Palindromic rheumatism: a reappraisal

Palindromic rheumatism (PR) is characterized by acute, usually monoarticular, arthritis occurring intermittently and lasting for a few days. A significant number of patients with PR develop chronic rheumatic disease, especially rheumatoid arthritis (RA). There remains controversy as to whether PR is a disease entity in itself, or just a preclinical or abortive form of RA. Recently, a high frequency of anticitrullinated peptide/protein antibodies, the most specific biomarkers of RA, have been found in serum from PR patients, further strengthening the link with RA. However, although rheumatoid factor and anticitrullinated peptide/protein antibodies positivity are predictors of progression to RA in PR, a significant number of patients with these autoantibodies do not develop RA after a long follow-up. No controlled clinical trials have been carried out in PR and the treatment and management is still empirical. This review exhaustively analyzes and updates the epidemiological, clinical, diagnostic, prognostic and therapeutic aspects of PR, an entity that remains somewhat enigmatic and poorly treated in rheumatology texts.

KEYWORDS: anticitrullinated peptide/protein antibodies = citrullinated = genetic palindromic rheumatism = prognostic = rheumatoid arthritis

Palindromic rheumatism (PR) is an intermittent form of arthritis that in a variable percentage of cases may evolve to chronic disease, usually rheumatoid arthritis (RA). The signs and symptoms of PR are characteristic and although PR is well recognised by rheumatologists, it remains almost unknown by others specialities. PR requires a differential diagnosis with other entities presenting with intermittent arthritis such as microcrystalline arthritis or inflammatory bowel disease, among others. Since the original description of PR by Hench and Rosenberg in 1944 [1], only 193 PubMed entries have dealt with PR, with only 40 in the last 10 years (until May 2013). Likewise, medical textbooks, including those on rheumatology [2,3], pay little attention to PR, which is usually included as a marginal entry in chapters on RA and identified as a presentation of RA.

It has recently been suggested that PR is much more common than previously thought [4] and there is renewed interest in determining whether it is really a separate entity or merely a presentation of RA, as suggested decades ago [5-7]. The high frequency of serological markers, characteristic of RA, in the serum of patients with PR, such as rheumatoid factor (RF) and anticitrullinated peptid/protein antibodies (ACPA) [8] strongly suggest a close relationship between PR and RA, but not all patients with PR develop persistent RA, even after a long follow-up [9]. The risk factors for RA and the optimum therapeutic strategy for PR remain under investigation [5,10]. This manuscript reviews and updates the clinical, diagnostic, prognostic and therapeutic aspects of PR, based on a thorough review of the medical literature, including older reports and data from our series of patients with PR.

Definition & epidemiology

The term 'palindromic' derives from the Greek, 'palin dromein', which means 'returning, recurring', and was used by Hippocrates to denote erysipelas and other conditions that tend to appear repeatedly in the same individual [1]. PR was first observed in 1928 by Hench, who, together with Rosenberg, described the first 34 cases of PR in 1944 [1], characterized by multiple, recurrent, painful attacks of inflammation of the joints and adjacent tissues.

There are few studies on the prevalence of PR, which is often considered a rare disease by nonrheumatologists, but the frequency is significantly lower than that of RA, with some authors suggesting a PR/RA ratio of 1/20 [11]. However, recent epidemiological data from Canada show that the incidence of PR in a cohort of new cases of arthritis seen in a 2-year period was one case of PR for every 1.8 cases of RA [4]. PR affects both sexes, although most series show a predominance of females [9], and the mean age of onset is around 40 years (21–73 years). Familial cases have also been described [12,13]. Some authors suggest that 10–15% of patients with RA begin with an episode of PR [6]. A study in hospitals

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in Catalonia (Spain) found that the presenting disease was PR in 17.5% of patients with RA diagnosed between 2009 and 2010, with a latency period between the onset of symptoms and RA of 15.8 months [14].

