CASE REPORT

Tumor Necrosis Factor Receptor-1 Associated Periodic Syndrome in Two Brothers: Case Report

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Abstract

Hereditary periodic fever syndromes are a rare group of diseases that should be considered in the differential diagnosis of recurrent fevers of unknown origin. We report a case of two brothers with recurrent, self-limited fever episodes since three years of age associated with prostration, conjunctival hyperemia, abdominal pain, polyarthralgia, and myalgia. Acute phase reactants (C-reactive protein and erythrocyte sedimentation rate) were markedly elevated during crisis and normal during asymptomatic periods. Genetic study identified a mutation in the *TNFRSF1A* gene (*c.242G>T*, *p.Cys81Phe*) and led to the diagnosis of tumor necrosis factor receptor-1 associated periodic syndrome. Treatment with an interleukin-1 receptor antagonist (anakinra) was initiated with symptomatic control. The children father, who suffered from renal failure in the context of AA amyloidosis was also tested and demonstrated to have the same mutation. Tumor necrosis factor receptor-1 associated periodic syndrome is one of the most common hereditary periodic fever syndromes. It has an autosomal dominant pattern with incomplete penetrance, and presents with high interindividual variability of symptoms. AA amyloidosis is the most severe complication of untreated tumor necrosis factor receptor-1 associated periodic syndrome. Based on evidence, treatment with an interleukin-1 receptor antagonist is effective in remitting symptoms and preventing complications.

Keywords: Child; Hereditary Autoinflammatory Diseases/complications; Hereditary Autoinflammatory Diseases/diagnosis; Hereditary Autoinflammatory Diseases/therapy; Interleukin 1 Receptor Antagonist Protein/therapeutic use; Receptors, Tumor Necrosis Factor, Type I/genetics

Keypoints

What is known:
- Hereditary periodic fever syndromes are rare but important diseases in the differential diagnosis of recurrent fevers of unknown origin in childhood.
- Tumor necrosis factor receptor-1 associated periodic syndrome diagnosis is challenging since clinical manifestations can overlap with other hereditary periodic fever syndromes.
- Irreversible long-term complications of AA amyloidosis could be the primary manifestation of the disease.

What is added:
- Identification of a child condition can lead to genetic testing and tumor necrosis factor receptor-1 associated periodic syndrome diagnosis in family members with unexplained symptoms.

Introduction

Fever is a common symptom in childhood, usually associated with self-limited viral infections. When febrile episodes are recurrent and infection, malignancy, and autoimmune diseases are excluded, periodic fever syndromes should be considered in the differential diagnosis. These are a group of rare autoinflammatory conditions leading to abnormal over-expression of the innate immune system.[1,2]

Periodic fevers are characterized by spontaneous recurrent or continuous inflammation manifested by episodes of fever that are associated most frequently with mucocutaneous, osteoarticular, muscular, and gastrointestinal symptoms.[3,4]

Tumor necrosis factor receptor-1 associated periodic

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syndrome (TRAPS) is one of the most common hereditary periodic fever syndromes, with an estimated prevalence of 1-2 per million.[5,6] Tumor necrosis factor receptor-1 associated periodic syndrome has an autosomal dominant pattern with incomplete penetrance, meaning that other members of the family can be affected but with different clinical manifestations.[7,8] Therefore, symptoms are variable and often overlap with those of other periodic fever syndromes. One of the most severe long-term complications is a renal failure caused by secondary amyloidosis. Similar to most rare diseases, a diagnosis of TRAPS is challenging and frequently made based on a high clinical suspicion.[5]

Case Report

We report a case of two male siblings, 6 and 8 years old, who were referred for a pediatric rheumatology consultation upon their father diagnosis of AA amyloidosis of unknown origin.

