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OPINION ARTICLE

Psoriasis and Psychiatric Disorders: The Next Frontier☆

Psoriasis y comorbilidad psiquiátrica: la próxima frontera

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In May 2015, the developers of brodalumab, a biologic drug that targets the alfa subunit of the interleukin (IL)-17 receptor, unexpectedly decided to halt clinical development of the drug despite the promising clinical outcomes expected on the basis of preliminary findings.[1] The reasons given for the decision at the time were based mainly on the observation of suicidal thoughts and behavior (in some cases successful) during clinical trials. The company considered that these would have to be clarified with the regulatory agencies and that they would lead to the inclusion in the Summary of Product Characteristics of restrictions that would have a negative impact on the sales of the drug in a very competitive market.

The news sounded an alarm among dermatologists and led to reflection on how the modulation of inflammatory pathways that are apparently specific to plaque psoriasis by targeting the IL-17 receptor could have an unexpected effect in areas that are, a priori, not connected, such as the patient's mental health.

However, although the controversy appeared novel at the time, a quick search of the literature reveals that, in 1993, Gupta et al. had reported that about 10% of patients with psoriasis reported ''a wish to be dead'' and that half of these patients reported active suicidal ideation.[2] In their conclusion, those authors argued that severe depression and suicidal ideation—until then considered to be a feature only of life-threatening diseases—could also, without venturing into pathogenic explanations, affect certain patients with psoriasis.

However, scant attention is paid to the psychiatric comorbidity that apparently affects patients with psoriasis as compared to the interest in other comorbidities, even though the association could be stronger than, for example, the relationship with cardiovascular complications.[3]

It is, in any case, difficult to measure psychiatric comorbidity because of the multiplicity of the elements involved. While the relationship between psoriasis and major psychiatric comorbidities, such as depression, anxiety and suicidal ideation, appears to be clear in severe forms of the disease, it is less evident in mild to moderate forms. However, even in the latter case, clinicians frequently detect certain personality disorders or traits in psoriasis patients, such as a negative or problematic attitude to life, impulsive or avoidance behavior, and less life satisfaction.[4]

However, in order to narrow the focus and concentrate on evidence, the aim in this article is to present findings that will stimulate reflection only on targets that are a priority for and can be identified by clinical dermatologists, namely, anxiety, depression and suicidal ideation.

The existence of a relationship between psoriasis and psychological comorbidities has been known for a long time. Prevalences of depression of up to 50% among patients with psoriasis have been reported by the authors of meta-analyses and cross-sectional population studies. A study that included data from nearly 150,000 patients and 750,000 controls found increased risks for depression, anxiety and suicide of 39%, 31%, and 44%, respectively, compared to the general population.[5] The risk of depression in patients with severe psoriasis was up to 76% and younger patients had

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higher risks for all outcomes compared to older patients. The number and intensity of psychological or psychiatric disorders is also greater when certain sites are affected, in the case of palmoplantar psoriasis and joint disease, for example. The impact of psoriasis on the quality of life of pediatric patients is also significant due to the negative repercussions of the disease during a period that is particularly important in the definition of the individual's relationship with his or her social and emotional environment. The repercussions of psoriasis also extend beyond the experience of patients, affecting those close to them in a manner and with an intensity that gives rise to concern, an aspect that is often neglected in the overall assessment of the burden of the disease.[6]

Moving beyond the undeniable epidemiological evidence of a relationship between psoriasis and psychiatric comorbidity, the clinician's curiosity may turn to the question of whether there is evidence that elucidates—given the clear statistical relationship—the extent to which psoriasis is the cause of psychiatric comorbidity or whether, on the contrary, it is the psychiatric comorbidity that conditions the course of the skin disease. While warning the reader that it would be difficult to provide a definitive answer to this question, we can say that a discussion of the evidence available does give rise to very interesting insights into our pathogenetic knowledge of both diseases.

One plausible explanation of the relationship between psoriasis and psychiatric disorders would be the existence of genetic links that could predispose the patient to both the skin disease and psychological or psychiatric problems. On this subject, we note that studies have found shared alterations in loci and single nucleotide polymorphisms in the HLA region associated with psoriasis, depression, and schizophrenia.[7] However, given the heterogeneity of the descriptions and the polygenic nature of psoriasis, such associations probably offer an explanation of the causal relationship in only some patients.

