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CASE REPORT

Tumor Necrosis Factor Receptor-associated Periodic Syndrome Mimicking Systemic Juvenile Idiopathic Arthritis

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ABSTRACT

Background: We report two cases of tumor necrosis factor receptor-associated periodic syndrome (TRAPS) in patients in whom systemic juvenile idiopathic arthritis (JIA) had initially been diagnosed or suspected. One patient, given a diagnosis of systemic JIA, was a 10-year-old boy who had presented with recurrent episodes of spike-fever, skin rash, arthritis, and myalgia. The other patient was his 7-year-old sister, who presented with similar symptoms and was suspected of having systemic JIA.

Methods: Serum levels of soluble tumor necrosis factor receptor super family 1A (TNFRSF1A), TNF-alpha, Interleukin (IL) -6, and C-reactive protein (CRP) were measured in two siblings and JIA patients. In addition, DNA sequencing of the *TNFRSF1A* gene in two siblings was also performed.

Results: A detailed family history showed that their mother had an episode of recurrent fever, arthritis, and myalgia with an increased serum CRP after the delivery of a daughter. Both siblings had serum levels of soluble TNFRSF1A that were below the normal reference range, and that did not reach a level corresponding to that of systemic JIA. On *TNFRSF1A* gene analysis, a single missense mutation resulting in C30Y was found in both siblings.

Conclusions: Based on the clinical features and the *TNFRSF1A* mutation, both siblings were given a diagnosis of TRAPS. The serum levels of soluble TNFRSF1A, measured along with the CRP level, may be a useful screening marker for differentiating TRAPS from systemic JIA.

KEY WORDS

C-reactive protein (CRP), International League of Associations for Rheumatology (ILAR) criteria, juvenile idiopathic arthritis (JIA), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), tumor necrosis factor receptor super family 1A (TNFRSF1A)

INTRODUCTION

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is a rare, autosomal dominant disease that is related to mutations in the soluble TNF receptor super family 1A (TNFRSF1A) gene.[1,2] Compared with normal subjects, TRAPS patients commonly have lower serum levels of soluble TNFRSF1A.[2-6] TRAPS is characterized by recurrent prolonged (>1 week) attacks of fever associated with skin rash, abdominal pain, arthralgia, and myalgia; such episodes may respond favorably to corticosteroid treatment.[2,7] In contrast, systemic juvenile idiopathic arthritis (JIA), a disorder of unknown etiology, is the major autoinflammatory disorder in children. JIA patients may present with symptoms similar to those of TRAPS, such as prolonged fever, skin rash, and arthritis, and may also respond to corti-

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Table 1 Characteristics of systemic JIA and TRAPS

	systemic JIA[8-10]	TRAPS[2,11]
etiology	unknown	mutation of *TNFRSF1A* gene
periodicity of attack	no	yes (1－2 months)
general symptoms	prolonged (＞2－week) spike-fever skin rash serositis (pericarditis) generalized lymphadenopathy enlargement of liver and spleen	prolonged (＞1－week) spike-fever skin rash serositis localized myalgia abdominal pain conjunctivitis periorbital edema
joint symptoms	arthritis	arthralgia (arthritis is less common)
number of joints involved	variable	mono- or oligoarticular
affected joints	variable	knee, shoulder, elbow, hip, finger, wrist, temporomandibular joint
joint destruction	common	rare?
laboratory findings	increased serum IL-1 beta, IL-6, and IL-12 increased serum soluble TNFRSF1A increased acute phase reactants (CRP, serum amyloid A)	increased serum IL-6 and IL-8 decreased serum soluble TNFRSF1A increased acute phase reactants (CRP, serum amyloid A)

costeroid treatment (Table 1).[2,8-11]

We present two cases of TRAPS; one was initially diagnosed as, and the other was suspected to be systemic JIA. The proper diagnosis was suggested when we compared the patients' serum soluble TNFRSF1A levels, measured along with the CRP level, with those found in systemic JIA patients.

