Tumour necrosis factor receptor-associated periodic syndrome caused by a rare mutation in the *TNFRSF1A* gene, and with excellent response to etanercept treatment

Sirs,

The tumour necrosis factor receptor-associated periodic syndrome (TRAPS) is a dominantly inherited multisystem chronic inflammatory disorder caused by mutations in the gene *TNFRSF1A* (12p13) encoding the 55-kD receptor for tumour necrosis factor-α, a transmembrane glycoprotein that consists of an extracellular domain constituted by 4 tandem repeat cystein-rich domains (CRD1-4), a transmembrane region and an intracellular death domain (1). TNFRSF1A extracellular domain mutations negatively affect both TNFRSF1A expression and function (1-3).

The majority of the mutations are localised in the CRD1 and CRD2 domains. In fact, most mutations described involve cysteine residues and are associated with a higher disease penetrance. However, several variants involving other residues have been reported (4).

Characteristic features of TRAPS include recurrent fever, lasting typically more than 1 week, periorbital oedema, a migratory erythematous plaque with underlying myalgia and arthralgia; serious membrane inflammation is also possible (1).

We report the first patients with a typical TRAPS phenotype associated to a heterozygous D12E mutation, characterized by a T to G transition in exon 2 which substitutes an acid aspartic for an acid glutamic at position 12 (D12E; c.123T>G) of *TNFRSF1A* gene, and also confirm etanercept as an efficacious treatment.

In April 2008 an 11-year-old female was admitted in our Unit for high fever unresponsive to antibiotic treatment over the past four days. Clinical examination revealed a mild hepatomegaly and splenomegaly, lower limb myalgia, conjunctivitis, an erythematous rash on the face and a maculopapular rash involving trunk, ankles and lower limbs.

Past medical history was relevant for a previous episode of fever of 2-weeks duration (November 2007) during which a chest x-ray showed a pulmonary opacity. The child was discharged with a diagnosis of pneumonia.

Laboratory investigations carried out during admission found an elevated eritrocyte sedimentation rate (120 mm/hour; normal<25), C-reactive protein (1.85 mg/dl; normal <0,5) and serum amyloid A (166 mg/L; normal<10) (SAA). A full infectious work-up, complement components, antinuclear autoantibodies and renal function were normal or negative. Urinary mevalonic acid concentrations during the febrile attack were also measured and were not found to be increased. A bone marrow aspiration ruled out a neoplasia. A second chest x-ray showed similar findings compared to the previous, despite antibiotic treatment. The fever resolved within 20 days. Based on the clinical picture and after the exclusion of autoimmune diseases, of haematological malignancies and of infectious pathologies, the patient was suspected of having TRAPS and was started on treatment with prednisone (1 mg/kg/daily).

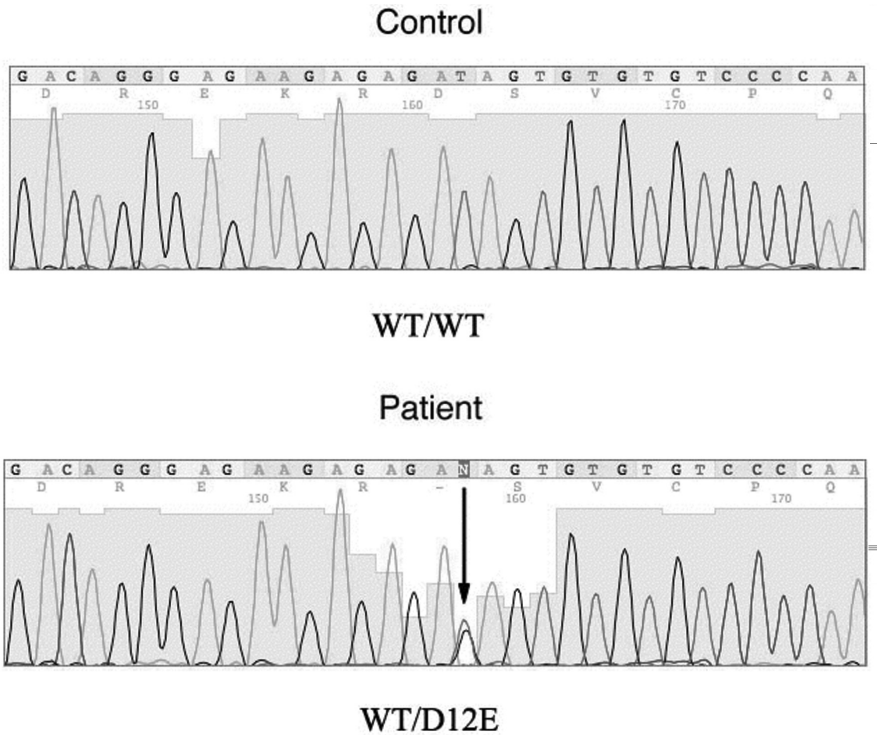

Fig. 1. DNA sequencing demonstrating the heterozygous D12E mutation; no mutation was revealed in healthy donors. WT = wild type.

After written consent, the patient's DNA was analysed for mutations in *TNFRSF1A* (Exons 2-4,6), *MEFV* (Exons 1-10) and *NLRP3* (Exon 3) genes.

The DNA analysis revealed a heterozygous D12E mutation in *TNFRSF1A* gene (Fig. 1). No mutations were found in *MEFV* and *NLRP3* genes. The patient was diagnosed with TRAPS. Since her mother, father and brother, who were clinically healthy, did not carry the mutation, the mutation is likely to have occurred *de novo*.

After a month of well being, the patient had an analogous febrile attack during the corticosteroid treatment and a chest x-ray examination revealed unchanged findings. The fever resolved within 3 weeks.

Prednisone did not prevent the recurrence of fever, the subsequent attack was not milder than the previous and the duration of fever was unchanged. Furthermore, SAA was increased during prednisone treatment, also during the symptom-free interval. Prednisone was interrupted and the patient started treatment with etanercept 0.4 mg/kg subcutaneously twice weekly with a rapid cessation of her clinical symptoms and normalization of SAA levels.

The chest x-ray, repeated 3 months after starting treatment, revealed the complete resolution of lung opacities, thus suggesting an atypical inflammatory involvement of lung parenchyma.

The D12E mutation was first supposed to determine a milder disease phenotype and a shorter duration of fever attacks (2). The same mutation has been subsequently described by Gattorno *et al*. in a patient carrying also a homozygous M680I mutation on the *MEFV* gene; that patient was classified as having familial Mediterranean fever (5). In our patient, since the age of 10, the fever was associated with most of the typical signs of TRAPS and also the prolonged duration of fever was typical of TRAPS.

Missense substitutions of cysteine or threonine residues are associated with a more aggressive disease course (3), whereas mutations not affecting cysteine residues determine a milder disease and a shorter duration of fever attacks. However, patients with severe TRAPS caused by a non-cysteine mutation (T50M) in the *TNFRSF1A* gene have been reported (4, 6, 7). The functional implication of the D12E mutation is under investigation.

Although TNF-α levels are not significantly elevated compared with healthy controls, etanercept has been shown to elicit a beneficial response in patients with TRAPS-associated amyloidosis (6), has a therapeutic

effect in most patients (8, 9) and can prevent flares (10). Failure has also been described (8, 9).

In summary, we report the first patients with a typical TRAPS phenotype associated to the D12E mutation, even if conclusions on phenotype-genotype correlation cannot be drawn based on a single report, and we also confirm etanercept as an efficacious treatment.

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