Another reasonable explanation might be the physical and psychological impact of the circumstances inherent in the disease itself: pain and itching, the presence of facial or genital lesions, stigmatization, sleep disorders, the impact on self-esteem, consequences of the low economic and sociocultural levels often associated with extensive forms of the disease. Such reactions are currently recognized as adjustment disorders (F43.2 in ICD-10 and 308.3 in DSM-5), a category encompassing depressive symptoms caused by a stressor—in this case psoriasis and the repercussions of the skin disease on the lives of these patients. What is clear is that, depending on each individual's idiosyncrasies, the psychological and psychiatric effects of psoriasis can be devastating.

A third, more speculative, hypothesis—but also undoubtedly one that is very attractive to clinicians—arises from the question of whether the inflammatory state of the skin and of the patient as a whole in psoriasis may serve to trigger or exacerbate psychiatric disorders by way of synergistic pathways shared by both processes, independent of reactive (adjustment) disorders caused by the psoriasis and its consequences (physical symptoms, isolation, effect on self-esteem, etc.).

On that point, it is of great interest and current relevance to highlight the fact that high serum concentrations of proinflammatory cytokines (tumor necrosis factor [TNF]-α, IL-6, prostaglandin E2, C-reactive protein, IL-1β, and IL-2) have been observed in a certain percentage of patients with severe depressive disorders, and that the presence of these cytokines has been demonstrated in studies based on high quality evidence, including meta-analyses.[8] The first question that comes to the mind of an interested dermatologist is what might be the phylogenetic explanation of the inflammatory nature of depression and anxiety and why they persist in human nature. One theory is that, in past ages, when the chief causes of death were interactions with infectious agents present in the environment and violent encounters with animals or human conspecifics, the state of persistent immune activation and avoidance behaviors associated with anxiety and depression ensured a state of alertness to potential unexpected attacks while minimizing risks and favoring energy conservation (sickness behavior), all of which would have afforded clear evolutionary advantages in a hostile environment.[9] Today, by contrast, in a scenario in which the risks have changed, a state of persistent inflammation is clearly disadvantageous and has become fertile breeding ground for autoimmune and autoinflammatory comorbidities and diseases.

Apart from the impossibility of demonstrating the truth of these proposals, and still on the subject of pathogenesis, we may wonder what are the key pathways and mechanisms that trigger and explain the inflammatory state in depression. On one hand, the sympathetic nervous system, in response to stress, anxiety or depression, promotes the release of amines, such as norepinephrine, which stimulate the synthesis of myeloid cells in bone marrow (monocytes, for example) and their release into peripheral blood. These cells then interact with other stress-induced substances, some of which are bacterial products—for example from the intestinal microbiome—such as lipopolysaccharides or flagellin, but more particularly stress-induced damage-associated molecular patterns. Both of these substances can activate inflammatory signaling pathways such as nuclear factor-κB (NF-κB) and structures such as NOD–, LRR–, and pyrin domain-containing protein 3 inflammasome. Stimulation of this protein activates caspase, leading to the production of IL-1β, IL-18, TNF, and IL-6. It is very interesting to note that this inflammatory activation also has an inhibitory effect on endogenous glucocorticoid receptors. This resistance to the regulatory effects of endogenous cortisol levels permits the activation of the hypothalamic-pituitary-adrenal (HPA) axis, which keeps the proinflammatory pathways open, enhancing and increasing the inflammatory response. These cytokines generated in the peripheral circulation not only act in the periphery but also transfer their effects to the central nervous system through humoral and neural pathways.

However, the central nervous system has its own mechanisms for generating and maintaining inflammation. Through these mechanisms, psychosocial stress may favor the activation of the microglia to create a proinflammatory phenotype capable of releasing CC-chemokine ligand 2, which has chemotactic effects on myeloid cells generated in the periphery. The central action of proinflammatory cytokines, whether they are generated peripherally or in the central nervous system, will lead to decreased availability of monoamines—serotonin, dopamine, and