Chapter

Palindromic Rheumatism: Biology and Treatment Options

Ayesha Noor, Ali Raza Ishaq, Fatima Noor, Tahira Younis, Afshan Syed Abbas, Fatima Jalal, Rahmawaty Samad, Sara Mumtaz and Faiza Jabeen

Abstract

Palindromic rheumatism is a syndrome characterized by recurrent, self-resolving, and inflammatory attacks in and around the joints that have long recognized association with rheumatoid arthritis. PR attacks mostly start in small joints i.e. knees, shoulder, and small joints of the hand. Whether PR should be considered as a single disease or prodrome of RA remains a thought-provoking question. Multiple genetic and environmental factors contribute to the development of PR. Many studies have explained the relationship between a high concentration of Anti-CCP antibodies and PR. Potential benefits of Gold therapy have been recognized in literature but still, there are some questions about toxicity and efficacy that need further considerations. In addition to that anti-malarial drugs, Abatacept, Tofacitinib, and Rituximab showed the variable result in different patients and needed further study to validate their medical use. Moreover, yarrow, oat, colchicum, dill, fennel, wild rue, bitter melon, willow, garlic, and burdock seem suitable candidates to treat rheumatoid although their use in PR is still not reported. Additional experimental researches on these drugs lead to an increase in our knowledge to fight against PR in the future using novel therapeutic approaches. We have attempted to cover this topic in a chapter form to provide a comprehensive view and hope that it will serve as a reference for clinicians who treat patients with PR.

Keywords: palindromic rheumatism, rheumatoid arthritis, environmental risk factors, genetic risk factors, therapies

1. Introduction

Palindromic rheumatism constitutes episodic and recurrent attack of articular inflammation that lasts from a few hours to several days which conclude without residual joint damage [1]. PR tends to affect small joints mostly, so the Knees, Shoulder, and small joints of hands are more prone to attack. Characteristic symptoms of PR include pain, swelling, redness, and disability of joints. This idiopathic condition was firstly described by Hench and Rosenberg in 1944 [2–6].

Distinctive features of PR include reoccurrence of attack at regular intervals and symptoms-free periods between attacks. Several studies have shown that about half of patients with PR develop Rheumatoid Arthritis (RA) and other joint diseases in later life [7]. PR is a single disease or spectrum of RE a leading question that is unanswered for 70 years. However, the target tissues are mostly the same in PR and RA [6, 8].

A high concentration of Rheumatoid factor and Anti -CCP antibodies in both PR and RA strengthen the correlation between the two diseases. However, despite these similarities, PR is different from RA in that joints are free of symptoms between attacks. According to research attacks of PR usually affect one joint but other structures can be affected in 30% cases and Rheumatoid nodules also appear in one-third cases of PR. Time of attack is not definite however according to Research in London 50% of patients develop attack of PR in the late afternoon and some others at night time [7–9].

2. Epidemiology

Indeed mounting studies highlight the frequency of PR is significantly lower than RA [9]. Epidemiological data from Canadian research suggest that females are most likely to develop PR than men in both conditions of Arthritis. However, it has been estimated that the average age was 56 years in RA and 49 in PR [10].

3. Etiology

Etiological factors for PR are under investigation and uncertain however intrinsic (gene mutations), extrinsic (external factor lifestyle and smoking) and idiopathic factors seem to be important in PR. Initially, it was believed that allergic agents and infectious agents may provoke the symptoms, but recent studies have shown that even the injection of histamine did not cause PR. It is thought that trauma, stress, anxiety, and cold can stimulate the flares of PR however recent data support the thought. Consumption of nitrate-containing food triggers PR [11].

Several etiological studies suggested that the mutated MEFV Gene seems to be an aggregating factor for the severity of PR [12]. According to Iranian research during the attack of PR level of C-reactive protein was increased in about 50%of cases. Erythrocyte sedimentation rate was also elevated during the attack of PR [13]. Anti-CCP antibodies level was also found high in PR patients [3, 14]. Another study showed that autoantibodies RF and anti-CCP concentration appear to be elevated in PR patients and is thought to be responsible for developing RA and other connective tissue diseases [15]. Further research conducted in PR patients also showed uplift RF concentration in 33.3% of patients and a high concentration of anti-CCP in 38.9% of patients. Another research showed the follow-up of 43 patients to other connective tissue diseases and of 28 patients to RA out of a total of 160 patients of PR [16, 17]. The recently high concentration of anti-CCP antibodies and anti-keratin was found in the patients of PR [11]. Studies have documented that ultrasonography of synovitis of PR patients showed a high concentration of ACPA antibodies in PR patients. These studies suggest the strong relationship between Anti-Cyclic Citrullinted Protein antibodies and Rheumatoid factor in PR and RA [17–19].

