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Original article

Guidelines for the management and treatment of periodic fever syndromes familial Mediterranean fever

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ABSTRACT

Objective: To establish guidelines based on scientific evidence for the management of familial Mediterranean fever.
Description of the evidence collection method: The Guideline was prepared from 5 clinical questions that were structured through PICO (Patient, Intervention or indicator, Comparison and Outcome), to search key primary scientific information databases. After defining the potential studies to support the recommendations, these were graduated considering their strength of evidence and grade of recommendation.
Results: 10,341 articles were retrieved and evaluated by title and abstract; from these, 46 articles were selected to support the recommendations.

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Fever
Autoinflammatory syndromes

Recommendations: 1. The diagnosis of FMF is based on clinical manifestations, characterized by recurrent febrile episodes associated with abdominal pain, chest or arthritis of large joints. 2. FMF is a genetic disease presenting an autosomal recessive trait, caused by mutation in the MEFV gene. 3. Laboratory tests are not specific, demonstrating high serum levels of inflammatory proteins in the acute phase of the disease, but also often showing high levels even between attacks. SAA serum levels may be especially useful in monitoring the effectiveness of treatment. 4. The therapy of choice is colchicine; this drug has proven its effectiveness in preventing acute inflammatory episodes and progression toward amyloidosis in adults. 5. Based on the available information, the use of biological drugs appears to be an alternative for patients with FMF who do not respond or are intolerant to therapy with colchicine.

Diretrizes de conduta e tratamento de síndromes febris periódicas associadas a febre familiar do Mediterrâneo

RESUMO

Palavras-chave:
Febre familiar do Mediterrâneo
Diretrizes
Infância
Febre
Síndromes autoinflamatórias

Objetivo: Estabelecer diretrizes baseadas em evidências científicas para manejo da Febre Familiar do Mediterrâneo (FFM).
Descrição do método de coleta de evidência: A Diretriz foi elaborada a partir de 5 questões clínicas que foram estruturadas por meio do P.I.C.O. (Paciente, Intervenção ou Indicador, Comparação e *Outcome*), com busca nas principais bases primárias de informação científica. Após definir os estudos potenciais para sustento das recomendações, estes foram graduados pela força da evidência e grau de recomendação.
Resultados: Foram recuperados, e avaliados pelo título e resumo, 10.341 trabalhos, tendo sido selecionados 46 artigos para sustentar as recomendações.
Recomendações: 1. O diagnóstico da FFM é baseado nas manifestações clínicas, caracterizadas por episódios febris recorrentes associados a dor abdominal, torácica ou artrite de grandes articulações; 2. A FFM é uma doença genética apresentando traço autossômico recessivo ocasionada por mutação no gene MEFV; 3. Exames laboratoriais são inespecíficos demonstrando níveis séricos elevados de proteínas inflamatórias na fase aguda da doença, mas também, com frequência, demonstrando níveis elevados mesmo entre os ataques. Níveis séricos de SAA podem ser especialmente úteis no monitoramento da eficácia do tratamento; 4. A colchicina é a terapia de escolha tendo demonstrado eficácia na prevenção dos episódios inflamatórios agudos e progressão para amiloidose em adultos; 5. Com base na informação disponível, a utilização de medicamentos biológicos parece ser alternativa para pacientes com FFM que não respondem ou que são intolerantes à terapia com colchicina.

Introduction

Periodic fever syndromes are autoinflammatory syndromes and are a group of diseases clinically characterized by recurrent or continuous fever and systemic inflammation, lasting from a few days to several weeks, with intervals without symptoms that may vary in their duration. The presence of crises of predictable development in association with a similar family history may suggest a periodic fever syndrome. Recent advances in the understanding of the molecular basis of inflammation mechanisms allowed the identification of genetic alterations involved in the pathogenesis of these diseases. Currently, the following syndromes are described: familial Mediterranean fever, hyperimmunoglobulinemia D syndrome (HIDS), tumor necrosis factor (TNF) alpha receptor-associated periodic syndrome (TRAPS), periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome, and cryopyrinopathies which include three syndromes: Muckle–Wells syndrome (MWS), familial cold-associated urticaria (FCU) and chronic infantile neurological, cutaneous and articular (CINCA) syndrome. Due to their clinical relevance, the Pediatric Rheumatology Commission of the Brazilian Society of Rheumatology selected three periodic fever syndromes and developed Brazilian Guidelines for the conduct and treatment of familial Mediterranean fever, cryopyrinopathies, and periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome.