Clinical picture

PR is characterized by multiple, sudden, irregularly-recurring afebrile attacks of pain, swelling and/or erythema that affect the joints and adjacent structures. Swelling is considered a fundamental feature of PR; diagnosis should be doubted if all attacks present with only pain and no swelling. Almost any joint may be affected, although there is a predilection for the joints of the hands. In order of frequency, the mostaffected joints are: the metacarpophalangeal joints, the proximal interphalangeal joints, the wrists, knees, shoulders, feet and ankles [7,10,15]. Attacks are usually monoarticular, rarely involving two or more joints simultaneously and the periarticular structures may be affected in up to 30% of cases [16]. There are often repeated attacks in the same joint, although presentations in new locations are common [17]. Attacks commence abruptly, the pain is variable, usually mild, but may sometimes become very severe and disabling [1]. Attacks may last from a few hours to a week, but usually last 24-72 h. The frequency may vary between monthly and daily, and this factor may determine the need for treatment. Constitutional symptoms and fever are rare. The attacks remit spontaneously and patients are completely asymptomatic between them. During attacks, patients may present raised, painful, erythematous plaques, which are nonpitting to pressure, appear and disappear suddenly, have a similar duration and may be located in the affected joint or elsewhere; most often in the forearms, hands, feet and ankles [7]. Up to a third of cases may present intradermal or subcutaneous nodules, principally in the hands, which usually appear in parallel with the joint manifestations [18] and normally disappear within a few days [19]. Remission of attacks during pregnancy and their reactivation 2-3 months later has also been reported [20,21].

Etiologic factors

The etiology of PR has been investigated by various studies but remains uncertain. The sudden onset was initially thought to suggest a possible allergic cause, but studies in patients and their families found no evidence for this. Skin tests were negative or doubtful, and the attacks could not be provoked by the injection of histamine or cured by adrenaline. The original reports on PR also considered an infectious origin, but synovial, nasopharyngeal and serological cultures showed negative results [1]. The possibility that PR attacks are related to a deficit of C1 esterase inhibitor, or complement activation, has been studied without success [22], and the presence of circulating immune complexes has not been demonstrated [23]. It has been reported that stress, excitement, vigorous exercise, cold and psychological factors, such as anxiety, can trigger attacks of PR, although no evidence has been found [24]. Dietary elimination to improve the crises, including the elimination of food that may trigger attacks, such as cheese, fish, canned vegetables (e.g., corn and peas) and eggs, has been suggested [25]. Cases have also been related to the consumption of strawberries [26], grapefruit [27], mint and foods containing nitrate [28], but most of these studies had few patients and were conducted many years ago.

Pathologic findings

Schumacher studied synovial fluid in five patients with PR and found variable cell counts, while histopathology revealed synovial hyperplasia with neutrophilic infiltration [29]. Internal inspection of the joint during attacks revealed no cartilage destruction, pannus formation or tendency to villous proliferation of the synovial membrane. The histological aspect of the subcutaneous nodules is characteristic of nonspecific chronic inflammation [29].

Laboratory findings

The erythrocyte sedimentation rate may be increased during the crisis or just after the attacks, but rarely between attacks [1,19,22]. An Iranian study found that C-reactive protein was elevated in 59% of cases during the attacks, and was normal in the intercritical period [30]. No hemogram or other biochemical alterations have been found [19]. The finding of a high percentage of RF positivity in the first descriptions has been confirmed by all series [24]. RF is positive from the onset in between 30 and 60% of cases [31]. RF positivity predisposes to an increased risk of developing RA and to more severe attacks [16]. More recent studies have shown a high prevalence of ACPA, the most specific serological marker of RA, in the serum of patients with PR, underlining the close relationship between PR and RA [24]. Our group identified a high frequency of ACPA in patients with pure PR, including those not associated with any other rheumatic disease, including RA [8]. We found a prevalence of ACPA of 56.6% in

patients with pure PR (very similar to that of a control group with established RA) and serum titers of ACPA did not differ from those observed in patients with RA; results confirmed by other studies [30,32,33].

In a subsequent follow-up study of 71 patients with pure PR, we found that 52.1% were ACPA positive, mostly at high titers. This study also demonstrated that seroconversion from negative to positive was very uncommon, suggesting that, as seen in RA, ACPA positivity is present in the early stages of the disease and remains stable over time [9]. A recent study has shown that the clinical characteristics of PR differ according to ACPA positivity or negativity [30], with more-frequent attacks of shorter duration in ACPA-positive patients. Antinuclear antibodies may be positive with different prevalent rates reported [32,34].