Another report has elucidated the role of the HLA Gene on Chromosome 6 which is thought to be responsible for about 30% of all cases of RA [20–22]. It is also reported that the HLA-DRB1 alleles encode for a shared epitope [10] which may be a risk factor for PR and RA [23]. Recent studies also showed a strong prevalence of HLA-DR shared epitope alleles in PR. The homozygosity of SE alleles in PR patients is responsible for the progress of half of the PR cases to RA. A Korean study showed a great prevalence of HLA-DRB1*0803 and HLA-DRB1*1302 in PR patients and these alleles are distinct in PR [24].

Many investigations have concluded that gene involvement in gene–environment interaction is not only one factor for a mutation in HLA-DRB1 but factors affecting gene linkage equilibrium may also cause variation in the gene [25].

Other researchers have demonstrated the role of PADI4 (Protein-arginine deiminase type-4) which is a gene that encodes for enzymes that are responsible for the formation of Citrulline from arginine. It has recently been found that any effect in the stability of PADI4 results in a high level of Anti-CCP antibodies [26]. According to a Chinese study, periodic and episodic attacks of PR show a strong link with PADI4 [18, 22, 26].

TNFα (Tumor Necrosis factor) which are short-lived pro-inflammatory cytokines showed a strong relationship with PR. Another case study investigated TNFRSF1A and TNFRSF1B mutations in PR patients in the Chinese population [27, 28]. Another novel study has indicated that the concentration of cytokines like IL-6 and TNFα was elevated in synovium and serum of patients [29, 30]. It has been reported that TNFα microsatellite polymorphism indicates a close connection with the disease by its association with HLA-DRB1 SE. Autoinflammatory diseases like PR are caused by deregulation in inflammasome components [31]. According to Novel research, the PYCARD\ASC Splice variant has been found in PR patients. This inflammasome-associated mutation may be a risk factor for PR patients. According to this research exon2, PYCARD\ASC is more expressed in patients with PR. PYCARD\ASC mature IL-IB for innate immunity. The inflexibility of PYCARD\ASC leads to more secretions of IL-IB so the exon2 splice variant may be a risk factor for disease in PR patients [32]. The presence of conserved exon2 in DNA of all patients of PR, high amount of NLRP3 (Nucleotide-binding oligomerization domain, Leucine-rich Repeat, and Pyrin domain), and high concentration of IL-1B and IL-18 show the strong association between PR and this gene [33]. Comprehensive pathophysiology of Palindromic rheumatism has shown in **Figure 1**.

Polymorphism in the promoter sequence of Stromelysin 1(MMB- gene) and HLA gene have been studied in recent years. Recent studies indicated a close