Both children presented with recurrent, self-limited febrile episodes since 3 years of age, lasting between seven and 15 days, with six month intervals between symptoms. Fever was high (> 39ºC), typically spiked twice a day with associated fatigue, anorexia, bilateral conjunctival hyperemia, intense diffuse abdominal pain, polyarthralgia (predominant in the knees), lower limb and cervical myalgia, and high acute phase reactant values, namely C-reactive protein and erythrocyte sedimentation rate. There were no clinical fever warning signs or presence of oral aphthous ulcers, pharyngitis, other gastrointestinal symptoms, thoracic and neurological symptoms, or such cutaneous manifestations as skin rash. The eldest child had been hospitalized five times between the ages of 3 and 5, and the younger one had been hospitalized once at the age of 4 due to suspected infections without microbiological confirmation. Both siblings had no other previous medical history.

Regarding family history, the father mentioned recurrent febrile periods accompanied by headaches and myalgias since 9 years of age that faded with age. At the age of 44, in the context of nephrotic syndrome, a kidney biopsy revealed AA amyloidosis. There was no history of consanguinity or hereditary diseases.

In the first clinical appointment, both brothers were asymptomatic with no relevant findings on physical exam. Shortly after, the older brother was admitted to inpatient care with an eight-day history of fever, abdominal pain, and neck soreness. On examination he had bilateral conjunctival and pharyngeal hyperemia, small bilateral cervical adenopathies, discomfort with cervical movement and diffuse abdominal tenderness. Blood work revealed leukocytosis (26 000 cells/µL) with neutrophilia (23 900 cells/µL), thrombocytosis (647 000 cells/µL), elevated C-reactive protein (23.65 mg/dL) and erythrocyte sedimentation rate (86 mm/h). Blood and urine culture, rose Bengal and Widal tests as well as serology for Epstein-Barr virus were negative. Chest radiography and abdominal ultrasound showed no abnormal findings. Only antipyretics were administered. At this point, considering the recurrent febrile episodes since a young age in both brothers, absence of confirmed infection and family history, an investigation was initiated for hereditary periodic fever syndrome. Genetic sequencing of the *MEFV* gene for familial Mediterranean fever was performed with no pathogenic mutations found.

In the next year of follow-up, both brothers had two febrile episodes with similar accompanying symptoms and laboratory workup revealed increased C-reactive protein and erythrocyte sedimentation rate, leukocytosis with neutrophilia and thrombocytosis. During crisis, increased levels of serum amyloid A were also documented (769 mg/L and 765 mg/L maximum values for the older and younger brother, respectively). Inflammatory markers returned to normal reference ranges between crisis periods.

The children were started on colchicine (1 mg/day). However, no significant change was observed in the older brother crisis patterns, and the younger brother could not tolerate the drug due to gastrointestinal side effects. The subsequent strategy was to initiate oral glucocorticoids at the beginning of the febrile periods (prednisolone 1 mg/kg/day) with subsequent gradual tapering. Symptoms were quickly and effectively controlled, and the fever resolved within a couple of days.

At this stage, investigation for TRAPS was initiated and identification of the heterozygous mutation *c.242G>T* (*p.Cys81Phe*) in the *TNFRSF1A* gene on chromosome 12 confirmed the diagnosis of tumor necrosis factor receptor-1 associated periodic syndrome. Upon diagnosis, the brothers started anakinra, a recombinant interleukin (IL)-1 receptor antagonist (2 mg/kg/day). In the five-year follow-up period, the older brother had only two febrile episodes, after 11 and 19 months of IL-1 therapy, and the younger brother had three febrile episodes, after 11, 19 and 55 months of anakinra therapy (the first episodes were associated with noncompliance with the therapeutic). There were no significant side effects of treatment.

The father was also tested for tumor necrosis factor

(TNF) receptor mutations after the children diagnosis, and the same mutation was found in the *TNFRSF1A* gene. He developed end-stage renal failure and started anakinra while on hemodialysis, with a striking reduction in serum amyloid A protein levels. He underwent a renal transplant with success and maintained treatment with anti-IL-1.

Discussion

In autoinflammatory diseases, anomalies in the innate immune response create unregulated inflammation.[3] Tumor necrosis factor receptor-1 associated periodic syndrome is caused by mutations in the tumor necrosis factor receptor superfamily member 1A (*TNFRSF1A*) gene on chromosome 12, which leads to the production of an abnormal tumor necrosis factor type 1A receptor.[6] More than 170 sequence variants are known and mostly affect the cysteines underlying the spatial structure of the extracellular portion of the receptor.

