Reumatismo, 2003; 55(1):6-15

RASSEGNA

Psoriatic arthritis as a mountain

L'artrite psoriasica vista come una montagna

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RIASSUNTO

Il concetto di artrite psoriasica (AP) non è ancora universalmente accettato. In effetti, poche fra le principali caratteristiche dell'AP sono considerate realmente patognomoniche, tanto che uno stesso paziente può essere giudicato affetto da artrite reumatoide (AR), spondiloartrite (SpA) o AP, a seconda del medico che lo ha visitato. L'eterogeneità dell'AP, la mancanza di differenze significative nell'artrite precoce con o senza psoriasi, ed una patogenesi piuttosto diversa fra AP e psoriasi, sono altri fattori che depongono contro l'originalità dell'AP. Tuttavia, sebbene l'AP possa essere semplicemente considerata quale una sindrome dipendente dalla combinazione di numerosi cofattori (forse condivisi con le SpA e/o con l'AR), le sue forme più complete meritano di essere separate dalle altre SpA o dall'AR. L'AP è anche la forma clinica più apparentabile alla sindrome SAPHO. Inoltre l'AP, in confronto con l'AR e le SpA, presenta un profilo di citochine sinoviali alquanto differente ed un quadro peculiare di vascolarizzazione sinoviale, confermato da diversi gruppi. Questi ultimi aspetti possono contribuire alla particolare disponibilità dell'AP a svilupparsi dopo un trauma. Sia il maggiore rischio familiare per l'AP, rispetto all'AR o alla psoriasi cutanea isolata, che l'elevata trasmissione paterna dell'AP, suggeriscono fortemente l'esistenza di una predisposizione genetica, sebbene finora solo il MICA-A9 (espresso sulle cellule epiteliali intestinali) sembra associato con la suscettibilità all'AP indipendentemente da quella per la psoriasi. Affinché gli studi di genetica apportino informazioni più utili e sicure, è però necessaria una più attenta scelta di casi che vanno raggruppati per caratteristiche realmente comuni, ciò che richiede criteri di selezione dei pazienti situabili "in cima alla montagna" dell'AP. A questo scopo possono essere utili i criteri recentemente proposti da McGonagle o da Fournié.

Reumatismo, 2003; 55(1):6-15

THE CONCEPT OF PSORIATIC ARTHRITIS (PsA)

There is no doubt that inflammatory arthritis/enthesitis and psoriasis coexist more frequently than would be expected by chance: for instance, in a study of 1285 patients with psoriasis seen in an hospital, 483 (38%) were suffering from arthritis/enthesitis, including 40 patients classified as Rheumatoid Arthritis (RA) (3%), 177 (14%) as undifferentiated arthritis (UA), and 266 (21%) as Psoriatic Arthritis (PsA) (1). Although lower percentages have been noticed in the general population with psoriasis (6% of PsA in an extensive study of 1844 patients with psoriasis) (2), they were superior to 5% (i.e. at least 5 times greater than the figures found for patients without psoriasis) (3-7). Similarly, psoriasis is slightly more frequent in patients with arthritis than in the population without arthritis (8). These observations, and the recognition of clinical or radiological features rather specific for PsA naturally led to the hypothesis that this condition did exist as an original entity, nosologically different from RA and other rheumatisms, although presenting as different subtypes (9).

The reported features of PsA supporting this assumption, are: 1-frequent arthritis of distal interphalangeal joints (DIP) (10-12) (ascribed to the preferential involvement of enthesis (13) and related structures (14)), leading sometimes to dactylitis/osteitis of the whole distal phalanx (15)); 2-involvement of a single digit (inflammation in a ray pattern); 3-inflammation of the spine (including the cervical segment in most cases) (16-17), which remains often clinically silent (9) but can lead to some ankylosis, although usually less severe than

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in classical ankylosing spondylitis (AS); 4-sacroiliitis, frequently less pronounced than in AS, and possibly asymptomatic; 5-asymmetrical oligoarthritis or enthesitis (including spinal/sacroiliac joints/enthesis) (2)); 6-coarse syndesmophytosis (which can mimick diffuse idiopathic hyperostosis), tumoral enthesopathy (18), and frequent succession/combination in a single joint/enthesis of destructive changes and bone proliferation (19-20); 7-characteristic radiological modifications of toes and fingers like "cup and stem", "pencil pointing in cupping", and mixture of osteolysis and ankylosis (21); 8-possibility of late onset (after 60 years old, PsA being often severe then) (22), as opposed to the rarity of juvenile PsA (23); 9-usual lack of rheumatoid factor and anti-citrullinated peptides antibodies; 10-less stringent association with HLA phenotypes than in AS and RA, which depends on the subset of PsA (HLA-B27 being overall present in less than 50% of cases).

