

The Clinical Genetics of Psoriasis

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Abstract: Psoriasis is a common chronic inflammatory disease of the skin affecting approximately 2% of Caucasians. Psoriasis has a worldwide distribution, with prevalence varying according to race and geographic location. Numerous population-, family- and twin-based studies point to a very strong genetic component of this disease. Psoriasis is a complex disease, as suggested by a very unclear and variable pattern of inheritance and a higher frequency in families of dizygotic twins than in those of monozygotic twins. So far 9 psoriasis susceptibility loci have been identified (PSORS1-9) but only three (PSORS1, PSORS2 and PSORS4) have been replicated in more than one study. The strongest genetic association has been found with the HLA-C region on the short arm of chromosome 6. Failure to reach 100% concordance in monozygotic twins points to a multifactorial aetiology of psoriasis where environmental factors play an important role in genetically predisposed individuals. Clinical, histological and ultrastructural evidence suggests that psoriasis is a T cell-mediated disease where T cell activation is followed by release of pro-inflammatory cytokines, leukocytic infiltration of the skin, abnormal keratinocyte proliferation and angiogenesis. It is not known which exogenous or endogenous antigen(s) is responsible for triggering T cell activation or which genes play a fundamental role in psoriasis. Research is being carried out in an attempt to answer these questions. Here we review the main pathogenetic and epidemiological aspects of this skin condition.

Key Words: Psoriasis, epidemiology, prevalence, genetics, pathogenesis, multifactorial disease.

INTRODUCTION

Psoriasis is a common, chronic disfiguring inflammatory disease of the skin characterised in most cases by well-defined scaly, red and indurated plaques mainly over extensor surfaces but also often involving other areas of the body. Its course is usually relapsing and remitting with variation in severity and clinical manifestations even within the same individual. It is now universally accepted that psoriasis has a genetic component as supported by frequent familial clustering and high concordance rates in monozygotic twins. However, failure to reach 100% concordance in monozygotic twins and evidence of isolated cases of psoriasis point to a strong environmental contribution. Genome-wide scans and linkage analyses consistently implicate genes on chromosome 6p23 in the MHC class I region, although other potential candidate regions have been detected. Psoriasis is now considered to be a multifactorial disease triggered by environmental antigens in genetically susceptible individuals.

CLINICAL FEATURES

The clinical features of psoriasis have been reviewed in detail [1-3]. Psoriasis is a chronic inflammatory skin disease that varies in age and mode of onset, severity, course, duration and clinical morphology from one individual to another. There are many distinct clinical subtypes, which often overlap: chronic plaque, guttate, generalised pustular,

palmoplantar pustular and erythrodermic. Psoriasis can also involve the musculoskeletal system (psoriatic arthritis) and the nail apparatus. Its classical form, chronic plaque psoriasis (CPP) accounts for around 80% of diagnoses. It is characterised by well-demarcated erythematous plaques with a loosely adherent silvery-white scale, which preferentially affect elbows, knees, lumbosacral area, inter-gluteal cleft and scalp (Fig. 1). Lesions often develop at sites of skin injury (Koebner phenomenon). Any kind of trauma to the skin can trigger this response: excoriation, burn, contact dermatitis, chemical irritation, infection and photosensitivity. As the plaques regress, either spontaneously or in response to treatment, they often start to clear in the central area with a persisting erythematous margin, which confers an annular appearance. Even CPP, the most common subtype of psoriasis, exhibits clinical variation between patients with regard to shape (annular, serpiginous, geographic), extent and response to treatment. Patients with guttate psoriasis (GP) usually present with acute onset of round erythematous scaly papules scattered mainly over the trunk and extremities (Fig. 2). GP often occurs in children or young adults with a positive family history of plaque psoriasis, and it is estimated that up to 80% of juvenile guttate psoriasis cases are preceded by streptococcal infections [1, 4-6]. It is usually self-limiting, however a significant proportion of affected individuals eventually develop a more chronic form of psoriasis. GP and CPP seem to be genetically similar conditions as in both cases there is a strong HLA association, especially with the Cw*6 allele.

