Macrophage activation syndrome as the initial manifestation of tumour necrosis factor receptor 1-associated periodic syndrome (TRAPS)

G. Horneff, A. Rhouma, C. Weber, P. Lohse

ABSTRACT
An 11-year-old Turkish girl from a non-consanguineous family was suffering from joint pain, fever, hepatosplenomegaly, and respiratory insufficiency. Laboratory abnormalities were thrombocytopenia, elevated levels of serum transaminases, lactate dehydrogenase, and C-reactive protein (up to 193 mg/l), a hyperferritinaemia of 8030 ng/ml, and an increased sCD25. The tentative diagnosis of macrophage activation syndrome (MAS) was confirmed by the detection of a histiocytosis with haemophagocytosis in the bone marrow. Treatment with dexamethasone, cyclosporine A, and VP16 was successful. However, the diagnosis of MAS on the background of a systemic juvenile idiopathic arthritis was questionable because of recurrent, spontaneously remitting fever phases of 5 to 7 days duration without an obvious infectious aetiology. A positive family history of febrile episodes in three consecutive generations raised the suspicion of a dominantly inherited disease. Genetic studies revealed a likely pathogenetically relevant E56D/p.Glu85Asp mutation in exon 3 of the TNFRSF1A gene. Alterations of the MEFV gene, in contrast, were not found.

To our knowledge, this is the first case of a macrophage activation syndrome as the initial manifestation of TRAPS. Similar case reports in patients with the far more common familial Mediterranean fever (FMF) have been published already.

Introduction
The macrophage activation syndrome (MAS) is a severe, life-threatening complication of rheumatoid diseases, particularly systemic juvenile idiopathic arthritis (sJIA; 1). It results from an uncontrolled activation of macrophages with excessive release of cytokines as a consequence of an immunodysregulation. In analogy to genetic (primary) histiocytosis syndromes with defects in cellular cytotoxicity, NK cell dysfunction is pathogenetically relevant (2). Histiocytotic syndroms observed in the context of autoimmune diseases, immunodeficiencies, malignancies, viral infections, or after exposure to drugs are regarded as secondary histiocytosis and in paediatric rheumatology traditionally known as MAS (3).

Typical symptoms of MAS are persistent fever (as opposed to alternating fever in sJIA), hepatosplenomegaly, lymphadenopathy, and encephalopathy. Less commonly, pneumonia, rash, panniculitis, and signs of bleeding are observed. Classical clinical laboratory characteristics are reduced number of leukocytes and platelets, anaemia, increased transaminases, increased LDH, coagulation disorders with increased prothrombin and partial thromboplastin time, a reduced fibrinogen, and elevated D-dimers, a decreasing or “conspicuously” normal erythrocyte sedimentation rate, and elevated serum triglycerides. Immunological characteristics are increased soluble interleukin-2 receptors (sCD25) and a decreased NK cell activity. The latter in combination with a decreased responsibility of NK cells to interleukin (IL)-18 has also been described as a hallmark of immunodysregulation in systemic JIA (4). In addition, elevated serum ferritin levels up to 50,000 ng/ml are very characteristic. The diagnosis is confirmed by the presence of a haemophagocytosis in bone marrow or in tissues (liver, lymph nodes) (5).

The tumour necrosis factor receptor 1-associated periodic syndrome...
(TRAPS) is an autosomal dominantly inherited autoinflammatory disease characterised by recurrent attacks of fever (6). It is caused by mutations in the TNFRSF1A gene on chromosome 12p13.31, which encodes the TNF receptor 1 (TNFR1). By activating the “nuclear factor kappa B” (NF-κB), this receptor is involved in inflammatory reactions (7).

Over 120 different mutations have been identified in the TNFRSF1A gene (8). The clinical spectrum of patients with TRAPS is very heterogeneous. The frequent R92Q variant is also found in healthy individuals or leads to a less distinctive and milder phenotype (9). Clinically, periods of fever with a duration of more than five days are characteristic symptoms of affected children. During the fever flares, parameters of inflammation such as the C-reactive protein (CRP), the erythrocyte sedimentation rate (ESR), serum amyloid A (SAA), and the interleukins IL-6 and IL-8 are increased and may decrease or normalise in between (10). A reactive SAA amyloidosis develops in about 15%–25% of the patients (11).