CRITICISMS OF THE CONCEPT OF PsA

However, and despite it has been discussed for more than a century, the concept of PsA is not yet universally accepted, which precludes precise conclusions about its prevalence, estimated to be about 1/1000 (i.e. 5 to 10 times less frequent than RA or SpA) (2, 24).

The first reason for this reluctance of some physicians to admit PsA as a distinct disorder might be that, although still obscure for both, the pathogenesis of psoriasis and PsA could differ significantly: for instance, although T cells (response of Th1 type) are present in both skin and joints (25-26), their role seem more important in skin. Indeed ciclosporine (27), and other drugs targeting memory T cells (28) or Th1 lymphocytes (29), are (much) more effective to treat psoriasis than PsA. Moreover, although peripheral T lymphocytes from psoriasis do express large amount of CD44 and CD11a which might favour their migration in joints (30), the homing mechanism associated with cutaneous lymphocyte antigen (CLA, an E-selectin) is solely relevant to the skin, but not to the joint inflammation (31). In other words, psoriasis and PsA could be rather independent consequences of a combination of common genetic or environmental factors rather than the expression in skin and joints of a same disturbance of the immune system. This would fit with the facts that: 1- there is few parallelism between cutaneous changes and PsA, except for the involvement of nails which is over-represented in PsA (9, 14, 32); 2-the injection of T cells from human psoriatic plaques to SCID mice can induce psoriatic lesions but not PsA in those rodents (33).

The second reason is that few (if any) of the items listed above are really pathognomonic for "PsA": most can be encountered in other subsets of spondyloarthropathies (SpA), while arthritis of DIP can also be noticed in other disorders. In this respect, it might be ironically emphasized that even in the famous article by Arnett *et al* detailing the classification criteria for RA (34), 79% of the 262 patients who served for the definition of RA had some swelling of DIP and 26% had pain on motion of these joints (34). In fact arthritis of DIP is much less specific for PsA than the succession of osteolysis and bone formation (19, 21) that can occur in long lasting PsA. This may explain why in a Dutch study using two standardized patients with PsA visiting *incognito* 23 rheumatologists, the male patient with arthritis of DIP as sole complaint was unfrequently recognized as PsA, while overall only 14/23 rheumatologists diagnosed PsA as expected (35). Similarly, the usefulness of asymmetry to distinguish PsA from other conditions has been denied (36).

The third observation which could argue against the validity of the concept of PsA is the frustrating heterogeneity of its presentation. This is perhaps best illustrated by the fact that even the authors of the most famous classification of PsA (9) have criticized their initial description in 5 subtypes (37). Indeed, patients classified as PsA frequently evolve from a subset to another (64 out of 100 patients studied by Jones et al (38)), a phenomenon which confirms that, although most authors consider PsA as a subset of SpA (39), both its presentation and nosology remain fuzzy. We made similar observations when asking 20 international experts to classify 10 "paper cases" of patients with early arthritis: major differences were noticed between experts, especially when classifying a patient as PsA or not, although most experts declared to feel rather confident in their choices (40).

The fourth reason to disregard the possibility of PsA as a distinct disorder is that many patients with psoriasis and arthritis fulfil the criteria for RA (34) (including sometimes the rheumatoid factor criterion) and/or SpA (ESSG (41) and/or "Amor" criteria (42)). Hence, physicians facing such patients do not feel an imperious need to look for the more precise diagnosis of PsA (especially for the 25% of patients with "PsA-like" features but still free from psoriasis). In other words the diagnosis of PsA

most often relies on the presence of psoriasis, regardless of the pattern of arthritis, as suggested by the curiously constant percentages of patients classified as PsA (2 to 4% of all early-arthritis) reported in all previous studies devoted to the outcome of early arthritis (43) or early undifferentiated SpA (only 2% after 2 years (44) and 5% after 11 years of follow-up (45)). The poor definition of PsA is also illustrated by previous unsuccessful attempts to better delineate PsA from RA and SpA by sets of criteria specific for this condition (9, 46-49). The first ones required the presence of psoriasis (cutaneous or ungueal) (49). Only two recent sets of criteria do not longer ask for a personal psoriasis, but either a family history of psoriasis (50), or a combination of 9 criteria (weighted from 1 to 6 points (including the criteria: "psoriasis" which gives 6 points, 11 points being the threshold optimised (51) (Tab. 1)). The Fournié's criteria have been constructed using a retrospective cohort of 100 patients diagnosed as PsA who have been compared to 80 patients classified as RA (fulfilling the 1987 ACR criteria) and 80 patients (fulfilling Amor's criteria) considered by the authors as SpA different from PsA (51). Unfortunately, none of these sets of criteria has yet been validated by an appropriate methodology, namely the prospective follow-up of a unbiased cohort of population-based patients for several years with collection of criteria at each visit, and final clinical diagnosis by a college of experts different from those who proposed the new set of criteria and/or gathered them. Hence, one could fear that the sensitivity of 0,95 and specificity of 0,98 found by Fournié *et al* when using their criteria were very optimistic (51), and partly explained by the methodology of their study which leaves a large room for circular reasoning (52). Nevertheless, these criteria surely deserve to be tested in a prospective and multicenter long-term follow-up study. Their validation could resolve some of the nosological issues previously discussed, in as much they are correctly used later on! Indeed we recently observed that even trained rheumatologists understood quite differently the 1987 criteria for RA and 1991 ESSG criteria for SpA (53).