CLINICAL SUMMARY

A 10-year-old Japanese boy was referred to our hospital because of a recurrent prolonged (about 2-week) fever, skin rash, abdominal pain, arthritis, and myalgia. He had a history of repetitive episodes of these attacks that had started at age 6 months and recurred at intervals of 1−2 months. At 3 years of age, pericarditis developed. Because of the irregularity of the recurrent attacks, his condition was misdiagnosed as systemic JIA based on the prolonged spike-fever, skin rash, arthritis, and pericarditis, which fulfilled the International League of Associations for Rheumatology (ILAR) criteria.[8] Then he was started on oral predonisolone (about 0.9 mg/kg/day) and cyclosporine. The patient's 7-year-old sister had, at 3 years of age, also presented with similar symptoms, including prolonged fever (<2 weeks), neck pain, abdominal pain, and arthralgia. Although the clinical symptoms did not strictly fulfill the ILAR criteria, she had also been suspected of having systemic JIA and treated with oral prednisolone (1 mg/kg/day). Furthermore, although their 38-year-old mother had not had an obvious episode of periodic fever, she did have an episode of prolonged (<1 month) elevation of C-reactive protein (CRP) accompanied only by fatigue. Moreover, after the delivery of a daughter she had recurrent fever, arthralgia, and myalgia (Fig. 1-a). At the time of referral to our hospital, the 10-year-old boy presented with a low-grade fever, fatigue, and mild arthralgia in the shoulder and knee. No skin rash, abdominal pain, or conjunctivitis was noted. At that time, the patient had a mild to moderate acute phase response, as indicated by the WBC count (25400 /μl), CRP (48 mg/l) and erythrocyte sedimentation rate (68 mm/hour). (However, at a later time when his symptoms were not present, the acute phase response was not observed.) Other initial laboratory investigations showed increased metalloprotease-3 (142 ng/ml), but normal levels of ferritin (63.1 ng/ml), hyaluronic acid (30.4 ng/ml), and immunoglobulin D (0.6 mg/dl). Magnetic resonance imaging with T2 enhancement showed a synovial fluid collection without joint destruction in the left knee (Fig. 2). Since the patient's past history, family history, and the following laboratory findings strongly suggested the diagnosis of TRAPS, we tapered and stopped oral prednisolone treatment during a febrile periods, and added short-term non-steroidal anti-inflammatory drugs during the febrile attacks. During a febrile attack, serum levels of acute-phase reactant protein, cytokines, and cytokine receptors were as follows: CRP 166 mg/l; interleukin-6 (IL-6) 97.9 pg/ml; tumor necrosis factor-alpha (TNF-alpha) <5 pg/ml; soluble TNFRSF1A 1220 pg/ml. During the afebrile period, CRP was 6 mg/l; IL-6 was 0.9 pg/ml; TNF-alpha was <5 pg/ml; and soluble TNFRSF1A was 378 pg/ml (Fig. 3). Serum soluble TNFRSF1A was measured by ELISA (Quantikine Human sTNFR1, R & D Systems Inc.,

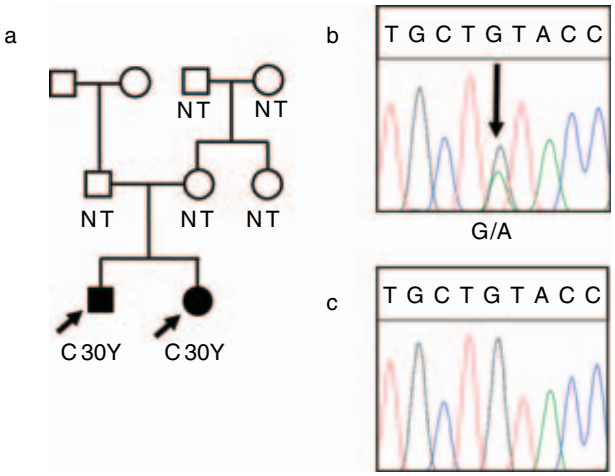

Fig. 1 Gene analysis of family members and DNA sequence of the *TNFRSF1A* gene. **a** Pedigree of the family. Patients (arrow), affected (closed symbol), unaffected (open symbol). NT no genetic analysis performed. **b** DNA sequence electrophoretogram of C30Y mutation (TGT → TAT, indicated by arrow) in TNFRSF1A which was found in both siblings. **c** DNA sequence of control donor with normal pattern (TGT) at position 30.

