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NOVELTIES IN DERMATOLOGY

Advances in the Diagnosis and Treatment of Tumor Necrosis Factor Receptor–Associated Periodic Syndrome☆

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Abstract Tumor necrosis factor receptor–associated periodic syndrome (TRAPS) is a rare autosomal dominant disease included in the group of autoinflammatory syndromes. It is characterized by recurrent episodes of fever and inflammation in different regions of the body. The main clinical manifestations are myalgia, migratory erythematous rash, periorbital edema, and abdominal pain. The diagnosis is reached using gene analysis and prognosis depends on the appearance of amyloidosis secondary to the recurrent episodes of inflammation. Tumor necrosis factor inhibitors and corticosteroids are the most widely used treatments. In recent years, significant advances have been made in the diagnosis and treatment of TRAPS, thanks to a better understanding of its pathogenesis. Dermatologists must be aware that the skin manifestations of TRAPS are particularly important, as they are often diagnostic.

PALABRAS CLAVE
Enfermedades autoinflamatorias;
Receptor del factor de necrosis tumoral;
Síndrome;
Síndrome periódico asociado al receptor del factor de necrosis tumoral

Novedades en el diagnóstico y tratamiento del síndrome periódico asociado al receptor del factor de necrosis tumoral

Resumen El síndrome periódico asociado al receptor del factor de necrosis tumoral (TRAPS) es una rara enfermedad autosómica dominante que forma parte de los síndromes autoinflamatorios. Se caracteriza por episodios recurrentes de fiebre e inflamación en distintos sitios del organismo, siendo sus principales manifestaciones: las mialgias, el exantema eritematoso migratorio, el edema periorbitario y el dolor abdominal. El diagnóstico se realiza mediante el análisis genético y su pronóstico está determinado por el desarrollo de amiloidosis, secundaria a los episodios inflamatorios repetidos. Los tratamientos más utilizados son los corticoides y los inhibidores del TNF. Durante los últimos años, gracias a un mayor conocimiento de su patogénesis, se han logrado importantes avances en su diagnóstico y tratamiento. Como dermatólogos es importante tener en cuenta que las manifestaciones cutáneas son particularmente importantes en el TRAPS, ya que muchas veces guían al clínico hacia su correcto diagnóstico.

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Concept

Autoinflammatory syndromes are a group of disorders characterized by recurrent fever, localized inflammation, an absence of autoantibodies, and a tendency toward familial aggregation.[1] Autoinflammatory diseases cause several different types of febrile episodes, including fever of unknown origin, periodic fever, and recurrent fever. Differential diagnosis of febrile episodes should therefore include autoinflammatory diseases once infections, malignancies, and autoimmune diseases have been ruled out.[2]

Cytokines are secreted by macrophages and other cells of the immune system in response to pathogens, against which they mount and inflammatory response. In autoinflammatory diseases cytokines are secreted in the absence of pathogenic stimuli.[3]

There are several systemic autoinflammatory diseases with a Mendelian pattern of inheritance for which the causative gene has been identified. This group of diseases is divided into several subgroups (Table 1).[4]

Hereditary periodic fever syndromes constitute the most important subgroup of systemic autoinflammatory diseases. This subgroup comprises 2 diseases with a recessive pattern of inheritance (familial Mediterranean fever [FMF], and hyperimmunoglobulinemia D and periodic fever syndrome [HIDS]) and 1 dominantly-inherited condition (tumor necrosis factor [TNF] receptor-associated periodic syndrome [TRAPS]).

In recent years there has been an exponential increase in interest in autoinflammatory diseases by doctors of different specialties, and in the study of these diseases.

In this review we summarize and discuss new data relating to TRAPS that has been published in the last 5 years. To gather this data, we searched the PubMed database using the search term *TRAPS*. We retrieved 8221 articles, some of which did not pertain to TRAPS. The search term *TRAPS TNF receptor* returned 179 articles. We selected articles that were published within the last 5 years (78 articles in total). We also reviewed the most important references cited in the selected articles.

Table 1 Classification of Hereditary Systemic Autoinflammatory Diseases.

Hereditary periodic fever syndromes
Familial Mediterranean fever
Hyperimmunoglobulinemia D syndrome with periodic fever (HIDS)
TNF receptor-associated periodic syndrome (TRAPS)
Cryopyrin-associated periodic syndromes
FCAS
Muckle-Wells syndrome
CINCA-NOMID syndrome
Pediatric systemic granulomatosis
Blau syndrome
Early onset sarcoidosis
Other hereditary systemic autoinflammatory diseases
PAPA syndrome
CRMO

Abbreviations: CINCA, chronic infantile neurological, cutaneous, and articular syndrome; CRMO, chronic recurrent multifocal osteomyelitis; FCAS, familial cold-induced autoinflammatory syndrome; NOMID, neonatal-onset multisystemic inflammatory disease; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum and acne syndrome.

Table 2 Diagnostic Criteria for Tumor Necrosis Factor Receptor-Associated Periodic Syndrome.

Recurrent episodes of inflammatory symptoms
Fever
Abdominal pain
Myalgia
Migratory macular erythema
Eyelid edema or conjunctivitis
Chest pain
Arthralgia or monoarticular synovitis
Episodes lasting more than 5 days and occurring every 2 to 9 months
Respond to corticosteroids but not to colchicine
Affected family members (not in all cases)
Any ethnic group can be affected

It is not necessary for patients to meet all criteria nor is there a minimum number of criteria required to suspect this syndrome.

Clinical Manifestations

A 1982 study described members of a family of Scandinavian origin who presented episodes of prolonged fever, abdominal pain, myalgia, erythema, conjunctivitis, and/or periorbital edema.[5] This condition was termed Hibernian fever, as distinct from Mediterranean fever.

In 1999, 6 missense mutations (i.e., mutations that result in amino acid changes) were discovered in the gene encoding tumor necrosis factor receptor 1 (*TNFR1*), located on chromosome 12p, in individuals affected by this condition.[6] Following this discovery the acronym TRAPS (TNF-receptor-associated periodic syndrome) was coined.

Although the first cases were described in Irish and Central European populations, TRAPS has been reported in countries throughout the world, including Spain.[7] The sex distribution is approximately 1:1. The main clinical characteristics of TRAPS are summarized in Table 2.[1]

The symptoms of TRAPS generally appear around 3 years of age (preschool age). Attacks are usually prolonged (lasting up to 3 weeks) and recur with variable frequency.

However, some patients present persistent symptoms that increase and decrease in intensity without clear asymptomatic intervals. Some patients have reported that certain factors or situations can trigger the episodes (physical or psychological stress, ovulation, or menstruation) and in some cases patients experience prodromal symptoms (periorbital edema, general malaise, headache).[8]

Patients have described prodromal symptoms such as deep muscle pain that increases progressively to reach maximum intensity after 2 to 3 days and subsequently subsides.

Fever is always present in children but may be absent in adults. The most notable differentiating symptom of TRAPS is myalgia, which normally affects only 1 region of the