome (HIDS), which is characterized by fixed small lesion. Toro et al. also found ecchymosis in six patients. Drewe et al.[5] reported the clinical course of seven patients suffering from TRAPS. Four of these patients developed skin rash. Toro et al.[3] reported cutaneous findings in 25 patients with a clinical and molecular diagnosis of TRAPS. In these patients, the skin eruptions usually lasted 4 to 21 days (mean, 13 days). Twenty-one (84%) of these 25 patients presented with migratory erythematous macules and patches and 10 (40%) had edematous dermal plaques. Conjunctivitis, characterized by pain and redness and/or periorbital edema, was present in 11 patients (44%). Interestingly, the

majority of these patients had their first skin eruption during the first two years of life and all patients had fever associated with the skin eruption. Most of these patients had associated abdominal pain [22 (88%)] and myalgia [20 (80%)]. Other symptoms included arthralgia [13 (52%)], pleuritic chest pain [10 (40%)] and headache [17 (68%)]. It has been reported that cutaneous histologic findings of TRAPS are nonspecific. In this study, TRAPS could not be differentiated histologically from a viral exanthem or serum sickness-like reaction.[3] Histologic examination of ten biopsy specimens of lesional skin revealed a superficial and deep perivascular and interstitial infiltrate of lymphocytes and monocytes.[3] Immunohistochemically, the infiltrate consisted of $CD3^+$, $CD4^+$, $CD8^+$, $CD68^+$, $CD79a^-$ and $CD20^-$ cells. None of these biopsy specimens that were analyzed histologically and immunohistochemically showed multinucleated macrophages or granulomatous or leukocytoclastic vasculitis. Sequence analysis revealed that in these patients, all the mutations were missense mutations in exons 2 through 4 of *TNFRSF1A*, directly affecting the extracellular domain of the protein.[3]

Treatment of Skin Lesions and other Symptoms in TRAPS

Any study of a periodic fever syndrome is problematic due to its low prevalence and the unpredictable frequency and severity of attacks. The symptoms in most patients with TRAPS respond poorly to colchicine use.[3] This is in contrast to familial Mediterranean fever (FMF), another well-characterized inherited periodic fever syndrome, where the clinical response to colchicine use is an important clinical feature. About 90 to 95% of patients with FMF note marked improvement after treatment with the drug and about 75% of patients with FMF experience almost complete remission.[3] Neutrophils in patients with FMF receiving colchicine have reduced migratory ability.[15,16] In addition, it has been shown that colchicine alters the expression of the E-selectin on vascular endothelium and L-selectin in neutrophils.[17] Both these adhesion molecules are essential for extravasation and migration to the site of inflammation. How colchicine prevents or ameliorates the attacks of FMF is still unknown. Additionally, colchicine is effective in preventing the development of amyloidosis in patients with FMF.[18] Variable results with cyclosporine, intravenous immunoglobulin and corticosteroids have been observed in patients with inherited periodic fever syndromes including HIDS. Articular manifestations in HIDS respond to either nonsteroidal anti-inflammatory drugs or corticosteroids. Preliminary results[19] using lovastatin have been encouraging for the treatment of HIDS. In most individuals with TRAPS, the symptoms respond rapidly to corticosteroid use.[3] Oral glucocorticoid therapy has been shown to be effective when used in dosages greater than 20 mg/day. Nonsteroidal anti-inflammatory drugs are effective in mild attacks. The pathogenic hypothesis involving defective TNFRSF1A shedding suggests that medications targeting TNF may be effective in TRAPS.[2] Drewe et al. reported their findings in TRAPS patients treated with TNF-targeting etanercept.[5] In this clinical study, all seven patients completed 24 weeks of etanercept therapy and no serious adverse events or hospital admissions were reported. Only minor injection site reactions and in one patient upper respiratory tract infections were noted whilst patients were treated with etanercept. Corticosteroid requirements were reduced during etanercept treatment in all five steroid-responsive patients giving a Wilcoxon Signed Rank Test value of $p = 0.028$.[5] No severe attacks requiring methylprednisolone infusions occurred during treatment with etanercept. CRP and ESR were reduced in five patients out of the seven patients whilst on etanercept and this reached statistical significance for three out of the five TRAPS patients (Mann-Whitney test). All patients completed daily scores whilst on etanercept although scores were incomplete for two patients whilst off treatment. One patient demonstrated the greatest difference in scores with 91 and 90% on etanercept compared with 71 and 67% off treatment for general well-being and pain and stiffness, respectively. Six out of the seven patients showed a significant difference in either or both of the two scoring systems.One patient reported 16 and 18 days with fever of at least 37.5°C whilst on etanercept compared with 13 and 39 days with fever off treatment for the two treatment cycles. Another patient developed an unanticipated remission of her nephrotic syndrome as previously reported.[7]

The availability of a p55TNFr-Ig fusion protein for patients with a mutation in this receptor prompted Drewe et al.[7] to give a single infusion of p55TNFr-Ig to a severely affected TRAPS patient. The p55TNFr-Ig infusion appeared well tolerated, although administration during an attack could have potentially masked side-effects. Following p55TNFr-Ig treatment the patient continued with one of his severest attacks of TRAPS. The subsequent finding that he had become steroid dependent raises the possibility that this attack could have been exacerbated or even precipitated by discontinuation of corticosteroids immediately prior to the p55TNFr-Ig infusion. Once the patient was established on permanent oral corticosteroids (day 10 onwards), he continued to experience TRAPS-related symptoms. It has been reported that a single infusion of p55TNFr-Ig may improve symptoms for up to 8 weeks in rheumatoid arthritis.[7] The p55TNFr-Ig could therefore have provided some benefit to the TRAPS patient treated in weeks 2–10 when corticosteroid withdrawal was not a complicating factor. The effect of p55TNFr-Ig given during an acute attack of TRAPS is inconclusive and p55TNFr-Ig has also not been studied on a prophylactic basis in TRAPS. It has been suggested that the use of p55TNFr-Ig could be considered for other patients with TRAPS, although possibly using prophylactic administration.[7] Published data demonstrating reduction in corticosteroid use support the use of etanercept in TRAPS.[7] This could be of great value to patients who have failed with multiple immunosuppressive strategies. Different TNFRSF1A mutations may affect treatment response, but larger studies are warranted to assess the place of etanercept and other therapeutic options in the treatment of TRAPS.

Topical treatment of TRAPS skin lesions, that may include options to alter the immune response such as topical application of antiinflammatory agents (e.g., corticosteroids or tacrolimus) or cooling dressings, has not been reported to be of high clinical

effeccacy. However, topical treatment with antiinflammatory agents (e.g., corticosteroids) may be of benefit in some patients.

Conclusions

Cutaneous findings are of particular importance in TRAPS, for they have been shown to give direction to the diagnosis of TRAPS and in most cases their treatment is challenging. As the incidence of TRAPS is very low, no prospective randomized controlled trials and only a few studies with case numbers up to twenty-five patients have been published. Recent progress in our understanding of TRAPS pathogenesis has resulted in new therapeutic options to treat this chronic disease. Larger studies are warranted to establish diagnostic and therapeutic guidelines and to assess the place of etanercept and other therapeutic options in the treatment of TRAPS.

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