Familial Mediterranean fever

Description of the method of evidence collection

The Guideline was prepared from 5 relevant clinical questions related to the management of familial Mediterranean fever (FMF). The questions were structured by the use of PICO (Patient, Intervention or indicator, Comparison and Outcome), allowing the generation of strategies for searching evidence (described after each question, with the number of recovered articles), in the main primary databases of scientific information (Medline/Pubmed, Embase, Lilacs/Scielo, Cochrane Library). The recovered evidence has been selected from a critical evaluation using discriminatory instruments (scores): JADAD and GRADE for Randomized Clinical Trials, and New Castle Ottawa scale for observational studies. After defining the potential studies to support the recommendations, these articles were rated based on the strength of evidence and grade of recommendation, according to the classification of Oxford (available at www.cebm.net), including available evidence of greatest strength.

Summary of grades of recommendation and strength of evidence

A: Experimental or observational studies of higher consistency
B: Experimental or observational studies of lower consistency
C: Case reports (noncontrolled studies).
D: Expert opinion without explicit critical appraisal, or based on physiology or bench research.

Objective

To establish guidelines based on scientific evidence for the management of familial Mediterranean fever (FMF).

1. *When should we suspect that an individual is a carrier of familial Mediterranean fever?*

Strategy

(Familial Mediterranean Fever OR Familial Mediterranean Fever, Autosomal Recessive OR Familial Paroxysmal Polyserositis OR Familial Paroxysmal Polyserositides OR Paroxysmal Polyserositides, Familial OR Paroxysmal Polyserositis, Familial OR Polyserositides, Familial Paroxysmal OR Mediterranean Fever, Familial OR Periodic Disease OR Periodic Diseases OR Wolff's Periodic Disease OR Periodic Peritonitis OR Periodic Peritonitides OR Peritonitis, Periodic OR Polyserositis, Familial Paroxysmal OR Polyserositis, Recurrent) AND Signs and Symptoms. $n = 2518$.

The diagnostic suspicion of familial Mediterranean fever (FMF) is based on clinical manifestations, which are characterized by recurrent febrile episodes associated with abdominal and/or chest pain caused by serositis (peritonitis, pericarditis or pleurisy) and arthritis/synovitis of large joints, accompanied by erysipeloid erythema, whose emergence, in most patients, occurs before the age of 30 (60 and 90% before 10 and 20 years old, respectively)[1,2] (D). The episodes have short duration (1–3 days) with resolution occurring even in the absence of treatment; the periodicity is irregular, varying from once a week to once a year. Between attacks, patients remain asymptomatic. Mediterranean region ancestry is a frequent finding.

The attacks can be triggered by emotional stress, intense physical activity, temperature extremes, viral infection, or even menstruation. The disease usually occurs along with the symptoms of peritonitis and arthritis. However, it may manifest atypically, with only isolated episodes of sudden onset of fever with spontaneous resolution in the absence of signs of serositis[3] (B)[4,5] (D). Patients with FMF may also present nonspecific signs and symptoms mimicking infection, acute appendicitis, cholecystitis and arthritis, which may delay the establishment of the definitive diagnosis.

Abdominal pain is the most common feature of FMF, occurring in around 95% of patients. It may be diffuse or localized, being mild to severe in terms of intensity. Joint involvement is the second most common manifestation. In most cases the arthritis has an acute onset and affects large joints of lower limbs and can last longer than the other manifestations of the disease. Monoarthritis may be the only manifestation of a crisis in 75% of cases.[6] Pain and swelling in the scrotum may occur in preschool children. The most important long-term complication is secondary amyloidosis (AA type)[4] (D).

Recommendation

The diagnosis of FMF is based on clinical manifestations, characterized by recurrent febrile episodes associated with abdominal and chest pain, or arthritis of large joints.

2. *How one determines the genetic diagnosis of familial Mediterranean fever?*

Strategy

(Familial Mediterranean Fever OR Familial Mediterranean Fever, Autosomal Recessive OR Familial Paroxysmal Polyserositis OR Familial Paroxysmal Polyserositides OR Paroxysmal Polyserositides, Familial OR Paroxysmal Polyserositis, Familial OR Polyserositides, Familial Paroxysmal OR Mediterranean Fever, Familial OR Periodic Disease OR Periodic Diseases OR Wolff's Periodic Disease OR Periodic Peritonitis OR Periodic Peritonitides OR Peritonitis, Periodic OR Polyserositis, Familial Paroxysmal OR Polyserositis, Recurrent) AND (Diagnosis[filter]). $n = 705$.