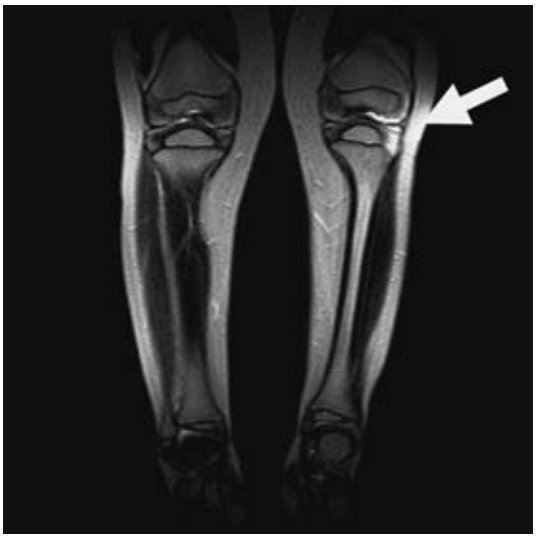

Fig. 2 Magnetic resonance imaging (T2 enhancement) of the 10-year-old boy shows synovial fluid collection in the knee joints (indicated by the arrow).

Minneapolis, USA) and its reference range was 749–1966 pg/ml. Since the patient's 7-year-old sister was also suspected of having TRAPS, her oral prednisolone was discontinued during afebrile periods. Attacks of fever, abdominal pain, and arthralgia were observed at intervals of 1 to 2 months, but disappeared after several days of short-term oral prednisolone treatment. During a febrile attack, the serum level of soluble TNFRSF1A was 1660 pg/ml (CRP: 73 mg/l), and while she was afebrile it was 683 pg/ml (CRP: 3 mg/l). Then, we investigated the serum levels of soluble TNFRSF1A in systemic JIA. In our patients with systemic JIA, soluble TNFRSF1A levels are within the normal range when serum CRP levels are low (<50 mg/l), and markedly increased (>2000 pg/ml) when serum CRP levels are high (>50 mg/l) (Fig. 3).

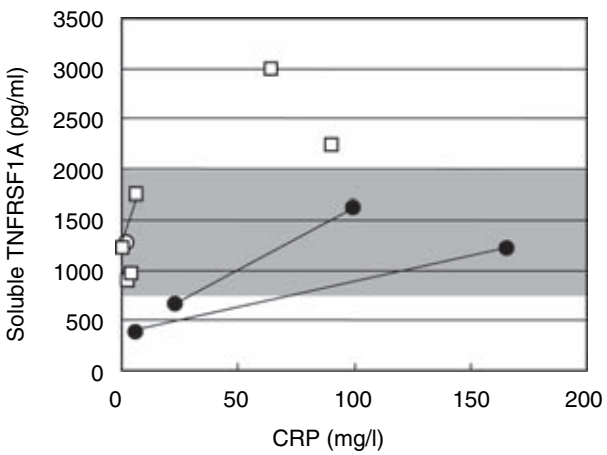

Fig. 3 Measurements of soluble TNFRSF1A and CRP in TRAPS (closed circle), systemic JIA (open square) and normal child (open circle). Connected samples are from the same patients. The normal reference range of soluble TNFRSF1A is indicated by the shaded area.

PATHOLOGICAL FINDINGS

After informed consent for the genetic analysis was obtained from their parents, DNA sequencing of exon 1–10 in the *TNFRSF1A* gene was performed. In both siblings, we found a single missense mutation, a heterozygous G to A transition in exon 2, which substitutes a tyrosine for a cysteine at position 30 (C30Y) (Fig. 1-b). As the same point mutation had been already reported,[12] we confirmed the diagnosis of TRAPS. However, we could not obtain consent for serological nor genetic analysis of the parents themselves.