Table I - Fournié's criteria (51).

Personal psoriasis antedating or concomitant with joint symptom onset	6 points
Familial history of psoriasis (if criterion 1 negative) Or psoriasis postdating joint symptom onset	3 points
Arthritis of a distal interphalangeal joint	3 points
Inflammatory involvement of the cervical and thoracic spine	3 points
Asymmetric Monoarthritis or oligoarthritis	1 point
Buttocks pain, heel pain, spontaneous anterior chest-wall pain, or diffuse inflammatory pain in the entheses	2 points
Presence of HLA B16 (B38,B39) or B17	6 points
Negative Waaler-Rose test	4 points
Radiological digit criteria (1,2,3,4 or 5) - n°1: erosive arthritis of at least one DIP - n°2: Interphalangeal osteolysis producing a widened, sharply demarcated joint space - n°3: ankylosis of an interphalangeal joint - n°4: juxta-articular periostitis of finger(s) or toe(s) producing a speculated or band-like image in a finger or toe. - n°5: phalangeal tuft resorption or osteoperiostitis of a distal phalanx	5 points
The threshold of positivity is 11 points	

A fifth reason against the concept of PsA might be that the larger prospective study of population-based recent-onset arthritis (less prone to hospital selection bias) published so far could not find significant clinical and radiological differences between the 51 patients suffering form psoriasis and the 915 other early arthritis studied, despite several years of follow-up (solely a trend towards more frequent male and DIP joint involvement) (54), confirming previous transversal studies (55), and studies of familial SpA (56). The rather similar outcome of patients with and without psoriasis (at least within the first years) can cast doubt on the rationale to demarcate PsA solely at the clinical level from other SpA (or RA), and/or suggests the existence of a major overlap between early-PsA and early-RA and/or early-SpA. This would be in accordance with the poorer performances of ACR criteria for RA within the context of early-arthritis than in the original study by Arnett *et al* (57-58). A naïve image could be proposed to patients to explain this, namely that inflammatory rheumatisms should not be seen as "buildings" well demarcated from each other, but rather as "mountains" raising over a common base of undifferentiated arthritis (UA) (52). Those "mountains" (RA, SpA) might be tangled at their bottom (explaining the clinical overlap) due to the induction of these arthritis by closely related or similar exogenous factors, like

virus (59), bacteria persisting in a "silent" form (60-62) (including classical bacteria like *Streptococcus* (59) or *Salmonella* (62)). The most severe cases of rheumatisms (top of the mountains), more easily recognised as "typical" SpA, RA, or PsA, might result from the successive involvement of other co-factors (genetics and/or environmental), leading to more achieved arthritis (52), easier to discriminate from each other and/or from UA than mild or recent cases.

In fact, the development of diagnostic or classification criteria for early inflammatory arthritis poses two kind of dilemmas (64). The first one is that not all physicians consider that UA can evolve either in RA, SpA or PsA (as postulated when referring to the image of mountains), but rather believe that early arthritis later diagnosed as PsA are, since their onset, nosologically different from other conditions, including undifferentiated SpA (e.g."distinct buildings") (52). The other issue is to know what should be the gold-standard for early arthritis: indeed, physicians' diagnoses are often less secure within the context of early-arthritis, and it would be even more difficult to build widely accepted criteria for early-PsA (64). It is indeed pretty difficult to ascertain where a mountain does begin.

The sixth reason to deny the interest of classifying a patient as PsA (instead of RA or SpA) is that several studies concluded to similar severities between PsA and RA, both for radiological features (65) and disability/quality of life (66-67), although peripheral joint damage might be somewhat lower in PsA than in RA (66) and remission slightly more frequent in peripheral PsA than in RA (18% of 391 patients, with an average duration of 2,6 years) (68). Moreover, treatments for these conditions are pretty similar (69), anti-TNF alpha molecules being as effective in PsA (70-71) and psoriasis (72) as in SpA or RA.