Genetic factors

Studies of the role of HLA genes, the relationship with PR and the likely evolution to RA have mostly included few patients and shown inconsistent results. Some studies suggest an association with HLA-DR4 [12,35], or DR5 [13], but others have found no relationship [36]. An Italian study found a high frequency of HLA-B16 [37]. Early studies of HLA-DRB1 found no relationship with PR, although few patients were included [34,35]. Later, Maksymowych et al. studied the distribution of HLA-DRB1 in 147 patients and found a significantly higher prevalence of the shared epitope (SE) in patients with PR (65%) and in the RA group (77%) compared with the control group (39%). The increased frequency of the SE was due to increased DRB1-0401 and 0404 alleles and not to the DRB1-01 allele [38]. A high prevalence of DRB1-0803 has been reported in Korean patients with PR [39], while a Taiwanese study found a relationship between PR and mutations in TNF- α receptor 1. Of the ten polymorphisms found, the TNFRSF1A +36 allele and TNFRSF1A +36 A/G genotype were associated with persistent PR. These results suggest that the TNFRSF1A polymorphism plays a role in the etiopathogenesis of PR [40]. In a multicenter study, our group found an unexpectedly high frequency of certain mutations of the MEFV gene in patients with PR, almost exclusively in patients with negative ACPA (12.3%), suggesting that these genes may be involved in some cases of intermittent arthritis indistinguishable from ACPA-negative PR. These patients do not meet the classical criteria for Familial Mediterranean fever [41].

A Japanese group reported that the frequency of homozygous susceptibility of the *PADI4* haplotype was higher in patients with PR, but found no difference between patients who did or did not progress to RA [33].

Diagnostic criteria & differential diagnosis

The diagnosis of PR is essentially clinical. Diagnostic criteria have been described by Guerne, Pasero and Barbieri, and Hannonen et al. (Box 1) [7,11,16]. All emphasize that other causes of intermittent or recurrent arthritis, especially microcrystalline arthritis, autoinflammatory syndromes and arthritis associated with bowel disease, must be ruled out. TABLE 1 shows the entities that may present with intermittent arthritis and require a differential diagnosis with PR. In our opinion, all patients with suspected PR but with negative autoantibodies (RF/ACPA) must be re-evaluated for a correct diagnosis. In Box 2, we suggest some clinical and laboratory data in patients with suspected PR that should alert the clinician to the possibility of other diagnoses.

Imaging studies

The original studies found that radiography showed no joint destruction (erosions) in patients with PR, even those who had suffered more than 100 acute attacks [1]. In cases that have evolved to RA, erosions are not very different from those found in typical cases of RA [19,34].

Box 1. Diagnostic criteria for palindromic rheumatism.

Pasero & Barbieri (1986) [11]

- A history of brief sudden-onset, recurrent attacks of monoarthritis
- Direct observation of one attack by a physician
- More than five attacks in the last 2 years
- Three or more joints involved in different attacks
- Negative x-rays, acute phase reactants and rheumatoid factor
- Exclusion of other recurrent monoarthritides: gout; chondrocalcinosis; intermittent hydrarthrosis; and periodic diseases

Hannonen et al. (1987) [16]

- Recurrent attacks of sudden-onset mono- or poly-arthritis of para-articular soft-tissue inflammation lasting from a few hours to 1 week
- Verification of a least one attack by a physician
- Subsequent attacks in at least three different joints
- Exclusion of other forms of arthritides

Guerne & Weisman (1992) [7]

- Six-month history of brief-sudden-onset and recurrent episodes of monoarthritis or, rarely, polyarthritis or of soft tissue inflammation
- Direct observation of one attack by a physician
- Three or more joints involved in different attacks
- Absence of erosions on radiographs
- Exclusion of other arthritides

