Teaching Point
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A nephrotic patient with tumour necrosis factor receptor-associated periodic syndrome, IgA nephropathy and CNS involvement

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Introduction

The periodic fever syndromes are a heterogeneous group of disorders characterized by repeated attacks of fever and localized inflammation, primarily affecting serosal surfaces, the skin and the musculoskeletal system [1]. To date, five periodic fever syndromes have been characterized on the basis of their clinical features. Except for the periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome, the affected genes are known. Familial Mediterranean fever (FMF) caused by mutations in the Mediterranean fever (MEFV) gene, and the hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS) due to mutations in the mevalonate kinase (MVK) gene have an autosomal recessive inheritance [1]. The others are autosomal dominant disorders: Cryopyrin-associated periodic syndrome (CAPS) as a consequence of heterozygous mutations in the cold-induced autoinflammatory syndrome 1 (CIAS1) gene, and the tumour necrosis factor receptor-associated periodic syndrome (TRAPS) caused by dominantly inherited mutations in the tumour necrosis factor receptor superfamily IA (TNFRSF1A) gene [1].

FMF, CAPS and TRAPS are accompanied by elevated levels of amyloid A (SAA) [2,3], an acute-phase protein. The recurring fever attacks result in a deposition and degradation of SAA, which can lead to amyloidosis in patients suffering from these syndromes [2,3]. This report describes a 39-year-old man diagnosed with TRAPS.

Case

A 39-year-old white male complained of recurrent attacks of fever from 39 to 40°C with chills, abdominal pain, vomiting, severe myalgia and arthralgia, sore throat and conjunctivitis since the age of 6 months. These fever episodes were accompanied by a brisk increase in inflammatory parameters. The attacks returned after irregular intervals of 2 or 3 months and lasted for 2–3 weeks. Periorbital oedemas, skin lesions or lymphadenopathy were never observed.

At 13 and 15 years of age, the patient had two laparotomies because of acute abdomen with appendectomy on the second occasion. During adolescence, he received a long-term steroid treatment, which partially alleviated the symptoms. In addition, he was treated with colchicine without any detectable benefit under the erroneous assumption that he suffered from FMF. During the last 5 years, a painful migratory erythematous skin rash presented during the attacks. Within the last year, the patient developed neurological symptoms such as diplopia, dizziness and paraesthesia of the left side of his face. Conventional T1-weighted magnetic resonance imaging (MRI) of the brain disclosed a singular hyperintense lesion of 20 mm in the left cerebellar peduncle (Figure 1). The lesion’s location was atypical for multiple sclerosis. Cerebrospinal fluid analysis and electroencephalography were normal. A stereotactic biopsy was performed. Histological examination of the serial biopsy from the pontine region showed a dense polymorphocellular infiltration of inflammatory cells. There was a predominance of CD3-immunopositive...
T-Cells, which were predominantly CD-8-positive cytotoxic T-Cells. Furthermore, there were also mononuclear cells of monocytic and histiocytic appearance and a very small portion of CD-20-immunopositive B-cells. Granulocytes could not be found (Figure 2A). A moderate reactive gliosis was present and a diffuse activation of CD68-positive microglial cells could be found. Malignant aspects such as lymphoblastoid elements were absent. Special stainings (PAS, Ziehl-Neelsen, Grocott and Gram) did not give an indication for an infectious agent. Correlates of specific demyelination were also absent.

Ultrastructural investigations confirmed the lymphohistocytoid infiltrate. Activated lymphocytes, monocytes and histiocytic differentiations could be seen, some with Langerhans cell-like manifestations in form of the Birbeck-like granules (Figure 2B). Brain parenchyma was altered in an unspecific manner with figures of recurrent de- and remyelination. No correlates of primary demyelination with activated microglial proliferations and myelin shredding were observed.

The patient’s SAA concentration was elevated (217 mg/l; normal value: < 5.0 mg/l). Furthermore, between the fever attacks, the man had elevated IgD (511 IU/ml; normal value: < 100 IU/ml), IgA (8.5 g/l; normal value: < 4 g/l) and IgG values (18.1 g/l; normal value: < 16 g/l). This prompted us to search for genetic variations in the TNFRSF1A and MVK genes. The genetic analyses disclosed a heterozygous T → C nucleotide substitution (c.250T > C) within exon 3 of the TNFRSF1A gene, resulting in the substitution of cysteine (TGT) at amino acid position 55 by arginine (CGT; C55R). In contrast, no pathogenic mutation was detected in the coding exons and in the neighbouring intronic sequences of the MVK gene.