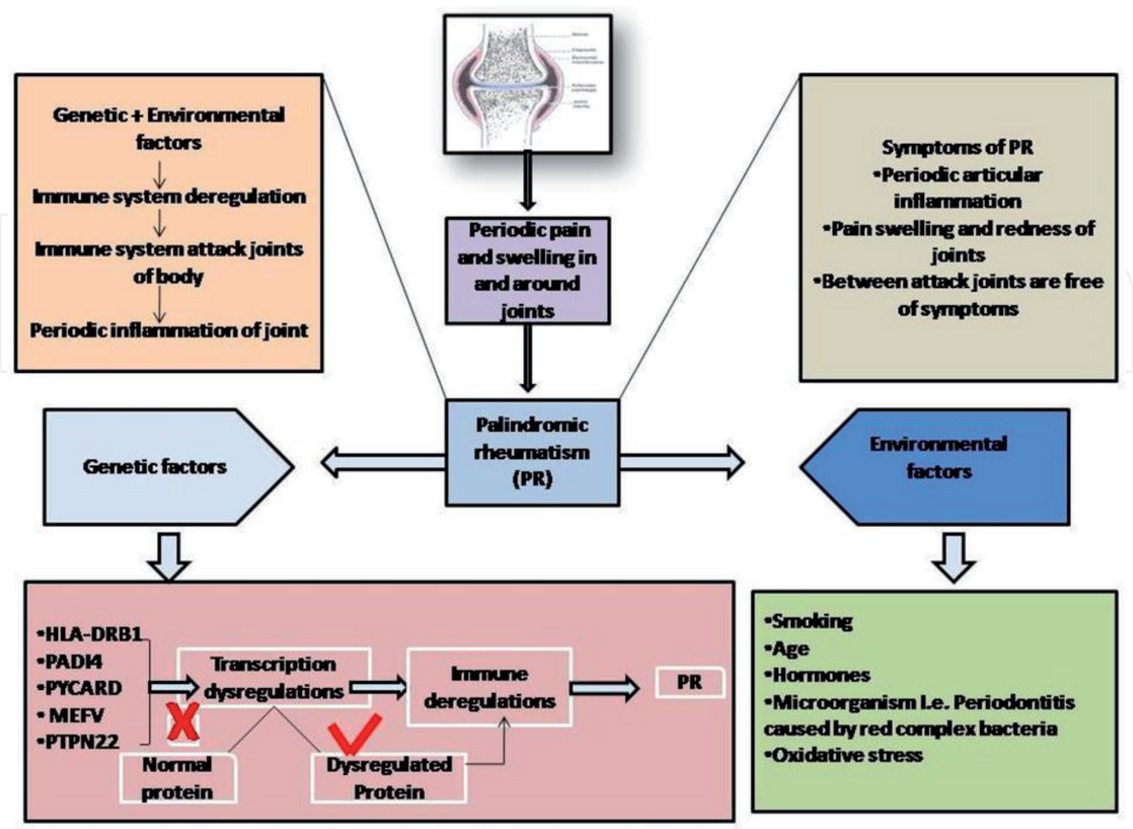

Figure 1.
Overviews of Palindromic rheumatism.

Disease	Clinical characteristics	Gene mutation	References
Gout (Urate crystals deposing disease)	Presence of needle-like crystals in synovial fluid of joints	URAT1, GLUT-9 (Transporters) involvement	[36]
Reactive Arthritis	Infections history in genitourinary and Gastrointestinal tract (GI)	HLA-B27(In 80% of population)	[37]
Arthritis associated with Bowel disease	Gut inflammation,10%arthritis precedes enteritis	HLA-B27,NOD2, *ATG16L1*	[37]
Whipple's disease	Weight loss, diarrhea, and fever caused by *Tropheryma whipplei*	HLA-B27(50–75% of population)	[37]
Behcet disease	T cells abnormality and neutrophils hyperfunction, inflammatory lesion	HLA-B51(10–80%)	[37]
Sarcoidosis	Granuloma formation and the possibility of erosive bone lesion	HLA-DRB1 Involvement	[37]
Celiac disease	Nonerosive arthritis	Transglutaminase antibodies and malabsorption parameters	[37]
Familial Mediterranean fever	Familial history, MEFV mutation, Chronic arthritis (5%)	MEFV mutation	[37]
TRAPS	Autosomal dominant	TNF alpha	[37]
Hyperlipidemia	Xanthomas	High cholesterol and triglycerides	[37]
Intermittent Hydrarthrosis	No inflammatory sign	MEFV involvement	[37]
Relapsing polychondritis	Cartilaginous structure involves only	Nonspecific	[37]

Table 1.
Palindromic rheumatism and other relapsing diseases.

association between MEFV and PR. Another research investigated that smoking and PTPN22 Showed an association with an increase in ACPA. It is also reported that PTPN22 (Protein Tyrosine Phosphatase Non-receptor Type 22) which encodes for protein tyrosine phosphate clearly shows an association of microsatellite STP PTPN22gene with rheumatism [34]. According to a Chinese report Anti-MCV (Anti Mutated Citrullinated Vimentin) antibodies have also been reported as a biomarker in patients with Rheumatoid Arthritis although their role in PR is not studied [35] (**Table 1**).

4. Environmental factors

In recent year's association of periodontitis (PD) and PR association has been studied. PD is inflammation of periodontal tissues caused by red-complex bacteria i.e.*P.gingivalis* which affects the process of Citrullination by expressing peptidyl- arginine deiminase enzyme (PAD) [38]. According to research in Israel avoiding offending diet and intake of proper diet may affect the flares of PR. Smoking can also trigger the process of Citrullination by affecting the immune reactions of the HLA Gene [39]. Most of the case study reports that the onset of