Disease	Joint pattern	Duration	Clinical characteristics	Systemic symptoms	Laboratory
Microcrystalline arthritis: gout	Monoarticular 1st MTP (70%)	Days	Presence of crystals in SF Family history	May be present	Uric acid ↑
Microcrystalline arthritis: calcium pyrophosphate crystals	Mono-oligoarticular	Days–weeks	Presence of crystals in SF Typical radiologic findings: chondrocalcinosis	May be present	Nonspecific
Reactive arthritis	Mono-oligoarticular Asymmetric Lower limb dominance	Weeks-months	History of infection (diarrhea and urethritis)	Frequent ocular manifestations	HLA-B27+ (60–80% axial manifestations)
Arthritis associated with inflammatory bowel disease	Mono-oligoarticular Asymmetric Large joints (LL) Axial manifestation (<30%)	Days-months	10% arthritis precedes enteritis Parallel trend to the diseases	Diarrhea, abdominal pain	HLA-B27 ⁺ (50–75% axial manifestations)
Whipple's disease	Mono-oligoarticular Large joints (LL) Axial manifestation (20%)	Days	Multisystemic infection Articular symptoms precedes diagnosis by months/years	Abdominal manifestations: abdominal pain, diarrhea, malabsortion Fever, lymphadenopathy	PAS granules in macrophages (<i>Tropheryma wipplei</i>) <i>HLA-B27</i> + (28%)
Behçet disease	Mono-oligoarticular Asymmetric Large joints	Days–weeks	Ethnic variations	Recurrent ulcers (genital–oral), uveitis, folliculitis, erythema nodosum, CNS involvement	<i>HLA-B51</i> + (10–80%)
Sarcoidosis	Oligopolyarticular Symmetric	Weeks	Possibility of erosive bone lesions	Bilateral hilar lymphadenopathy, pulmonary infiltrates, skin and ocular injuries	ACE ↑ 60%
Familial Mediterranean fever	Monoarticular Large joints (LL)	Hours–days (6–96 h)	Familial history, childhood onset and mutation (<i>MEFV</i>) Chronic arthritis (5%)	Fever, abdominal pain, serositis, proteinuria Complication: amyloidosis	<i>MEFV</i> mutation
TRAPS	Arthralgia of large joints (rare arthritis)	Days–weeks	Childhood onset Autosomal dominant	Fever, myalgia, abdominal pain, serositis, conjunctivitis	<i>TNF-1</i> α gen receptor mutation
HIDS	Large joints (LL)	Days	Childhood onset Autosomal recessive	Fever, diarrhea, lymphadenopathy, rash, oral and genital ulcers	Mevalonate kinase mutation (<i>MVK</i>) IgD ↑, IgA ↑
Celiac disease	Oligopolyarthritis Asymmetric LL dominance Axial manifestation (8%)	Weeks	Asymmetric (nonerosive arthritis)	Abdominal manifestation (diarrhea, abdominal pain, weight loss, malabsorption)	Transglutaminase antibodies + Malabsorption parameters
Intermittent hydrarthrosis	Mono-oligoarticular (knee)	Days	Absence of inflammatory signs Periodic intervals	None	Nonspecific Carriers of mutation <i>MEFV</i> SF: non- or mildly-inflammatory
Relapsing polychondritis	Oligopolyarticular Asymmetric	Days-weeks	Involvement of cartilaginous structures	Ocular, skin, vascular manifestations	Nonspecific
Hyperlipidemia type II–IV	Oligoarticular Small and large joints	Days-weeks	Hyperlipidemia, xanthomas	Fever, rare noninflammatory SF	Elevation of cholesterol and/or triglycerides

Table 1. Differential diagnosis of palindromic rheumatism

Table 1. Differential diagnosis of palindromic rheumatism (cont.).									
Disease	Joint pattern	Duration	Clinical characteristics	Systemic symptoms	Laboratory				
Hereditary angioedema	Periarticular with edema	Days	Nonpainful swelling, facial manifestation	Occasional abdominal pain	Deficit of C1 esterase inhibitor (85%)				
Lyme arthritis	Mono-oligoarticular	Weeks-months	History of tick bite	Erythema migraine	Specific serology				
Allergic eosinophilic synovitis	Oligopolyarticular	Weeks	History of allergies or parasitosis	SF with elevated eosinophils (>10%)	lgE ↑				
ACE: Angiotensin-converting enzyme; HIDS: Hyper immunoglobulin D syndrome; LL: Lower limbs; MTP: Metatarsophalangeal; SF: Synovial fluid; TRAPS: TNF receptor-associated periodic syndrome.									

There are virtually no studies using other imaging techniques such as ultrasound or MRI in patients with PR, although these techniques could detect changes in joint destruction or subclinical synovitis not seen by conventional radiography [42]. Chen *et al.* studied 84 patients diagnosed with PR using ultrasound during the acute attack and found changes suggestive of active synovitis in only 36% of cases, although the percentage was higher in ACPA- and RF-positive patients [43].

The first report using MRI in PR was of a single patient during the acute crisis and found synovial pannus in the carpal bone, and even bone erosions [44]. A study used ultrasound to analyze changes during the acute attack in 15 ACPA-positive PR patients without criteria for RA and confirmed synovitis in nine patients (60%) and positive Doppler signal in six patients (40%). No significant differences between patients with or without synovitis were found with respect to the clinical features, although the possibility that ultrasound evaluation underestimated subtle or rapidly-remitting synovial inflammation could not be excluded: this suggests that synovial pathology may be mild in PR, even in seropositive patients, also this study carried out MRI scans in four patients and found synovitis in three cases and bone oedema in all four patients; findings similar to those found in patients with RA [45]. There are no published studies on imaging during the intercritical phase of PR. Preliminary results from our group suggest that most patients with PR do not have subclinical synovitis with ultrasound Doppler during the intercritical stage [46].