FMF is classified as a hereditary periodic fever syndrome[7] (D). It was first described in 1945, being known under the name of "benign paroxysmal peritonitis"[8] (D). This is a genetic autoinflammatory disease with an autosomal recessive trait, caused by a mutation in the MEFV gene (Mediterranean fever gene) located on the short arm of chromosome 16 (16p13) and encoding a protein composed of 781 amino acids named pyrin or marenostrin. Apparently, this protein plays a critical role in regulating the inflammatory process (modulating interleukin production) and apoptosis[9,10] (D). At least 299 mutations have been described, many of which occur in exon 10 (the greatest in this gene), where one can identify the four primary mutations in the majority of patients with FMF: M694V, V726A,

M680I and M694I[11] (D). The mutation p.Met694V relates to the more severe form of the disease, conferring a high risk for occurrence of amyloidosis[12] (C)[13] (B). However, there is no linearity in genotype–phenotype correlation, with great diversity in clinical expression of patients' carriers of the same mutation in the MEFV gene[14] (C).

The presence of two mutations leading to a homozygous state is found in 60% of subjects, and in 10% a mutation was not identified[3] (B). However, 30% of patients with a typical clinical presentation of FMF show only a single mutation. An evaluation of a population sample identified that the number of individuals with the doubly mutated and not expressed MEFV gene exceeds the number of patients with a diagnosis of FMF. This fact, coupled with the phenotypic variability of FMF, suggests an important role of environmental factors on the clinical expression of FMF[15,16] (B).

Recommendation

FMF is a genetic disease presenting an autosomal recessive trait, and caused by a mutation in the MEFV gene. A more severe disease with high risk for amyloidosis can be seen in patients with p.Met694V mutation, revealing the potential of a genotype–phenotype correlation. Mutations and polymorphisms in genes other than MEFV may have an impact on the development of FMF, or even on the severity of the disease.

3. *Besides genetic studies, what tests should be required for the evaluation of patients with familial Mediterranean fever?*

Strategy

(Familial Mediterranean Fever OR Familial Mediterranean Fever, Autosomal Recessive OR Familial Paroxysmal Polyserositis OR Familial Paroxysmal Polyserositides OR Paroxysmal Polyserositides, Familial OR Paroxysmal Polyserositis, Familial OR Polyserositides, Familial Paroxysmal OR Mediterranean Fever, Familial OR Periodic Disease OR Periodic Diseases OR Wolff's Periodic Disease OR Periodic Peritonitis OR Periodic Peritonitides OR Peritonitis, Periodic OR Polyserositis, Familial Paroxysmal OR Polyserositis, Recurrent) AND (Diagnosis/Broad[filter]). *n* = 6126.

Crises related to FMF are characterized by leukocytosis and high levels of acute phase proteins, for instance, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, haptoglobulin, C3 and C4 fractions of complement, and serum amyloid A protein (SAA)[17] (C). These inflammatory markers help the physician to distinguish FMF-related crises from other diseases such as viral infection, fibromyalgia and irritable bowel syndrome. A persistently high SAA leads to higher probability of developing amyloidosis. Proteinuria, as an indicator of renal amyloidosis, develops years after the onset of an untreated FMF, constituting a late complication. In patients with severe or uncontrolled disease, the levels of acute phase proteins may remain high in the interval between episodes[18] (C).

Recommendation

Laboratory tests are not specific, with high serum levels of inflammatory proteins in the acute phase of this disease, but often, high levels are found even between attacks. SAA levels may be particularly useful in monitoring the effectiveness of treatment.

4. *What is the role of colchicine in the treatment of familial Mediterranean fever?*

Strategy

(Familial Mediterranean Fever OR Familial Mediterranean Fever, Autosomal Recessive OR Familial Paroxysmal Polyserositis OR Familial Paroxysmal Polyserositides OR Paroxysmal Polyserositides, Familial OR Paroxysmal Polyserositis, Familial OR Polyserositides, Familial Paroxysmal OR Mediterranean Fever, Familial OR Periodic Disease OR Periodic Diseases OR Wolff's Periodic Disease OR Periodic Peritonitis OR Periodic Peritonitides OR Peritonitis, Periodic OR Polyserositis, Familial Paroxysmal OR Polyserositis, Recurrent) AND Colchicine AND (Therapy/Broad[filter]). *n* = 696.

Colchicine is a tricyclic alkaloid extracted from plants belonging to *Colchicum* and *Gloriosa* genera. This was the first microtubule destabilizing agent identified, showing antiproliferative activity[19] (D). Over the past 50 years, colchicine has been used in an increasing number of diseases, including FMF, Behcet's syndrome, scleroderma and amyloidosis.