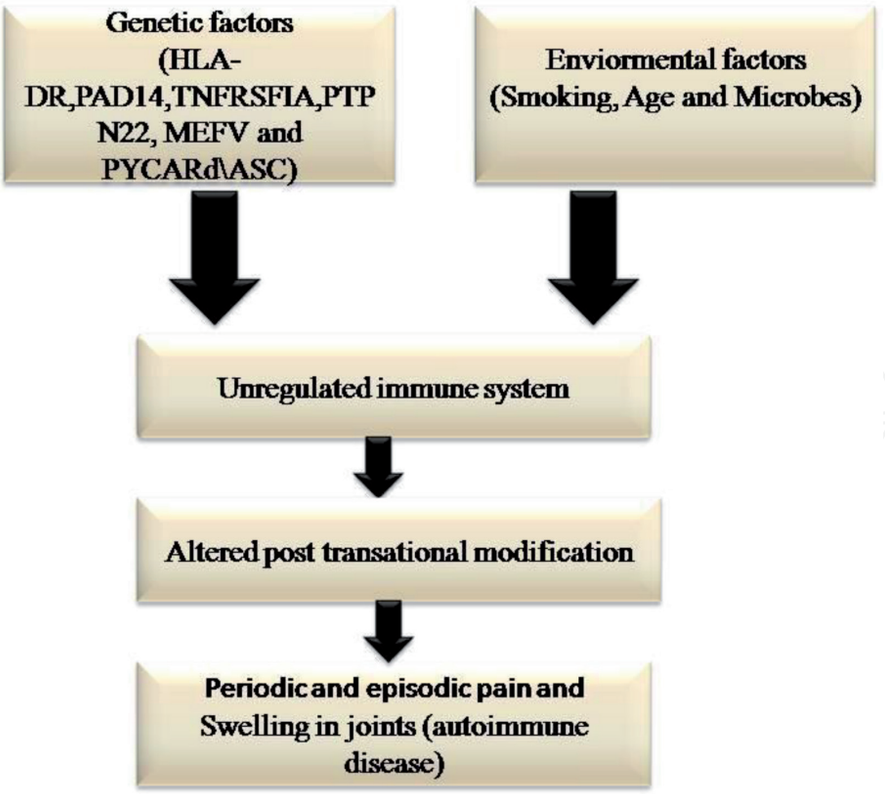

Figure 2.
Schematic representation of factors for development of Palindromic Rheumatism.

PR frequently begins in the late afternoon and early morning [40, 41]. Several factors responsible for the progression of PR as shown in **Figure 2**.

5. Palindromic rheumatism and diet

It has been observed that certain types of food can trigger a periodic attack of Palindromic rheumatism and elimination of that type of food from the diet has resulted in a reduction of attacks. According to a clinical trial conducted for evaluation of the role that certain type of food can play in PR, patients show that patients who were offended to eat eggs, cheese, fish, and canned vegetables resulted in the complete cessation of attack, and those patients who were presented with these food show more reoccurrence of attack. Therefore, offending food should be avoided to reduce the occurrence of PR although this needs more research that which type of specific food should be avoided [4, 42].

6. PR progression to RA

According to research in Japan, Anti-CPA in PR patients who developed RA was higher than those who did not develop RA in a future life [15]. According to a British case study of 39 patients of PR 19 showed progression to RA. Another study also indicated that most cases of PR progressed to other chronic arthritis and 35\60 progressed to RA [43]. The reason for this progression is multifactorial and one of the factors for this progression is a misdiagnosis of PR as there is no specific test and diagnosis is made mostly on physician's judgment and others may include progression duration which may vary from months to20 years [14, 44, 45].

7. Treatment options for PR

There is no specific treatment for PR for several reasons described earlier. Research has reported Non- Steroidal anti-inflammatory drugs appeared to delay flares of PR. In recent years Gold therapy is emerging as a promising treatment option for relieving joint pain and swelling. According to a study, about 60% of patients showed an improved result of gold salt. However, other studies have reported a high mucocutaneous side effect of gold therapy [8, 46]. The use of sulfasalazine also proves to be good for treating episodic flares of PR. In another study use of Chloroquine marked good results in the severity of an attack of PR where 41 patients out of 51 showed improvement [47]. Another study also focused on the delay effect of antimalarial drugs in PR flares [48]. Antimalarial drugs prove to be good in treating PR by their inhibitory effect on TNFα and IL-1. The case of the application of antimalarial in 71 patients mostly showed good results by decreasing flares of PR [47].

According to recent research PR patients who did not respond well to drugs mostly use in PR showed a very good response to Rituximab [49]. Biological DMARDs (Abatacept) affect the immune system by inhibiting T-cells stimulation and prove to be good for patients who poorly respond to methotrexate. Tofacitinib is also used in patients of PR who poorly or intolerantly respond to DMARDS [50]. The possible treatment options are shown in **Figure 3**.

