Adult-onset tumour necrosis factor receptor-associated periodic syndrome presenting with refractory chronic arthritis

Sirs,

Tumour necrosis factor receptor-associated periodic syndrome (TRAPS) is the most common autosomal dominant autoinflammatory disorder, caused by mutations in the *TNFRSF1A* gene, encoding the 55-kD receptor for tumour necrosis factor (TNF)-α (TNFRSF1A) (1). The actual knowledge of TRAPS, its pathogenetic mechanisms, and its genotype-phenotype correlations are still limited due to both rarity of the disease and continuous stream of discoveries of new genetic variants. Common TRAPS clinical features include recurrent fever episodes, periorbital oedema, a migratory erythematous skin rash, myalgia, musculoskeletal symptoms and serosal membranes inflammation, while systemic amyloidosis is the main deadly long-term complication. With regard to joint involvement, arthralgia may occur during fever attacks in about 2/3 of patients; on the contrary, the development of frank arthritis is less common (2, 3). Although disease onset usually occurs during childhood, a delayed onset has also been described and it seems to be related to low-penetrance *TNFRSF1A* mutations, also responsible for milder phenotypes, atypical inflammatory responses and/or oligosymptomatic disease course (4, 5).

We herein describe three patients carrying mutations in the *TNFRSF1A* gene and presenting with unusual clinical features of TRAPS, characterised by the development of chronic arthritis involving the peripheral joints in one patient and sacroiliac joints in the other two.

All these patients underwent detailed investigations to rule out potential underlying diseases, such as chronic infections, autoimmune diseases, or blood disorders. Since the most common causes of sacroiliitis were excluded, patients were diagnosed with TRAPS relying on clinical features and genetic test confirmation. Table I summarises the patients' main general and clinical manifestations.

TRAPS is the most variable entity among autoinflammatory diseases in terms of clinical manifestations and wideness of *TNFRSF1A* mutation spectrum (6). In general terms, patients with TRAPS complain of febrile episodes, sometimes associated with atypical inflammatory symptoms, mimicking other autoinflammatory or autoimmune diseases and hindering appropriate differential diagnosis. Musculoskeletal involvement in TRAPS is mostly characterised by arthralgias rather than arthritides, which might occur as asymmetrical nonerosive oligo-monoarthritis with predilection for large joints, mainly involving knees, shoulders, elbows, hips, temporo-mandibular joints, and wrists (7). Our patients showed recurring and longlasting episodes of fever associated with arthritides involving the small joints of feet (T50M), wrists (R92Q) and sacroiliac joints (V95M; R92Q), as atypical signs of TRAPS. Joint involvement had a chronic course in all cases, and treatment with non-steroidal anti-inflammatory drugs was ineffective. Prednisone was able to induce an amelioration of joint symptoms, though at the highest doses, and was suspended. Furthermore, following the

Table I. Main general data related to TRAPS patients presented in this report.

Patient	1	2	3
Gender	Male	Female	Female
TRAPS mutation	T50M	V95M	R92Q
Age at disease onset (years)	19	33	15
Disease duration (years)	17	5	3
Fever peaks	Up to 39.7°C	Up to 40°C	Up to 42°C
Fever duration (days)	21	7-10	5-8
Fever episodes/year	6-7	10-12	Up to 10
Triggers	Unknown	Unknown	Physical/mental stress
Disease course	Recurrent	Recurrent	Chronic
Arthritis course	Chronic	Chronic	Chronic
Skin features	Erythematous skin rash in the left abdominal region and at the level of the ankles	-	-
Arthralgia	Ankles	Low-back pain, shoulders	Low-back pain, wrists, ankles
Myalgia	+	+	-
Arthritis	First, second and third MTF joints of the right foot, first and second MTF joints of the left foot, left knee synovitis	-	Wrist
Sacroileitis	-	+	+
Ocular manifestations	-	-	-
Gastrointestinal manifestations	Abdominal pain with constipation	Abdominal pain	-
Lymphadenopathy	Laterocervical, axillary and inguinal	-	Laterocervical
Cardio-respiratory symptoms	-	-	-
Headache	-	-	+
Fatigue	+	+	+
Past failing treatments	NSAIDs, corticosteroids	NSAIDs, corticosteroids	NSAIDs, corticosteroids, anakinra (100 mg/day)
Current treatment	Canakinumab (150 mg/4 weeks)	Canakinumab (150 mg/4 weeks)	Etanercept (50 mg weekly)
Inflammatory markers during febrile flares			
ESR (n.v. <25 mm/h)	120	86	52
CRP (n.v. <0.5 mg/dL)	20.60	4.56	2.84
SAA (n.v. <10 mg/L)	547.6	740	Up to 134.7

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; SAA: serum amyloid-A; NSAIDs: non-steroidal anti-inflammatory drugs; n.v.: normal values; MTF: metatarsophalangeal.

previous failure of standard treatments, one patient (R92Q) also showed to be resistant to anakinra administration. The other two patients (V95M; T50M) were treated with canakinumab, which led to both clinical amelioration and rapid decrease in inflammatory markers, as already shown in the medical literature (8-10). The patient refractory to anakinra underwent treatment with etanercept, which induced a partial amelioration of symptoms.

Sacroiliitis had been previously reported as a possible clinical expression of TRAPS: firstly, Trost *et al*. have described sacroiliitis in association with myocarditis in an Afro-American boy carrying the P46L low-penetrance *TNFRSF1A* mutation, successfully treated with intravenous methylprednisolone (11). Later, we reported the coexistence of the R92Q mutation in a TRAPS patient with sacroiliitis: in this patient corticosteroid therapy was ineffective, whereas symptoms improved when treatment with etanercept was started (12).

On the basis of our findings it is possible to note how TRAPS occurring in adulthood may be characterised by the presence of unusual signs, such as the development of chronic refractory arthritis, both axial (sacroiliitis) and peripheral (small joints of feet), poorly responsive to conventional treatments. Therefore, compared to childhood, the development of chronic arthritides could represent a hallmark characterising TRAPS in adulthood. In the end, it would be advisable to consider TRAPS diagnosis in those patients with persistent sacroiliitis or peripheral arthritis associated with prolonged fevers, placing TRAPS itself with adult onset in the differential diagnosis with spondyloarthropathies.

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