Studies have demonstrated that colchicine inhibits the synthesis of TNFα, leukotriene B4, cyclooxygenase 2 activity, prostaglandin E2, and thromboxane A2[20,21] (D). In monocytes, colchicine reaches higher concentrations than the levels present in the plasma, and their levels are dependent on glycoprotein P. This feature makes it difficult to predict, based on plasma levels, the concentration of colchicine which can be achieved in inflammatory cells, and also explains the lack of response by some patients with FMF, due to the polymorphism of the gene encoding P-glycoprotein. Studies have shown that daily administration of colchicine prevents both the inflammatory attacks and the occurrence of secondary amyloidosis, a major long-term complication of FMF. While most anti-inflammatory effects of colchicine are related to the disruption of microtubule function, with inhibition of chemotaxis of neutrophils and suppression of inflammation, effects on NLRP3 inflammasome activity in macrophages and in the production and maturation of cytokines from dendritic cells have also been observed[22] (C)[23] (D).

The most effective results have been obtained using colchicine for FMF prophylaxis; in such patients, this agent prevented the occurrence of episodes of acute inflammation and also the development of amyloidosis[24–26] (B)[27] (C). Three crossover clinical trials have demonstrated efficacy of colchicine by decreasing the recurrence of inflammatory episodes. One study identified that, among 43 patients, the number of inflammatory episodes fell from 178 during the use of placebo to 29 with the administration of colchicine. In this study, their authors observed a significant fall in the severity of attacks, since 70% of the episodes were considered mild, compared to only 25% with the use of placebo[26] (B).

However, this treatment did not show efficacy in the control of acute attacks, when administered early during the episodes[28] (C).

Although colchicine cannot completely prevent febrile episodes, its use may halt the progression of amyloidosis, reversing proteinuria in the absence of irreversible glomerular damage[29] (C). One study showed that proteinuria development rate after a period of 9–11 years was 1.7% in 960 adult patients who have made a proper use of colchicine versus 49% in 54 patients who did not properly use the drug[24] (B). Among the 86 patients without proteinuria at nephrotic levels before the introduction of colchicine, this drug promoted resolution in five patients and stabilization of proteinuria in 68[24] (B).

Recommendation

Colchicine is the therapy of choice; this drug showed efficacy in preventing acute inflammatory episodes and progression toward amyloidosis in adults.

5. *What is the role of biological agents in the treatment of familial Mediterranean fever?*

Strategy (FMF IL-1 receptor antagonist)

(Familial Mediterranean Fever OR Familial Mediterranean Fever, Autosomal Recessive OR Familial Paroxysmal Polyserositis OR Familial Paroxysmal Polyserositides OR Paroxysmal Polyserositides, Familial OR Paroxysmal Polyserositis, Familial OR Polyserositides, Familial Paroxysmal OR Mediterranean Fever, Familial OR Periodic Disease OR Periodic Diseases OR Wolff's Periodic Disease OR Periodic Peritonitis OR Periodic Peritonitides OR Peritonitis, Periodic OR Polyserositis, Familial Paroxysmal OR Polyserositis, Recurrent) AND (Interleukin 1 Receptor Antagonist Protein OR Anakinra OR Urine-Derived IL1 Inhibitor OR IL1 Inhibitor, Urine-Derived OR Urine Derived IL1 Inhibitor OR IL1 Febrile Inhibitor OR Febrile Inhibitor, IL1) AND (Therapy/Broad[filter]). *n* = 113.

Strategy (FMF and anti-TNF agents)

(Familial Mediterranean Fever OR Familial Mediterranean Fever, Autosomal Recessive OR Familial Paroxysmal Polyserositis OR Familial Paroxysmal Polyserositides OR Paroxysmal Polyserositides, Familial OR Paroxysmal Polyserositis, Familial OR Polyserositides, Familial Paroxysmal OR Mediterranean Fever, Familial OR Periodic Disease OR Periodic Diseases OR Wolff's Periodic Disease OR Periodic Peritonitis OR Periodic Peritonitides OR Peritonitis, Periodic OR Polyserositis, Familial Paroxysmal OR Polyserositis, Recurrent) AND (infliximab OR etanercept OR adalimumab OR golimumab OR certolizumab OR Tumor Necrosis Factor alpha OR Cachectin-Tumor Necrosis Factor OR Cachectin Tumor Necrosis Factor OR TNF alpha OR TNF-alpha OR Tumor Necrosis Factor OR Tumor Necrosis Factor Ligand Superfamily Member 2) AND (Therapy/Broad[filter]). *n* = 183.