Evolution

The original report by Hench and Rosenberg did not report evolution from PR to RA, but this was demonstrated by later reports [6,8,10,13,15,16]. Classically, the clinical course of PR may follow three patterns: clinical remission of attacks; persistent attacks; and evolution to chronic arthritis or systemic disease (more than 50%), with RA being by far the most frequent. The latency period ranges from weeks to more than 10 years, although it has been found that the risk is much higher in the early years when the symptoms are evolving [47], Ansell and Bywaters suggested that PR is merely a variant or mode of presentation of RA, and that almost all patients with PR eventually evolve to RA if followed long term [6].

A review of PR analyzed data from nine studies (653 patients); 48% of patients continued with persistent PR, 33% progressed to chronic arthritis, 4% progressed to other rheumatic diseases and 15% were in prolonged remission [7]. The differences in progression to chronic diseases may be attributed to immunogenetic factors, the prevalence of RF, patient selection, the diagnostic criteria used and the duration of follow-up. The spectrum of rheumatic diseases involved in addition to RA included: systemic lupus erythematosus, spondyloarthropathy, Wegener's disease, Sjögren's syndrome, psoriatic arthritis, systemic sclerosis, antiphospholipid syndrome, Behçet's disease and polymyalgia rheumatica, among others [7,22].

Prognosis

One of the most interesting and intriguing features of PR is that we do not know the prognostic factors for evolution to chronicity and RA. Knowledge of these factors could allow early identification of and specific therapy for patients with this risk. Studies have analyzed some of the possible clinical, genetic and immunological prognostic factors of evolution. The frequency of attacks (more than one attack per month) could be a risk factor for evolution to RA [34]. Youseff et al. found that RF positivity may be a risk factor for the development of RA in patients with PR [48]. A study of 127 patients, with a mean followup of 6 years, found that female gender, RF positivity, involvement of the small joints (especially proximal interphalangeal joints), and older age at disease onset were associated with an increased risk of evolution to connective tissue disease.

Box 2. Clinical and laboratory data that should alert the clinician to other possible diagnoses in patients with suspected palindromic rheumatism.

- Duration of the crisis for more than a week
- Presence of fever
- Oligoarticular/polyarticular attacks
- = Elevated acute phase reactants (especially during the intercrisis)
- Absence of autoantibodies
- Presence of symptoms suggestive of other entities (skin lesions, intestinal symptoms and serositis, among others)

Female gender, RF positivity and involvement of the small joints together represented an eightfold greater risk of evolution to RA or other connective tissue disease [10]. In a Canadian study of the distribution of *HLA-DRB1* in patients with PR, the multivariate analysis showed that only SE homozygosity was a risk factor for progression to RA, regardless of RF status [38]. A Japanese study found that ACPA positivity and proximal interphalangeal joint involvement were significant predictors of progression to RA, as was, to a lesser extent, *HLA-DRB1*SE* [33].

Currently, it can be affirmed that PR is the only entity where the frequency and levels of ACPA are similar to those seen in RA. It has been shown that ACPA positivity may occur many years before RA develops, and this has been associated with smoking and some genetic characteristics: carriers of the rheumatoid epitope (HLADRB molecules) or PTPN22. A Canadian study found that ACPA positivity in the first year after the diagnosis of PR is associated with a high probability of developing RA (sensitivity of 83% and specificity of 68%) [32]. However, our group recently reported that 72.8% of ACPA-positive PR patients do not evolve to RA or other rheumatic diseases after a mean of 7.5 years from the first determination of ACPA, and that the sensitivity and specificity of ACPA in predicting conversion to RA was 68.7 and 52.7%, respectively [9]. This apparent contradiction is explained by the timing of the ACPA measurement, which was clearly later in our cohort than in the Canadian study (5 and 1 years, respectively), which can create a selection bias toward a more stable form of PR in our patients [5].

Treatment

Various drugs have been used to treat PR, with inconsistent results. There have been no controlled clinical trials, due to the relative rarity of PR [7], the clinical characteristics (self-limited crises) and scarcity of knowledge of the factors that predict progression to RA. Therefore, there is no consensus on the best therapeutic strategy. In the first reports, suggested therapeutic measures included purine-free diets, vaccines, colchicine, eradication of the infectious focus, antihistamines and sulfonamides, all of which were inefficacious [1].