PsA IS A MOUNTAIN: JUST CONSIDER ITS TOP

However, and despite these numerous limitations, we should not throw away the baby with his bath's water. Indeed, and although PsA (like psoriasis which is more guttate-type and less associated with dystrophic nail changes in patients positive for HLA-CW6 (73) is possibly "just" a syndrome depending on the combination of numerous co-factors (some of which being shared with SpA and/or RA), the more achieved forms of PsA (e.g. the "top of the mountain") deserve a close interest and to be segregated from SpA/RA, for several reasons.

First, PsA best bridges the gap between other inflammatory rheumatisms and SAPHO syndrome, which shares with PsA several striking features (74): indeed, palmo-plantar pustulosis is indeed often indiscernible from pustulotic psoriasis, and osteolysis followed by bone formation and coarse enthesophytosis can be seen in both, as well as unilateral sclerosing sacro-iliitis, and aseptic osteitis (75-76), and not in RA or other SpA. In fact, familial history of PsA were over-represented in some cohorts of SAPHO syndromes (75), and psoriasis was found in 10% of a 120 SAPHO syndromes (i.e. quite higher than the 2 to 3% expected) (77).

Second, several authors noticed a special pattern of vascularisation in patients with typical PsA. Indeed, like in skin affected by psoriasis, vessels in PsA synovium are tortuous and their walls thicker as compared with other arthritis (25, 78-81). Part of this phenomenon could be mediated by an increase level of vascular endothelial growth factor (VEGF) in synovia (and perhaps enthesis), which can also be noticed in the blood of patients with severe psoriasis (82), especially those with arthritis (82). The local raise of VEGF could favour further destructive changes (83), while its systemic increase could contribute to the unusually high prevalence of distal extremity swelling with pitting edema observed in PsA (20%) as compared to other inflammatory arthritis (5%) (84). In fact, other molecules might act together with VEGF to favour these pattern of vascularisation, including TNF-alpha, TGF-beta and PDGF (85-86), while the number of mastocytes is also increased in the synovium of PsA as compared to RA (87).

Third, bone formation markers like bone-specific alkaline phosphatase are increased in blood of PsA, but not in AS or reactive arthritis (88), which fits with the bone formation frequently found around joints in PsA. Further studies of enthesis from PsA could help and understand which cells and/or cytokines are mainly responsible for this trend.

Fourth, several observations support the hypothesis that, besides the well known Köbner phenomenon (induction of psoriasis by trauma of skin), trauma could also favour the onset of arthritis/enthesitis in PsA. Although this occurs in a minority of cases, it does much more frequently than in RA (9% versus 1% (89), and 8% versus 2% (90)). Even tattooing has been reported as a trigger for both psoriasis and PsA (91).

Fifth, although it is unclear whether these changes reflect different pathogenesis or less aggressive/recent synovitis in PsA (differences being more quantitative than qualitative) (92), the profile of synovial cytokines seems somewhat different in RA and PsA (93-94). For instance, recent studies indicate that the ratio between synovial and blood IL-13 (an anti-inflammatory cytokine secreted by activated T-cell) was significantly greater in PsA than in RA (95), although other T cell derived cytokines were comparable in those two disorders (96) except for IL-2 which is often detectable in PsA and not in RA (97). Biochemical and immunohistochemical studies have also demonstrated differences between PsA and either RA or SpA. For instance, E-selectin and ELAM-1 expression seems clearly reduced in PsA synovium (98-99) as compared to RA.

Sixth, although sicca syndrome have been diagnosed in patients with PsA (100) (which can also lead to amyloidosis (101)), severe systemic features like rheumatoid vasculitis are not described in peripheral PsA.

Last, although quite probable in other conditions like RA, the involvement of the nervous system in the pathogenesis of psoriasis and PsA has been strongly supported by the results of quality of life studies (66-67,102) and the striking sparing of paretic limbs (103). At the molecular level, neuropeptides – substance P and vasoactive intestinal peptide – are indeed overexpressed both in lesional psoriatic skin and PsA synovium (103-104).

