

Accepted Article

TNF receptor-associated periodic syndrome (TRAPS) mimicking chronic spontaneous urticaria

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Keywords: urticaria, TNF receptor-associated periodic syndrome (TRAPS),
autoinflammatory disease, etanercept,

Words: 598

Tables : 1

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jdv.14327

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Funding

The authors declare that no funding was received for the present study.

Conflict of interest

The authors declare that they have no conflict of interest.

Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is a rare (about one per million) autosomal dominant autoinflammatory disease being typically characterized by recurrent fever episodes accompanied by variable gastrointestinal, musculoskeletal, neurological, lymphoid, urogenital and skin symptoms (table 1) [1-3].

We report on a 21 year old non atopic male with prediagnosed IgA deficiency, Marfan syndrome and hypothyroidism who first presented in our university allergy centre with three year history of antihistamine resistant, only slightly itching urticarial rash being accompanied by fatigue. Histology showed superficial perivascular lymphocytic dermatitis with eosinophils and intravascular neutrophil granulocytes. Routine laboratory parameters were within normal range but due to persistently elevated antistreptolysin-titers, without any focal infection detectable, he unsuccessfully received antibiotic treatment. Urticarial rash was only improved by recurrent cycles of systemic methylprednisolone. Under the diagnosis of chronic spontaneous urticaria (CSU) we then treated him with omalizumab subcutaneously (300-600mg once monthly). Symptoms initially seemed to improve during summer time but therapy was stopped after 18 months due to complete recurrence of urticarial rash and persistence of fatigue.

Further investigations showed elevated S-100 (0,499 ng/ml, normal <0,105) and serum amyloid A (SAA) 8,6 mg/l (<6,4), unilateral medio-cochlear sensorineural hearing loss at 2kHz and beginning osteoporosis. Under the suspicion of cryopyrine associated periodic syndrome, we applied IL-1 antagonists canakinumab (150 mg once subcutaneously) without any effect. Subsequently, cyclosporine A (CSA, 3mg/kg bodyweight) led to a complete remission of symptoms but due to side effects we had to stop this therapy and symptoms recurred.

Meanwhile, genetic analysis had revealed a mutation in TNFRSF1A gene in R92Q which led to diagnosis of TRAPS. The two commonest TNFRSF1A variants, P46L and R92Q, are present in 2% of Caucasian people, most of them asymptomatic, and how they cause

inflammatory disease in a minority is not fully understood [2]. It was suggested that a TNF receptor 1 protein is misfolded in TRAPS and thereby leads to trigger autoinflammatory pathways [2].

Out of 158 patients of the EURO-TRAPS registry, 88% reported that their symptoms occurred in recurrent episodes and only 7% had continuous symptoms. Just over a quarter of patients could identify triggers for their attacks, the commonest being emotional stress, menstrual cycle, fatigue, infections, exercise and vaccinations. Urticarial skin lesions were present in 25% but even though the R92Q variant, as in our patient, was reported to be associated with mild phenotype monosymptomatic manifestation seems to be atypical [2-4]. The median age of TRAPS symptom manifestation is 4.3 years, but in 22% of patients symptoms are reported to start in adulthood [2]. As there is no functional diagnostic test available the diagnosis relies on clinical symptoms in combination with genetic analysis. It is still unknown if in addition to TNFRSF1A gene mutations other contributing genetic and environmental factors are necessary to cause the disease [5]. Congenital IgA deficiency with recurrent infections may have been one trigger in our patient.

Therapy in TRAPS has been mainly based on TNF receptor antagonist etanercept, of which 50mg twice weekly quickly and persistently (6 months) resolved our patient's symptoms and led to SAA and S100 normalization. When TNF receptor antagonists are ineffective [6], therapy with IL-1 antagonists may be considered [7] but, as in our patient, non-responders may occur [8]. It was speculated that inefficacy to IL-1 antagonists might be due to a rarer TNFRSF1A variant (T50M) which is typically associated with more severe disease [2]. More recently, anti-IL6 receptor tocilizumab was also reported to be efficient in TRAPS [9].

In summary, we present a case of TRAPS with monosymptomatic urticarial rash being falsely diagnosed as CSU and showing a good clinical response to etanercept.

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Table 1: Mucocutaneous symptoms in 158 pediatric and adult patients with different variants of TRAPS (according to Lachmann et al. [2])

Skin	Mucosa
Urticarial rash without typical itching (25%)	Erythematous pharyngitis (18%)
Migratory rash (18%)	Aphthous stomatitis (10%)
Erysipelas exanthema (4%)	Exudative pharyngitis (3%)
Localized erythema (3%)	
Generalised erythema (2%)	
Pseudofolliculitis (2%)	
Palpable purpura (1%)	

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