Following confirmation of the diagnosis, our patient was treated with corticosteroids again, with good clinical response.

During the last few years, renal function has also deteriorated. The patient has had nephrotic range proteinuria (11.7 g/24h) and elevated serum creatinine (0.26 mmol/l; calculated glomerular filtration rate (GFR): 39 ml/min) and albumin concentrations (3.33 mmol/l). For further diagnostics, a kidney biopsy was performed. Interestingly, no signs of amyloidosis were found. Histologically, a tubular atrophy with segmental interstitial fibrosis and inflammation was detected, representing the signs of a mesangial IgA nephropathy. With respect to this finding, the patient’s history was studied and revealed no addiction to drinking.
A nephrotic patient with TRAPS

**Discussion**

Tumour necrosis factor-α (TNF-α) is a pleiotropic molecule, which induces cytokine secretion, activation of leukocytes, fever and cachexia [4]. Activation of the TNF receptor causes cleavage and shedding of its extracellular parts into circulation, where it acts as an inhibitor of TNF-α. Mutations in the extracellular domains of the TNF receptor type 1 cause the autosomal dominantly inherited chronic inflammatory disorder TRAPS. So far, more than 40 pathogenic mutations have been detected, most of them being located in the first two cysteine-rich subdomains of the protein encoded by exons 2, 3 and 4 of the TNFRSF1A gene [5–7]. In some, but not all, TNF-R1 variants, it was demonstrated that the structural changes of the protein interfere with receptor shedding, leading to continuous TNF-α signalling and, hence, uncontrolled inflammation [6].

While colchicine is usually ineffective in the treatment of this syndrome [8], patients respond to high doses of oral prednisolone (>20 mg). There is a dramatic initial response that wanes with time, necessitating a dose adjustment [9]. Given the pathological features of this disorder, inhibition of TNF signalling with etanercept is another therapeutic option. There is increasing evidence that this drug may be clinically useful in reducing disease activity and allowing dose reduction of corticosteroids [10,11]. There are also data that suggest a therapy with etanercept may reverse or slow the progression of systemic AA amyloidosis [12].

For patients with TRAPS, the prognosis is mainly determined by the presence or absence of amyloidosis. An AA amyloidosis occurs in up to 25% of the affected patients [11]. Amyloid deposits generally lead to renal impairment, but hepatic failure has also been noted [6]. Since proteinuria is the initial manifestation of renal amyloidosis, it is advisable to screen urine samples from TRAPS patients and their affected family members regularly [11]. Surprisingly, our TRAPS patient suffered from renal impairment, but showed no signs of amyloidosis in renal biopsy. In contrast, an IgA nephropathy was diagnosed in histology. Up to now, no association of TRAPS with an IgA nephropathy has been described. Therefore, we cannot exclude that the kidney disease is not due to the elevated serum IgA concentrations observed in the patient. A careful screening for signs of amyloidosis will nevertheless be necessary in the future. Development of an AA amyloidosis could influence the further therapeutic strategy, especially the use of etanercept.

Up to now, only one case of a TRAPS patient with central nervous symptoms has been described [13,14]. A therapy attempt with etanercept did not halt the progression [13]. Pathogenetically, the enhanced TNF/TNFR signalling, which plays a key role in TRAPS [11], might also be implicated in inflammatory processes of the central nervous system, so that one may speculate that the CNS symptoms seen in our patient are part of the TRAPS phenotype [15]. Although in MRI, it might look like a demyelinating disease [14], stereotactic biopsy performed in our patient revealed a T-cell-mediated lymphoproliferative process and showed no myelin destruction. ‘Why only some TRAPS patients develop neurological problems?’ is presently unclear and needs further investigation.

**Teaching points**

1. In patients with amyloidosis of unknown origin, the differential diagnosis should include periodic fever syndromes like FMF or TRAPS.
2. Patients with TRAPS or FMF should be regularly screened for proteinuria and amyloidosis every 6 months.
3. TRAPS patients may develop central nervous symptoms as part of the disease phenotype.
4. A corticosteroid therapy at the beginning of a fever attack or a regular treatment with etanercept can alleviate the symptoms in TRAPS patients and may reverse or slow the progression of systemic AA amyloidosis. Whether it has any influence on the central nervous symptoms and their progression is as yet unclear.

**Conflict of interest statement.** None declared.

**References**

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