Less than 3% of patients diagnosed with psoriasis present with a pustular eruption which can be either localised to palms and soles or, less frequently, more generalised [1, 7].

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Palmoplantar pustular psoriasis (PPP) is relatively rare with a prevalence of 0.01-0.05% [8, 9]. There is hyperkeratosis and clusters of sterile and painful pustules over the ventral aspect of hands and feet, especially over the thenar and hypothenar eminences of the palms and around the heels (Figs. 3 and 4). This condition is often resistant to therapy and leads to considerable debility and disability. Generalised pustular psoriasis (GPP) consists of sheets of sterile pustules on a background of erythema, although they can present also on previously normal skin (Fig. 5). Systemic symptoms are often present and include fever, arthralgia and malaise. Large lakes of pus can be formed when isolated sheets of pustules coalesce leading to disruption of the skin protective mechanisms and, if not treated to sepsis, hypothermia, and eventually death.



Fig. (1).

It is still controversial whether these pustular skin conditions should be considered as part of the psoriasis spectrum or as a separate clinical entity in view of the different morphology and histology. However, about 24% of individuals with PPP have evidence of psoriatic lesions elsewhere on their body, which suggests at least a strong association with psoriasis [10].

Erythrodermic psoriasis (EP) is a rare but life-threatening condition where severe erythema and scaling can involve up

to 100% of the skin surface with the same disruptive effects on skin defensive and thermoregulatory mechanisms as seen in GPP (Fig. 6). In addition, excessive exfoliation can lead to hypoalbumaemia and leg oedema. Fever, chills, malaise and pruritus often accompany it. EP may complicate plaque or pustular psoriasis or may be the initial manifestation of psoriasis.



Fig. (2).



Fig. (3).



Fig. (4).

Nail disease affects about 50% of people with psoriasis [11, 12]. It has a tendency to occur in the presence of severe skin disease and is associated with psoriatic arthritis and scalp involvement. Clinically, there may be nail discoloration, pitting, onycholysis (separation of the nail plate from the nail bed), and subungual hyperkeratosis.



Fig. (5).

Between 5-30% of patients have psoriatic arthritis, a seronegative arthritis with an overall prevalence of 0.1% [13-15]. The first episode of psoriatic arthritis most frequently

involves the knees, metatarsophalangeal joints, or wrists. Five distinct clinical patterns are recognised: 1. Oligoarticular; 2. Polyarticular; 3. Rheumatoid-like with involvement of the small joints of the hands; 4. Spondyloarthritis with symmetrical or asymmetrical sacroileitis; 5. Arthritis mutilans with disabling telescopic digit deformities. Cutaneous lesions precede joint disease in 60-70% of patients and the two begin simultaneously in 10-20% of cases [7].



Fig. (6).

PATHOGENESIS

The main pathological features seen in psoriasis are thickening of the epidermis, heavy inflammatory infiltrate and vascular changes. The epidermis shows 1. acanthosis (epidermal thickening), 2. parakeratosis (nucleated keratinocytes in the stratum corneum) with loss of keratinocyte differentiation, 3. loss of granular layer and 4. inflammatory infiltrates, mainly composed of neutrophils and lymphocytes [4].

Acanthosis and parakeratosis are caused by abnormal keratinocyte proliferation and differentiation. It has been shown that there is a seven-fold increase of the number of cycling cells in the basal and suprabasal layers of lesional epidermis at any one time [16]. Altered levels or structure of

inter-cellular adhesion molecules might interfere with normal skin desquamation, and explain the excessive scale and skin shedding in psoriasis. Integrin and corneodesmosin are two proteins that are important in keratinocyte adhesion and differentiation; it appears that in lesional skin integrin has altered cytoskeleton associations, whereas corneodesmosin is over-expressed [17-19]. It is not clear yet whether these abnormalities are responsible for reduced keratinocyte adhesion and therefore excessive scaling, or, on the contrary, cause increased inter-cellular adherence with subsequent formation of clumps of keratinocytes (scale) which fail to differentiate.