During crises, NSAIDs may be used. A study found that these drugs alleviated the crisis in twothirds of patients [49]. Grattan *et al.* found that NSAIDs improved symptoms during attacks in 68% of patients [50], while a Scandinavian study found that only two out of 60 patients showed improvement of symptoms [16]. Glucocorticoids have also been used, with some improvement during acute attacks [51].

In cases with a higher frequency of attacks, when the attacks are polyarticular, or when the patient has risk factors, the empirical use of disease-modifying antirheumatic drugs should be considered, fundamentally due to the similarity of PR to RA.

The most commonly used disease-modifying antirheumatic drugs are gold salts and antimalarials. Older studies using parenteral gold salts showed a good response in almost 60% of cases [19,52], especially in seropositive PR, with a rapid effect; although with adverse effects, especially mucocutaneous. However, another study found a response of only 20% of gold salts in 43 cases [34].

The response to antimalarials ranges between 15 [33,34] and 80% [48]. In a series of 71 patients treated with chloroquine, most patients showed a decrease in the frequency, duration and severity of the crisis, although 22% of treated patients developed persistent arthritis [48]. In a subsequent retrospective study of 113 patients with PR, in which 62 patients were treated with antimalarials and compared with an untreated control group, 39% of controls evolved to persistent arthritis, compared with 32% of the treated group, although the differences were not significant. However, analysis of the time of evolution to chronic disease showed between-group differences (162 months in the treated group vs 56 months in controls). The authors suggested that treatment with antimalarials slows progression to chronicity rather than preventing progression to RA, and that the treatment is safe in most cases, with few adverse effects [31].

Studies have also evaluated D-penicillamine [53], sulfasalazine [54], chlorambucil, dapsone [55], trimethoprim-sulfamethoxazole (mainly in seronegative patients) [56], minocycline [57], azathioprine [16] and colchicine [58], with varying results. There are no published studies on the use of leflunomide, methotrexate or biologics in PR, except for a case report of a patient with PR associated with hypertrophic osteoarthropathy who had a good response to methotrexate [59].

Conclusion

Controversy remains as to where PR is a separate disease entity, an incomplete or aborted expression of RA, or a preclinical form. Recent evidence that patients with PR have an immunogenic and immunological profile (RF and especially ACPA) that is comparable to RA, reinforces the idea that PR is a syndrome that falls within the clinical spectrum of RA. PR warrants investigation to determine which mechanisms lead to an intermittent disease course, and which result in a chronic course with more aggressive diseases requiring more specific treatment.

Future perspective

The relationship between PR and RA remains controversial. Recent studies have found immunogenetic and immunological similarities with RA, especially the high frequency of ACPA, the most specific serological biomarkers for RA. The reasons why some patients with PR evolve to chronic, destructive disease, such as RA, while others do not, requires further study. The number and type of the distinct citrullinated peptides recognized by ACPA in PR patients, with and without progression to RA, may be of particular interest. Imaging techniques, such as ultrasound and MRI, may shed light on the presence of subclinical synovitis and its significance. Well-designed epidemiological studies could more clearly reveal the prevalence and long-term evolution of PR. Multicenter trials of antirheumatic drugs would help to determine their real efficacy and potential to avoid progression to persistent arthritis.

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Executive summary

Background

Palindromic rheumatism (PR) is a form of intermittent arthritis that is normally little recognized outside the rheumatology community. Its relationship with rheumatoid arthritis (RA) is controversial, although some authors consider it to be an aborted or preclinical form of RA.

Epidemiology

Recent studies have shown that PR is more frequent than previously thought.

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Laboratory & genetic findings

PR shares serological markers with RA, including rheumatoid factor and, especially, anticitrullinated peptide/protein antibodies. Some studies suggest that the genetic background of PR is similar to that of RA, as supported by the presence of the rheumatoid epitope.

Differential diagnosis

There are various diagnostic criteria for PR; however, all agree that other causes of intermittent arthritis, including microcrystal arthritis, enteropathic arthritis, autoinflammatory syndromes and others, must be ruled out.

Evolution & prognosis

A significant number of patients with PR develop chronic arthritis or systemic disease during the evolution of PR, especially RA.
 Although some factors for progression have been identified, including anticitrullinated peptide/protein antibodies positivity, it is unclear why many patients, even anticitrullinated peptide/protein antibodies-positive patients, do not evolve to persistent arthritis.

Treatment

The best treatment strategy for PR remains unclear. Antimalarial drugs have shown clinical efficacy and may delay the evolution to RA.

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