WAITING FOR GENETIC AND MICROBIOLOGICAL STUDIES TO UNRAVEL THE ENIGMA OF PsA

Both the greater familial risk for PsA than for RA or psoriasis alone (105), and the excessive paternal transmission of PsA (106), strongly suggest a genetic background for the more typical form of PsA. Hence, further studies on genetics of PsA (107) (especially as compared with psoriasis alone) could bring very useful information on how gene-gene and gene-environment interactions can explain bone remodelling close to enthesitis, the role of trauma as trigger, and the pattern of microvascularisation noticed in PsA. As these studies could be hampered by uncorrect population stratification, a careful matching of cases is needed, as well as selection of unequivocal cases of PsA (108). It would not be surprising that the most specific genes for PsA (e.g. those independent from other SpA) are not linked to HLA, whose role remains controversial in the pathogenesis of PsA (59,108) : indeed, although B7 and B27 are noticed in roughly 50% of PsA and B16 and B17 listed in the Fournié's criteria (51), most HLA-class I associations (including HLA-CW6 and maybe HLA B16 and B17) might be with psoriasis rather than with PsA itself (59). In fact, so far only MICA-A9 (expressed on gut epithelial cells) seems to be associated with susceptibility to PsA independently from psoriasis (109). Hence, other locus should be explored than areas of known linkage with psoriasis (17q25, 6p, and 4q32-35 (110)), and especially genes exhibiting genome imprinting.

The possibility that some environmental co-factors might be more specific for PsA than for other rheumatisms (as suspected for SAPHO syndrome and *Propionibacterium acnes*) should also be actively considered : this might better fit with the above hypothesis that PsA is more a syndrome than a disease (as admitted by 19/30 international experts for RA and SpA)(53), and with the observations in animal models of SpA that the pattern of arthritis can vary according to the profile of bacterial flora of rats (111-113). In this respect the role of *Streptococci* in the pathogenesis of the more typical "PsA" should still be carefully considered, as several evidences suggest their role as a co-factor in the onset of many psoriasis (114-115). Yet, it has been reported that there is no disease-specific role for streptococci-responsive synovial T lymphocytes in the pathogenesis of PsA (116). However, it has been stressed that synovial fluid lymphocyte proliferation in response to crude microbial antigens is not useful to specifically indicate a bacterial cause of arthritis (117), and several works have conversely reported elevated titres of antibodies to streptococcal antigens in patients with psoriasis or PsA as compared with RA without psoriasis (118-119). Most of all, a PCR specific for *Streptococcus pyogenes* and *Streptococcus agalactiae* was found positive in the blood of 9/19 PsA patients as compared with 0/17 RA patients (120). The participation of some *Streptococcus* species to the pathogenesis of some PsA would be even more credible that crippling infection by some *Streptococcus* have been reported which had first been mistaken for axial PsA (121), as well as full Reiter's syndrome following infection by *Streptococcus viridans* (122). Others candidates previously considered were *enterobacteria* (123), superantigens from staphylococcus (124), and virus like

HCV (125) or herpes-viruses like EBV and CMV, suspected to serve as co-factors for several autoimmune disorders, including PsA (126).
Such dissection of genes and gene-pathogens interactions could be even more successful if only those patients with the more achieved form of PsA are studied, and not all arthritis associated with psoriasis. This is another reason to hope that either the Fournié's criteria (51) or other international criteria could be validated soon and used as an highly specific research tool, selecting only those patients at the "top of the mountain" of PsA.

SUMMARY

The concept of psoriatic arthritis (PsA) is not yet universally accepted. Indeed, few of the features said to be characteristic for PsA are pathognomonic, and a same patient can be classified as RA, SpA or PsA depending on the physician seen. The heterogeneity of PsA, the lack of significant differences in early-arthritis with and without psoriasis, and a pathogenesis somewhat different in PsA and psoriasis, also argue against the originality of PsA. Nevertheless, although PsA is possibly "just" a syndrome depending on the combination of numerous co-factors (perhaps shared with SpA and/or RA), its more achieved forms deserve to be segregated from other SpA and RA. Indeed, PsA best bridges the gap with SAPHO syndromes. Moreover, the profile of synovial cytokines seems somewhat different in PsA as compared to RA and SpA, and a special pattern of vascularisation has been confirmed by several teams which could account for the demonstrated link between trauma and some PsA onsets. Both the greater familial risk for PsA than for RA or psoriasis alone and the excessive paternal transmission of PsA strongly suggest a genetic background, although so far only MICA-A9 (expressed on gut epithelial cells) seems to be associated with susceptibility to PsA independently from psoriasis. To make further genetics studies informative, a careful selection of unequivocal cases of PsA is needed, which requires criteria selecting patients at the "top of the mountain" of PsA. One can expect that the sets of criteria proposed by McGonagle or Fournié could satisfy this wish.

Key words *- Psoriatic arthritis, nosology, genetics, psoriasis, enthesis.*
Parole chiave - Artrite psorisica, immunogenetica, psoriasi, entesi.

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