The inflammatory infiltrate seen in the dermis consists mainly of T cells and macrophages. Cutaneous vasculature is characterised by prominent proliferation with large and tortuous blood vessels in the dermis. Using autoradiographic and immunohistochemical methods, it has been shown that in pustular and plaque forms of psoriasis there is active proliferation of endothelial cells [20]. *In vivo* models of angiogenesis have demonstrated that cutaneous vascular proliferation is triggered and maintained by angiogenic cytokines and growth factors released by epidermal keratinocytes, such as interleukin-8, TGF β , TNF α , and most importantly vascular endothelial growth factor (VEGF) [21]. VEGF and its receptors are over-expressed in psoriatic epidermis and dermal vasculature respectively [22]. Furthermore, dermal vessels exhibit up-regulation of leucocytes homing molecules such as ICAM-1 and E-selectin [4]. These vascular changes occur early in the development of psoriatic lesions [23], suggesting that angiogenesis is an important element in this process.

This deranged cutaneous homeostasis is thought to be the result of a cascade of immunological events revolving around activation of T lymphocytes [24]. A central role for T cells was initially suggested by the effectiveness of immunosuppressive drugs directed against T cells or T cell receptors (e.g. ciclosporin, tacrolimus, IL-2 fusion toxin, anti-CD4 and -CD3 agents) [25-28]. Further clinical, histological and ultrastructural evidence has been developed since, that points to the pivotal role of T cells. Studies carried out on severe combined immunodeficient transgenic mice engrafted with non-lesional skin from psoriasis patients showed development of psoriasis following injection with autologous immunocytes [29]. In addition, it has been observed that patients receiving a syngeneic bone marrow transplant from donors with psoriasis developed the condition [30]. Immunohistochemical analysis of psoriatic skin has revealed increased amounts of T cell cytokines, especially of the T helper type 1 subclass with a postulated key role for IFN γ [24, 31]. Although there is no available animal model of disease-pathways, more insight has been gained over the years in the pathogenetic mechanisms of psoriasis [4, 24, 31]. Antigen presenting cells (APCs) seem to have an essential role in T cell activation. They comprise different types of cells including macrophages, dendritic cells and Langerhan's cells. After coming into contact with an unknown antigen in the epidermis, APCs migrate to lymphnodes where two separate signals trigger T cell proliferation. The first signal involves the specific MHC-associated antigen or superantigen; the second signal requires interaction between co-stimulatory accessory molecules on APCs and T cell receptors (e.g.

ICAM-1/LFA-1, B7/CD28, LFA-3/CD2). It is not clear whether the MHC receptor responsible for antigen detection and recognition belongs to class I or class II (in which case it would be in contrast to the possibility of HLA-Cw6 as a candidate susceptibility locus for psoriasis). These activating signals induce expression of skin homing receptors, such as CLA (cutaneous lymphocyte-associated antigen), on T lymphocytes, thus directing them to the skin. As mentioned before, E-selectin is induced in psoriatic dermal vasculature and facilitates the recruitment and extravasation of T-cells in the dermis [4, 31].

What factor or event triggers T cell activation remains yet to be elucidated. Both infectious and non-infectious potential triggering factors have been suggested on the basis of their capability to activate T cells: bacteria-derived superantigens (antigens which do not require intra-cellular processing), streptococcal M protein, retrovirus (human immunodeficiency virus 1), and human papilloma virus [32-36].

Until now, streptococcal antigens have been the focus of much interest. Streptococcal M protein is homologous to the 50 kDa type I keratin protein (K14), and a 67 kDa streptococcal protein is homologous to myosin and the β chain of the class II HLA antigens [36, 37]. These findings suggest T cell cross-reactivity as a very plausible disease mechanism for psoriasis. One hypothesis is that molecular mimicry between bacterial proteins and keratin 17 leads to activation of autoreactive T-cells and thus disease persistence [38, 39].