According to research in Japan successful use of Kampo therapy (a Chinese herbal medicine) in three patients with Rheumatoid reveal its pharmaceutical potential in treating rheumatism although it needs a deep study of these findings to uncover its biological potential [51]. According to research in Iran yarrow, oat, colchicum, dill, fennel, wild rue, bitter melon, willow, garlic, and burdock help treat rheumatoid although their use in PR is still not reported [52]. Heat therapy is a medication-free way to relieve muscle pain and stiffness and is also recommended to treat PR [41].

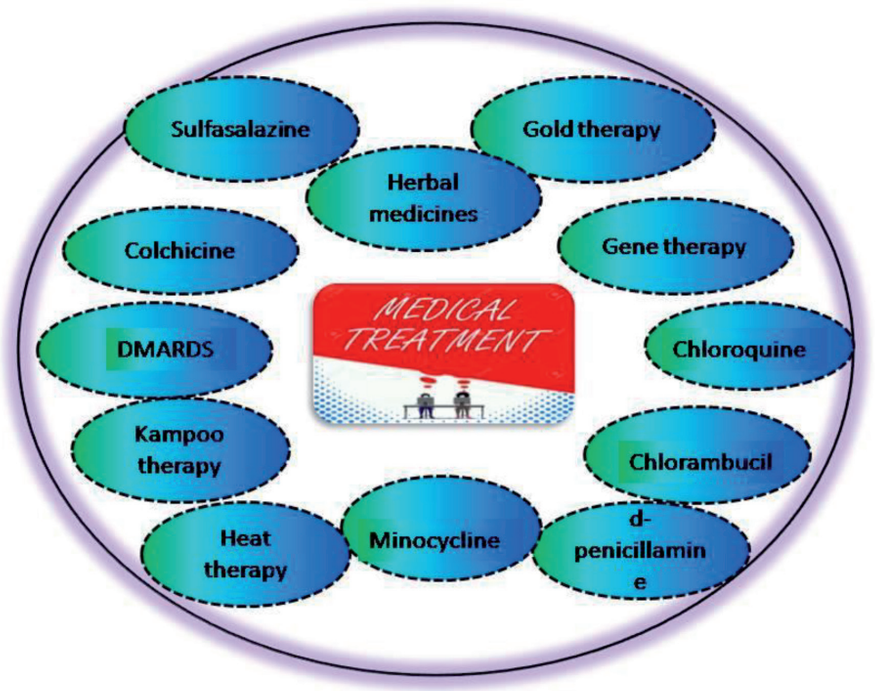

Figure 3.
Possible treatment options for PR.

8. Conclusion

Several risk factors such as genetic and environmental factors favor PR development. Most exposable genes are HLA-DRBI, PTPN22, TNFα, and PYCARD which mutate because of unbalancing in environmental factors. This study updates the information that Non- Steroidal anti-inflammatory drugs, Heat therapy, Chloroquine, and sulfasalazine show good results in the treatment of PR. Although many studies have validated these emerging therapies, still there is a need for further research to figure out their efficacy and precision. Side effects of these drugs and therapies must be considered before clinical applications for achieving stunning gains in the future. Additionally, these summarized genes might be capable of improving the therapeutic inventions for PR hence will serve as a significant pioneer for researchers who wants to identify the associative pathways involve in the pathogenesis of PR.

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All Authors contributed equally.

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Acronyms and abbreviations

PR	Palindromic Rheumatism
RA	Rheumatoid Arthritis
Anti-CCP	Anti-cyclic citrullinated peptide
ACPA	Anti-citrullinated protein antibodies
HLA-DRB1	Human Leukocyte Antigen-DRB1

PAD	Peptidyl- arginine deiminase enzyme
PADI	Protein-arginine deiminase type-4
TNFα	Tumor Necrosis factor
URAT1	Urate transporter1
GLUT9	Glucose transporter of member 9
HLA	Human leukocyte antigen Complex gene
MEFV	Mediterranean fever
Anti-MCV	Anti-Mutated Citrullinated Vimentin
PTPN22	Protein Tyrosine Phosphatase Non-receptor Type 22
NLRP3	Nucleotide-binding oligomerization domain, Leucine-rich Repeat, and Pyrin domain-3
TNFRSF1A/1B	Tumor necrosis factor receptor 1 A/B
PYCARD	PYD And CARD Domain Containing
ASC	Apoptosis-associated speck-like protein containing a CARD
IL-6	Inter-leukine-6
DMARDS	Disease-modifying antirheumatic drugs

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