IL-1 receptor antagonists

Carriers of FMF show significantly elevated levels of serum TNFα, IL-1β, IL-6 and IL-8[30] (B). Evidence has demonstrated an important role of pyrin in the regulation of caspase-1 activation and subsequent cleavage of the interleukin precursor in its biologically active form (pyrin binds procaspase-1, activating caspase-1, which cleaves pro-IL-1β to its active form)[31] (D). Thus, as elevated levels of IL-1 are related to inflammatory activity, some authors proposed the use of drugs targeting interleukin 1 (IL-1), a proinflammatory cytokine.

The use of IL-1 receptor antagonists in patients with FMF has been described in the following situations: patients with incomplete control of disease activity despite treatment with colchicine (5–10% may be resistant to colchicine); patients with maintenance of high serum levels of SAA, inability to use colchicine because of serious adverse effects, and in cases of disease associated to vasculitis[32–35] (C). Three different types of IL-1 receptor antagonists are available: anakinra is a human recombinant unglycosylated analog of the IL-1 receptor antagonist (rhIL-1Ra); rilonacept is a fusion protein that contains the extracellular portions of type I IL-1 receptor and IL-1 receptor accessory protein.

Anakinra and rilonacept target IL-1α and IL-1β; anakinra acts by binding to IL-1 receptor type I, inhibiting its biological effects, and rilonacept neutralizes IL-1 in blood circulation. On the other hand, canakinumab, a fully humanized monoclonal antibody of the class IgG1, acts specifically against IL-1β[36] (D).

A review conducted in MEDLINE primary database via PubMed could only identify case reports as evidence available to evaluate the effectiveness of IL-1 receptor antagonists in patients with a diagnosis of FMF. One has to consider that, in this kind of study, only positive results tend to be reported. In these studies, treatment with anakinra (children: 1 mg/kg in children; adults; 100 mg/day) or canakinumab (children under 40 kg: 2 mg/kg every eight weeks; adults: 150 mg every eight weeks) showed beneficial results, indicating that drugs targeted to IL-1 receptor antagonism can be good choices when one seeks an additional or alternative treatment for colchicine[37–41] (C). As to the safety of these drugs, pain and signs of inflammation at the injection site were the only adverse events reported during the administration of anakinra and canakinumab.

Despite the uncertainty related to the use of IL-1 receptor antagonists in the treatment of patients with FMF, these agents appear to be viable therapeutic alternatives for patients intolerant or unresponsive to the use of colchicine, as well as for those with renal impairment or elevated levels of SAA, even when taking colchicine.

Anti-TNF agents

The role of tumor necrosis factor α (TNF-α) in the pathogenesis of FMF is not yet clearly defined, but there is some evidence with respect to its clinical manifestations. Serum levels of TNF-α are increased during recurrences of attacks; and decreases in serum levels of TNF-α have been observed in patients under regular treatment with colchicine[42] (D)[30,43] (C). Thus, the use of drugs binding to circulating TNF-α molecules or attaching to the surface of effector cells, inhibiting binding to their receptor, thus obviating the biological effects of TNF-α, may be an alternative for patients with FMF[44] (C).

Studies on the use of anti-TNF agents such as adalimumab, infliximab, and etanercept in patients (mean age: 30 years) diagnosed with FMF and who presented chronic arthritis with or without sacroiliitis as clinical manifestation and that were

resistant to treatment with colchicine, identified, after a mean follow-up of 28 (±18) months, a lower frequency of relapses[45] (C). Recently, a review study conducted in MEDLINE primary database via PubMed found only case reports and case series of patients diagnosed with FMF under treatment with biologic drugs, making a total of 59 patients, of which 25 had been treated with anti-TNF agents (etanercept, infliximab, or adalimumab)[46] (B). Despite the clinical improvement identified among patients with arthritis and/or spondylitis, more robust evidence arising from well-designed clinical trials is needed to evaluate the efficacy and safety of these drugs.

Recommendation

Current data on the use of biological drugs in the treatment of FMF are limited to case reports or case series, and therefore it is a hard task to obtain a quantitative assessment of treatment responses. Based on available information, the use of biologicals appears to be an alternative for patients with FMF nonresponders or intolerant to colchicine. More controlled studies are needed to evaluate the efficacy and safety of this strategy.

Conflict of interests

Maria Teresa R.A. Terreri and Flavio Roberto Sztajnbok serve as speakers for Novartis. Clovis Artur Almeida da Silva has a conflict of interests with *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq 302724/2011-7), Federico Foundation and *Núcleo de Apoio à Pesquisa "Saúde da Criança e do Adolescente"*, USP (NAP-CriAd). The other authors declare no conflict of interests.

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