EPIDEMIOLOGY

Psoriasis is a common chronic disease that is more prevalent in Caucasian populations (estimated prevalence 1.5-3%), especially Northern European, with a reported peak prevalence between 3 and 4.8% in Norway [40, 41]. It has never been reported in Latin American Indians or Samoans. Psoriasis is also less common in Asian countries with an estimated prevalence of 0.4% in China, 0.3-1% in Japan and 0.8% in India. Epidemiological studies carried out on West African and American Black populations have reported prevalence figures of 0.3-0.7% and 0.7% respectively [42, 43]. This shows that there is a significant inter-racial and geographical variation in the distribution of this disease and explains why there are no accurate figures of its general prevalence. Other factors may contribute to the difficulty in generating valid general distribution figures: absence of universally recognised and validated diagnostic criteria for psoriasis, absence of epidemiological data from a vast number of populations and countries and finally, a probably high number of unreported cases of mild psoriasis. Prevalence is similar in both sexes [8, 38] except for palmoplantar pustular psoriasis, a clinical subtype that is more common in women [44, 45]. One study looked at seasonal variation of the disease, which appears to affect more people in spring and winter [46]. More than half of patients develops psoriasis before the age of 40, however a second smaller age peak occurs around the age of 60 [8, 9, 47]. Age of onset seems to be a genetically determined factor (see below).

Overwhelming evidence that psoriasis has a very strong genetic component comes from different population-, family- and twin-based studies. Two large-scale epidemiological studies showed increased incidence of psoriasis in relatives

of affected individuals compared to matched controls and general population. In 1963 Lomholt studied more than 10,000 inhabitants in the Faroe islands and discovered that 91% of people with psoriasis had at least one 1st or 2nd degree relative with the same condition [9]. In 1967 Hellgren reported a prevalence of psoriasis of 7.8% in 1st degree relatives of affected individuals compared with a prevalence of 3.14% in matched controls and 1.97% in the overall population in Sweden [8].

Familial aggregation of psoriasis has been studied in detail in numerous pedigree analyses attempting to discover the mode of inheritance of the disease. Abel *et al.* [48] suggested a simple autosomal dominant pattern with reduced penetrance after studying a large North Carolina kindred of British descent. A recessive mode of inheritance was later proposed by Swanbeck *et al.* [49] who studied 5197 families with psoriasis where parents of the probands were affected in 36% of cases. A German study of detailed pedigrees in 2035 families with psoriasis, including 30 twin pairs, rejected the hypotheses of the irregular dominant and the bi-factorial recessive inheritance in favour of a multifactorial aetiology of psoriasis with a polygenic mode of inheritance [50].

The most convincing evidence supporting a genetic predisposition to psoriasis is provided by high concordance rates in monozygotic twins. In Stanford, Farber *et al.* retrospectively looked at 61 twin pairs with at least one twin member affected. They found a concordance rate of about 75% in monozygotic (MZ) twins, much higher than that in dizygotic twins (DZ) (about 25%) [51]. Brandrup *et al.* studied 32 MZ twin pairs (including at least one partner with unquestionable psoriasis) obtained from the Danish Twin Register [52]. Psoriasis was present in both twins in 56% of cases yielding a calculated heritability of around 91%, similar to that extrapolated from Lomholt's data by Ananthakrishnan *et al.* [53]. In both studies, there were strong similarities in age of onset, severity and course of the disease in concordant MZ twins. In Farber's study, 8 concordant twins presented synchronous age of onset and striking similarities even in the morphology of the lesions. These findings suggest that these disease variables could be genetically determined. A third study of psoriasis in twins was carried out by Duffy *et al.* in Australia but failed to produce similar high concordance rates in MZ twins (35% in MZ vs. 12% in DZ twins) [54]. They used a community-based twin register as opposed to the Stanford study in which subjects were retrospectively recruited from dermatology clinics; this could have resulted in a bias toward concordant twins and therefore might explain the discrepancy in the concordance rates between these studies.

Andressen *et al.* calculated the risk of developing psoriasis in relatives of affected individuals: 14% risk if one parent was affected, 41% if both parents affected, 6% if one sibling affected, compared to 2% when no parent or sibling was affected [50]. In a large Swedish family data set, the estimated lifetime risk of psoriasis was 28% when one parent was affected, 65% when both parents and 24% when an affected sibling was present [55]. Interestingly, when the father suffers from psoriasis the offspring have a higher risk of developing the disease and they might do so at an earlier age (genetic anticipation), therefore suggesting that expression of the responsible gene(s) for psoriasis is influenced by

the sex of the contributing parent (genetic imprinting) [42, 50].