An accumulation of misfolded proteins in the endoplasmic reticulum can activate autophagy and the unfolded protein response, leading to increased levels of proinflammatory cytokines including IL-1β, TNFα, and IL-6.[3,6] The exact mechanisms by which *TNFRSF1A* mutations lead to recurrent overactive inflammation remain unclear.[5] Tumor necrosis factor receptor-1 associated periodic syndrome has autosomal dominant transmission, but some variants have incomplete penetrance. Therefore, although family history is commonly positive, there are disparities in terms of the age of onset and clinical manifestations.[2,3]

In accordance with our case report, TRAPS symptoms typically begin in childhood, at around 4 years of age.[4] There is substantial interindividual variability in the age at onset, main symptoms, and frequency and duration of each crisis. The classic symptoms are recurrent high-spiking fever (lasting from five days to three weeks) associated with abdominal pain (70%), myalgia (69%), arthralgia (69%), rash (60%), conjunctivitis (37%), chest pain (33%), periorbital edema (28%), headache (13%) and cervical lymphadenopathy (12%). Some researchers have described periorbital edema and migratory rash as the most specific symptoms of this variety of hereditary fever.[3,5,6] Episodes are usually separated by symptom-free intervals, though some individuals have near continuous manifestations.[3] Although precipitating factors are generally not identified, in some studies 25% of patients recognized triggers such as fatigue, infections, exercise, vaccinations, and emotional stress.[4] Tumor necrosis factor receptor-1 associated periodic syndrome symptoms often overlap with those of other monogenic periodic fever diseases, namely familial Mediterranean fever, cryopyrinopathies and mevalonate kinase deficiency.[3] In our patients, abdominal pain was present which was a typical feature of familial Mediterranean fever and mevalonate kinase deficiency. Arthralgia and myalgia are also symptoms included in the diagnostic criteria of cryopyrinopathies. In addition, neither of the brothers had the reportedly classic manifestations of migratory rash and periorbital edema. As the first approach, we opted for isolated genetic sequencing for familial Mediterranean fever due to its higher prevalence among populations of Mediterranean origin.[3,4]

Tumor necrosis factor receptor-1 associated periodic syndrome is a life-long disease and although fever episodes may spontaneously remit with age, there is a risk of irreversible long-term complications. Serum amyloid A is an acute-phase protein that significantly increases during inflammatory flares of TRAPS and deposits primarily in the kidney. Measurement of serum amyloid A levels has been performed periodically in both siblings to monitor the disease activity and response to therapy.[8] Inflammatory amyloidosis is the most severe complication of untreated tumor necrosis factor receptor-1 associated periodic syndrome, with an estimated prevalence of 18%.[5,6] The most frequent consequence of AA amyloidosis is renal failure, which was diagnosed in the children father and prompted the thorough investigation of the children.[9]

The diagnosis of autoinflammatory diseases is challenging and relies on high clinical suspicion.[5] Age at onset, febrile period duration, and associated manifestations must be systematically inquired. Family history is important to understand patterns of inheritance. Complementary diagnostic tests are warranted, since symptoms are associated with increased acute phase reactants (*eg* C-reactive protein, erythrocyte sedimentation rate, serum amyloid A, fibrinogen, and haptoglobin, as well as neutrophilic leukocytosis and thrombocytosis) during times of active disease.[6] Normalization of these parameters, particularly C-reactive protein, is expected during asymptomatic periods.[3,5] Genetic testing for *TNFRSF1A* mutations confirms the diagnosis. Due to the overlap of clinical manifestations in hereditary periodic fever syndromes, a gene panel should be requested when there is no evident phenotypical suspicion. Alternatively, if there is high clinical suspicion of a particular recurrent fever, Sanger sequencing of the suspected gene can be considered the first diagnostic approach.[3] Diagnostic delay is a common with TRAPS. A case series demonstrated a diagnostic delay of 2.7 years

and 10.3 years in children and adults, respectively.[4] Evidently, identification of a child condition in many cases has led to genetic testing and TRAPS diagnosis in one or several family members who had unexplained symptoms or whose symptoms had been misdiagnosed for years.[1,10-12]