Pathophysiologically, a disturbed shedding of TNF receptors with consecutive reduction of soluble TNF receptors in the blood and the lack of TNF neutralisation was initially described, but a disturbed protein folding with subsequent intracellular dysregulation of the NF-κB signalling pathway and an increased production of cytokines including IL-1β appears to be a much more common cause of the disease (6, 7). The latter mechanism may explain the frequent failure of extracellular TNF neutralisation with etanercept or TNF antibodies (11, 12). In contrast, a blockade of IL-1β with canakinumab, a human monoclonal antibody against this protein, was effective in an open trial of 20 patients regardless of the underlying mutation (13).

Case report

An 11-year-old Turkish girl from a non-consanguineous family in poor general condition presented with fever and polyarthralgia and arthritis of finger, shoulder and knee joints. Upon antibiotics, a generalised rash was noted in an outside clinic. Her outstanding symptom was a massive, painful hepatosplenomegaly. Because of respiratory failure, she received intensive medical treatment. Prominent laboratory abnormalities were a thrombocytopenia with inconspicuous remaining cell lines, a significant CRP increase of 193 mg/L and an increase of the serum transaminases ASAT (GOT) and ALT (GPT) as well as lactate dehydrogenase (LDH). Other laboratory findings included a significantly increased serum ferritin of 8030 ng/ml and an increase of the soluble interleukin-2 receptor sCD25. Bone marrow biopsy provided evidence of a histiocytosis with haemophagocytosis. With the diagnosis of a macrophage activation syndrome in the context of a systemic juvenile idiopathic arthritis, treatment with dexamethasone, cyclosporin A, and VP16 was instituted according to the HLH 2004 protocol (14).

Table I. Course of laboratory parameters upon combined treatment with dexamethasone, etoposide and cyclosporine A.

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<tr>
<td>Month 2</td>
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<td>327</td>
<td>80/46</td>
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<td>48/25</td>
<td>144.5</td>
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</table>

Treatment with dexamethasone was given for 2 months, etoposide for 2.5 months and cyclosporine A for 3 months.

Fig. 1. Pedigree of the family with fever episodes in three generations typical of an autosomal dominantly inherited disease. All affected family members carried a heterozygous G>C nucleotide substitution in exon 3 of the TNFRSF1A gene, which resulted in the replacement of amino acid 56 of the mature protein, glutamic acid (GAG), by aspartic acid (GAC; E56D or p.Glu85Asp). The father of the index patient was also a mutation carrier, but he was free of symptoms.
Because of the family history, the diagnosis of a hereditary autoinflammatory disease was suspected and a molecular genetic work-up was started. Genetic studies detected a likely pathogenetically relevant glutamic acid (GAG)-to-aspartic acid (GAC) substitution at amino acid position 56 of the mature protein (E56D or p.Glu85Asp) encoded by exon 3 of the TNFRSF1A gene while exons 2, 3 and 10 of the MEFV gene were not altered. The excretion of mevalonic acid in the urine also was not increased. Treatment with anakinra was continued under the diagnosis of TRAPS for four years now. During this time, the girl remained in complete remission with the exception of a febrile flare during a summer vacation due to a reduced compliance.

**Discussion**

The patient presented is to our knowledge the first case of a MAS as the initial manifestation of TRAPS. The diagnosis of MAS was made on the basis of characteristic blood changes, a massive hyperferritinaemia, an increase of soluble CD25, a significant CRP increase, and an increase in transaminases and LDH and was confirmed by the detection of histiocytosis with haemophagocytosis in bone marrow.

MAS can be fatal. Early detection is therefore highly important for rapid and appropriate treatment (1).

The terms haemophagocytosis syndrome (HS) and macrophage activation syndrome (MAS) are often used interchangeably. In HS, the circulating macrophages phagocytose particularly erythrocytes (15). A HS can occur both primary and secondary. In primary familial or sporadic forms, various genetic mutations in the **PRF1**, **UNCI3D**, **STX11**, and **STXBP2** genes are responsible for the disease (15). The secondary type can be found associated with infections, malignancies, or autoimmune diseases.