Nowadays, most authors agree that psoriasis is a genetically complex disease. Further more, failure to reach 100% concordance rate in MZ twins would also point to a multifactorial aetiology where environmental triggers play a fundamental role in the development of the disease. The evidence for a polygenic model for psoriasis includes the following:

- Segregational analyses of large multigenerational families have detected no clear pattern of inheritance [50, 56, 57].
- The risk ratios r calculated by Elder *et al.* after analysing the data from Lomholt's and Hellgren's population studies, decreased by a factor of 8 and 6 respectively, suggesting a multilocus model for psoriasis [56]. The r , as defined by the method of Rish, assesses the risk of disease in a relative of degree r in relation to the population prevalence [58]. For a monogenetic disease r should decrease by a factor of 2 with each degree of relationship, clearly not the case in psoriasis.
- From analysis of twin studies, it emerged that the familial frequency of psoriasis was higher in concordant DZ twin members than in concordant MZ twins. DZ twin members are only as genetically alike as ordinary siblings. Watson *et al.* have shown that the more siblings that are affected, the greater the frequency of psoriasis in relatives. This would fit with the polygenic inheritance hypothesis and can be explained on the basis of a greater number (pool) of genes from the parents [57].

A polygenic model for psoriasis means that no gene is either sufficient or necessary for the development of the disease. However, our hypothesis is that psoriasis represents a spectrum of genetic diseases ranging from rare monogenic forms to the more common polygenic/multifactorial ones. The rare cases in which changes in a single gene may be sufficient to cause the disease could explain why some families appear to inherit the disease in an autosomal dominant fashion. Within these families, there seems to be considerable genetic heterogeneity with individual families linked to various loci. Most of psoriasis patients fall at the opposite end of the spectrum, where multiple genes are likely to be involved and interact with each other (epistasis) and/or the environment (multifactorial aetiology). Representative patients may be those in which no family history is present or no clear pattern of inheritance is identified [42].

At least nine total or partial genome-wide scans have been reported and so far several putative susceptibility loci have been identified, 9 of which show significant linkage to psoriasis. Most of these linkage associations have not been consistent in all genome scans and replication of findings has been difficult (see Table 1 for references). The most consistently reported association involves an area in the MHC class I region on the short arm (p) of chromosome 6 (PSORS 1). Linkage disequilibrium analysis using densely spaced markers in the MHC region has narrowed down the area of interest to a 200kb segment containing approximately eight known genes [59-61]: HLA-C, TCF19, OTF3, HCR, CDSN, SEEK 1, SPR 1 and STG [62-69]. (See following chapters for further details).

Table 1. Summary of Susceptibility Loci Linked to Psoriasis Vulgaris in Genome Scan Studies

Locus name	Chromosomal Location	Reference
PSORS 1	6p21.3	[97, 113-117]
PSORS 2	17q24-25	[97, 114, 118]
PSORS 3	4q34	[114, 119]
PSORS 4	1q21	[120]
PSORS 5	3q21	[121]
PSORS 6	19p13-q13	[113]
PSORS 7	1p35-p34	[116]
PSORS 8	16q	[122]
PSORS 9	4q31	[117]