DISCUSSION

In TRAPS, there are about 50 reported missense mutations of the *TNFSF1A* gene, and many of them are sited at cysteine residues in the extracellular domains of TNFRSF1A. The mutation of C30Y, which was found in our two cases, has been first reported by Obici *et al.*[12,13] and shown to abrogate a disulfide bond in the first extracellular cysteine-rich subdomain of TNFRSF1A. This genetic modification may also result in defective TNFRSF1A shedding, and the

shedding impairment of TNFRSF1A is thought to induce the reduction of soluble TNFRSF1A in the serum.[3,5,14] Indeed, blood levels of soluble TNFRSF1A were below the normal range both in their one case[12] and our two cases. Moreover, the shedding impairment may result both in persistent and increased signal transduction of TNF-alpha and in the reduction of the capacity of soluble TNFRSF1A to catch free TNF-alpha. This can lead to excessive and prolonged inflammatory cytokine production, such as IL-6, as was seen in our cases.[2,12] These cytokines can induce the elevation of conventional inflammatory parameters and, at the same time, may cause various physical findings, including fever and arthritis. However, in TRAPS including the reported case of C30Y,[12] arthritis associated with joint swelling and synovial fluid, as observed in our cases, is less common than arthralgia.[2] It has also been reported that, in systemic JIA, serum levels of inflammatory cytokines, such as IL-1 beta, IL-6, and IL-12 are increased, and that these increased levels are related to disease activity. It has also been suggested that they would play an important role in the associated symptoms (spike-fever, arthritis, and skin rash). Of note, TNF-alpha levels in the serum of JIA patients, even during the active period, have been found to be comparable to those found in normal controls and those with various other diseases.[9] However, TNF-alpha should have a role in the pathogenesis of JIA.[10] Both of our patients showed serum elevations of IL-6 and other acute phase reactants during TRAPS attacks, when fever, arthralgia, and/or arthritis associated with joint swelling were present; these symptoms are commonly seen in systemic JIA. Acute phase reactants, such as CRP and erythrocyte sedimentation rate (ESR), which are induced by inflammatory cytokines, were also markedly increased during the TRAPS attacks. It should be stressed that these clinical and laboratory findings of TRAPS are occasionally mimicked by those of systemic JIA, and thus it is possible to confuse TRAPS with systemic JIA using conventional screening tests.

In our cases, the two affected siblings and the history of their mother with recurrent fever and arthralgia did suggest TRAPS. Usually, several TRAPS symptoms become apparent before the patient reaches 20 years of age,[2,7] but all of the mutation carriers did not present with typical symptoms.[5,15] Since the mother had only asymptomatic CRP elevation before the delivery of her daughter and only then presented with the suggesting symptoms, she may also be a TRAPS patient, but a 'silent mutation carrier' or 'late-onset patient'. It is not clear why there are silent mutation carriers and such late-onset patients. Additional mutations that are associated with periodic fever syndromes have been reported to modify the clinical symptoms or severity.[16] Thus, either sibling may have another mutation, including the *MVK* gene, which may cause differences in their clinical symptoms.

When details of the family history became apparent, we investigated the serum levels of soluble TNFRSF1A to differentiate TRAPS from systemic JIA. In TRAPS, soluble TNFRSF1A levels should be lower than 1000 pg/ml in most patients between attacks and remain low or increase transiently to normal values during attacks.[2-5] In our two cases, both patients showed low levels of soluble TNFRSF1A (378 ng/ml and 683 ng/ml) between the clinical attacks that were associated with low serum levels of CRP. However, the levels of soluble TNFRSF1A reached normal reference levels when serum CRP levels were found to be increased. On the other hand, in systemic JIA, the serum levels of soluble TNFRSF1 have been reported to be increased in the active phase and to have a positive correlation with serum CRP levels.[17] Thus, persistently high soluble TNFRSF1A values are thought to be good markers of systemic JIA activity.[18] However, in our two TRAPS patients, serum CRP levels were occasionally elevated even when they were asymptomatic. Thus, soluble TNFRSF1A levels should be measured repeatedly between the attacks, even when serum CRP levels may be increased. Accordingly, CRP and other acute phase reactants should also be measured at the same time. The measurement of inflammatory cytokines and soluble TNFRSF1A during attacks may also be useful in revealing defective TNFRSF1A shedding, though TNF-alpha and IL-6 were not always elevated in our patients when soluble TNFRSF1A was increased, which may be due to the short half-life of these cytokines.

In conclusion, serum levels of soluble TNFRSF1A and CRP measured at the same time can be useful in differentiating TRAPS from systemic JIA, which can present with similar findings.

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