The pathogenesis of MAS in the context of sJIA is not fully understood. A reduced cytotoxic activity may already be part of the pathogenesis of sJIA (16). When there is evidence for active sJIA, a low **PRF1** gene expression with a resulting reduced activity of NK (natural killer) cells and cytotoxic CD8+ T-lymphocytes has been described (16, 17, 18). This insufficiency consecutively reduces the inherent potency for limiting/interrupting the proinflammatory response (15). In patients with MAS, the NK cell and CD8+ T-lymphocyte inefficiency is maximal. The prolonged activation of lymphocytes and macrophages results in a cytokine overproduction and finally in haemophagocytosis.

Particularly in patients with systemic JIA, but also in other rheumatic diseases such as systemic lupus erythematosus, MAS has to be considered as an important differential diagnosis in the event of fever and other inflammatory conditions. The typical laboratory findings (cytopenias, transaminases and LDH increased, fibrinogen decreased, increasing fasting triglycerides) can be detected very rapidly in any laboratory. Particular interest should be given to the elevation of the acute phase protein ferritin.

Treatment is based on recommendations of the MAS Histiocytosis Society guidelines with methylprednisolone, cyclosporine, and etoposide (13, 19). Depending on the severity of the manifestation, successful treatment with corticosteroids and cyclosporine A, or the application of intravenous immunoglobulins, tumour necrosis factor antagonist (etanercept), and interleukin-1

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**CASE REPORT**

**Fig. 2.** Laboratory parameters CRP, ESR, and SAA during four years of anakinra treatment. (normal: CRP < 6mg/l, ESR < 20 mm/h, SAA < 10mg/l)

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sacroiliac joint, and status post MAS 3 years earlier.

At the initial presentation, the 14-year-old girl was in a reduced general status of health, had a significantly cushingoid moon face, was febrile with temperatures of 39.3°C, and had a pale skin color without a rash. Heart, lungs, and abdomen were unremarkable. There were also no signs of infection. Joint pain was present in both shoulders and hips. A joint swelling or movement restriction, however, were not found. The family history taken revealed fever episodes in three consecutive generations (Fig. 2). Kidney disease in the family was denied.

Laboratory findings included a leukocytosis with otherwise unremarkable blood counts, a significantly elevated CRP with 213 mg/l and an increased ESR with 50 mm in one hour. Serum amyloid A was slightly increased with 28 mg/l. A CMV or EBV infection could be excluded. Autoantibodies, ANA, ENA, anti-dsDNA, and ANCA were all negative. C3 and C4 complement were also normal. Chest x-ray, ECG, and ECHO provided no pathological result.

Treatment with the interleukin-1 receptor antagonist anakinra in a dosage of 2mg/kg body weight/day was started which led to the immediate disappearance of her fever and control of laboratory abnormalities (Fig. 1). Because of the family history, the diagnosis of a hereditary autoinflammatory disease was suspected and a molecular genetic work-up was started. Genetic studies detected a likely pathogenetically relevant glutamic acid (GAG)-to-aspartic acid (GAC) substitution at amino acid position 56 of the mature protein (E56D or p.Glu85Asp) encoded by exon 3 of the TNFRSF1A gene while exons 2, 3 and 10 of the MEFV gene were not altered. The excretion of mevalonic acid in the urine also was not increased. Treatment with anakinra was continued under the diagnosis of TRAPS for four years now. During this time, the girl remained in complete remission with the exception of a febrile flare during a summer vacation due to a reduced compliance.

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inhibitors (anakinra, canakinumab) as well as plasmapheresis have been described (13, 21).

To our knowledge, a MAS has not been described previously in connection with TRAPS. TRAPS is part of a family of rare hereditary autoinflammatory diseases that are characterised by recurrent bouts of fever and localised inflammation of various organs (6, 22).

In our patient, recurrent, spontaneously remitting fever episodes of 5 to 7 days duration without infectious etiology are documented. The family history revealed fever bouts in three consecutive generations, raising the suspicion of an autosomal dominantly inherited trait. Genetic studies detected a likely pathogenetically relevant point mutation in exon 3 of the TNFRSF1A gene, although the structure-function analysis program PolyPhen2 predicted that this is a benign variant (polymorphism). Treatment with anakinra was successfully continued under the diagnosis of TRAPS for 4 years now.

References