PSORS1 is estimated to account for 30-50% of familial psoriasis, which suggests the importance of other possible genetic loci and environmental factors for the development of the disease. However, this strong genetic association seems to be confined to early onset plaque and guttate psoriasis. As mentioned before, many studies have detected two types of psoriasis with different age of onset, severity and course of disease, and genetic background. From many epidemiological studies it became evident that patients with severe psoriasis would tend to have an earlier age of onset than patients with mild disease [70]. In 1985 Henseler *et al.* evaluated the age of onset in 2147 psoriasis patients and revealed two peaks, one occurring in the second decade and a second peak between the fifth and sixth decade [47]. Disease course was quite unstable, more severe and generalised in patients with early onset psoriasis. HLA tissue typing of 112 randomly selected patients showed that 85% of HLA-Cw6 positive patients belonged to the early onset group. They also observed that more than one half of patients with early onset psoriasis had a first degree family member affected, whereas a positive family history of psoriasis was nearly absent in the late onset group. These findings were supported by a study in Iceland where patients with familial psoriasis were HLA-C typed in order to compare the clinical features of HLA-Cw6 positive and negative individuals [71]. Once again, HLA-Cw6 positive patients had earlier onset of psoriasis, more extensive plaques and higher incidence of guttate-type onset. In a recent study, Ferrandiz *et al.* reported that guttate psoriasis, nail involvement, evidence of precipitating factors, a recurrent clinical course and a greater psychosocial impact were also more frequent in the early onset group of patients [72]. These studies support the concept of two distinct disease patterns in non-pustular psoriasis, one of which presents an inheritable form with early onset, more severe and unstable course, and comprises the majority of patients (type 1). The other form of psoriasis is of late onset, less severe and shows absence of heritability (type 2). Various studies have reported an association of type 2 psoriasis with HLA-Cw2, -B27 and Cw5 [70, 73, 74]. In various aspects, these disease patterns show similarities to the disease patterns known in diabetes mellitus, in which the

juvenile type in genetically predisposed persons is distinct from diabetes of late onset.

It is clear that there is a strong relationship between plaque psoriasis and guttate psoriasis. The majority of patients with acute GP is less than 20 years old, go on to develop chronic plaque psoriasis (CPP) and have usually a positive family history of CPP. In addition, guttate flares are common in patients with CPP [5, 75]. Linkage studies have confirmed a strong association of GP with all 3 candidate allelic variants of the HLA-C, CDSN and HCR genes. HLA-Cw6 association rate reached 100% in one study [5, 76].

The relationship between CPP and palmoplantar pustular psoriasis (PPP) is much more controversial. Clinically they seem to be different conditions as PPP usually develops at the age of 30-50, is more common in women and is strongly associated with tobacco smoking [10, 44, 45, 77]. Furthermore, some authors have suggested an association to thyroid dysfunction and thyroid autoantibodies [78, 79] which has never been reported in patients with CPP. On the other hand, CPP is more frequent in patients with PPP than in normal population (24%) and the histological features of PPP show similarities to those seen in other forms of pustular psoriasis [10]. So far, this link between the two conditions has not been supported by genetic studies as PPP does not appear to associate with any of the three potential susceptibility loci for CPP, even when the two disease co-exist. When PPP patients were stratified for age of onset in a Finnish study, no significant difference was detected in allele frequencies between patients with early onset (<40) and late onset (>40) [76]. In Japanese patients PPP has been reported to be associated to HLA class II DR9 and class III TNF-B*2 alleles [80, 81].

Hence, there seems to be a common genetic background for CPP and GP, and it follows that if the same alleles are associated with both diseases the type of disease is controlled by factors other than the PSORS1 locus. PPP appears to be a different clinical and genetic entity with possible overlapping genetic loci with CPP.

Although genetic factors play a very important role, it is clear that other unknown factors are involved in the aetiology of psoriasis. Several exogenous factors have been identified which seem to trigger exacerbation of psoriasis or its onset. Emotional stress and major stressful life events are established precipitating factors in the onset or worsening of psoriasis [82]. When questioned, 60% of patients believe that stress was a triggering factor in their disease [83].

Infection can also offset psoriasis. Infection with group A beta-haemolytic streptococci has been associated with onset of acute psoriasis and exacerbation of chronic psoriasis. Acute flares of guttate psoriasis follow a streptococcal throat infection in about 10% of cases [6]. Weisenseel *et al.* found that evidence of group A streptococcal infection was present exclusively in type 1 psoriasis patients [84]. The streptococcal trigger and genetic background of psoriasis suggest that individuals with psoriasis may display a genetically determined susceptibility to streptococcal infection. HIV infection is also associated with an increased risk of developing psoriasis [85]. In one study, 79% of HIV positive patients with CPP carried the HLA-Cw*0602 allele compared with

25% of controls (HIV-infected patients without psoriasis) [86]. This suggests that immunodysregulation resulting from HIV infection may trigger psoriasis in those genetically predisposed by the Cw*0602 allele.