The main goals of treatment are symptom control, systemic inflammation reduction and long-term complication prevention.[2,8] Not all patients require disease-modifying treatments. Although nonsteroidal anti-inflammatory drugs are effective for acute symptoms in 75% of patients, they do not affect the duration of febrile periods. As observed in this case report, colchicine has no proven effect on preventing TRAPS manifestations. Corticosteroids reduce the severity and duration of inflammatory bouts, though their effect tends to wane over time. Moreover, relapses are frequent after withdrawal and they are not useful for preventing amyloidosis.[6,8]

Current data presents IL-1 antagonists as the first-line therapy for TRAPS. Anakinra, an IL-1 receptor blocker, reliably suppresses and prevents all TRAPS clinical manifestations, including those related to AA amyloidosis.[3,5,8] In our case, after initial noncompliance, both brothers complied and tolerated maintenance therapy consisting of daily administration of anakinra. Some studies have also described favorable responses with an on-demand approach to treatment.[6,13] Canakinumab is a second IL-1 inhibitor approved for the treatment of TRAPS,[6] with a potential for better therapeutic adherence (administration every four weeks).[6] This could have been an alternative if the brothers had remained noncompliant to anakinra. At the time of diagnosis, canakinumab had not been approved yet in Europe. In renal transplant recipients, sustained treatment with IL-1 antagonists prevents further amyloid deposition in the renal graft.[9]

Great progress has been made in the diagnosis and treatment of TRAPS, and further understanding of the pathogenetic mechanisms behind TRAPS will help identify specific therapeutic targets and drugs. Additional studies are warranted to evaluate the long-term effects of the present treatments.[6,8]

Author Contribuitions

CR and MO participated in the study conception or design. AF and MMV participated in the drafting of the manuscript. MC, CR and MO participated in the critical revision of the manuscript. All authors approved the final manuscript and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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Síndrome Periódica Associada ao Recetor-1 do Fator de Necrose Tumoral em Dois Irmãos: Caso Clínico

Resumo

As síndromes febris periódicas hereditárias são doenças raras que devem ser consideradas no diagnóstico diferencial de febre recorrente de origem desconhecida. Relatamos o caso de dois irmãos com episódios febris recorrentes, autolimitados, com início aos 3 anos de idade, associados a prostração, hiperemia conjuntival, dor abdominal, poliartralgia e mialgias. Os reagentes da fase aguda (proteína C reativa e velocidade de sedimentação eritrocitária) aumentavam durante a crise e normalizavam na fase assintomática. O estudo genético identificou uma mutação no gene *TNFRSF1A* (*c.242G>T*, p.*Cys81Phe*), e foi assumido o diagnóstico de síndrome periódica associada ao recetor do fator de necrose tumoral. Foi iniciado tratamento com um antagonista do recetor de interleucina-1 (anakinra), com controlo dos sintomas. O pai das crianças, com insuficiência renal no contexto de amiloidose AA, foi também testado e a mesma mutação foi detetada. A síndrome periódica associada ao recetor do fator de necrose tumoral é uma das síndromes febris periódicas hereditárias mais comuns. Possui padrão autossómico dominante com penetrância incompleta, resultando numa grande variabilidade inter-individual de sintomas. A complicação mais grave de síndrome periódica associada ao recetor do fator de necrose tumoral não tratada é a amiloidose AA. O tratamento com antagonista do recetor de interleucina-1 é eficaz na remissão dos sintomas e prevenção de complicações.

Palavras-Chave: Criança; Doenças Hereditárias Autoinflamatórias/complicações; Doenças Hereditárias Autoinflamatórias/diagnóstico; Doenças Hereditárias Autoinflamatórias/tratamento; Proteína Antagonista do Receptor de Interleucina 1/uso terapêutico; Receptores Tipo I de Fatores de Necrose Tumoral/genética