A number of drugs have been implicated that may interact with disease status [87]. The association between psoriasis and beta-blockers is controversial. Adverse effects were reported with practolol in the past [88], but there is no substantial evidence that currently employed beta-blockers cause an exacerbation of psoriasis. Evidence is also lacking for drugs like ACE inhibitors and NSAIDs. Lithium and anti-malarials are the main drugs to have been linked to severe exacerbations [87]. Life-style factors such as alcohol and smoking may have an impact on the severity of psoriasis. Although alcohol does not appear to induce psoriasis, it has been reported to aggravate it [89]. Furthermore, heavy drinkers usually suffer from extensive disease, which is often resistant to therapy [90, 91]. This also would suggest that alcohol have a deleterious effect on psoriasis, however the stubbornness of the disease might be due to decreased compliance with medications in this group of patients. Abstinence from alcohol has been reported to induce remission [92]. The relationship with smoking is not clear; there seems to be an association with increased risk of palmoplantar pustular psoriasis. Other potential risk factors include skin trauma and sunlight. UVA and UVB rays improve psoriasis in most patients, but can also have an aggravating effect on others, especially older females or those with a pre-existent photosensitivity or skin type I [93]. There is some evidence that the course of psoriasis in females might be influenced by the hormonal status; in most observed cases psoriasis seems to become worse around puberty, it is more likely to improve during pregnancy and deteriorates again in the post-partum period [94, 95]. Although rare, GPP precipitated by pregnancy has been reported [96].

The epidemiology of psoriasis has also been studied in relation to other diseases. Psoriasis is more prevalent in patients with Crohn's disease, and a family history of psoriasis is frequently observed for this patients. Interestingly, a psoriasis susceptibility locus mapping to chromosome 16q shows evidence of linkage to Crohn's disease [97]. Both psoriasis and Crohn's patients are characterised by high levels of TNF- and inflammation of stratified epithelia, suggesting a common genetic pathway in the two diseases [98]. There is no evidence of an association of psoriasis with NOD2, which is the major disease susceptibility allele in Crohn's disease [99, 100].

Interestingly, cutaneous immune disorders such as allergic contact dermatitis, atopic dermatitis, and urticaria are under represented in patients with psoriasis [101]. A recent study identified loci for childhood atopic eczema on chromosome regions 1q21, 3q21, 17q25, and 20p, all of which have been implicated in psoriasis by at least one study [102]. Obviously these chromosomal regions are quite broad and the genes involved in these two diseases may be different. However, the fact that atopic dermatitis occurs less frequently in patients with psoriasis than in the normal population would suggest that the immunological and pathogenetic pathways leading to the two conditions are different and somehow mutually exclusive.

Severe psoriasis is associated with increased cardiovascular morbidity and mortality [103-106]. This could be explained by the abnormal lipid metabolism [103, 107-111] and higher prevalence of diabetes mellitus, hypertension, and obesity seen in psoriasis [103, 104]. Alternatively, the lipid peroxidation and high frequency of occlusive vascular events seen in psoriasis may result from chronic inflammation and consequent production of oxygen metabolites. Although excess mortality in psoriasis patients was reported in a Finnish study [112], there is no conclusive evidence that patients with chronic plaque or pustular psoriasis have a shorter life span.

FUTURE PERSPECTIVES

Significant progress has been made in the understanding of the genetic, immune and pathogenetic aspects of psoriasis. However, much work needs to be done to identify the responsible genes and the way they interact with the environment. This should enable us to develop an animal model for the study of pathogenetic pathways in psoriasis and hence to classify psoriasis according to different genotypes resulting in the different clinical forms known to us. Such a model would allow rapid screening of potential therapies and pharmacogenetic applications, thus leading to individually tailored therapies with maximum efficacy and minimal toxicity to patients.

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