Journal of Schizophrenia Research

Open Access

Austin Publishing Group

Research Article

Psoriasis, Schizophrenia and Disorders with Psychotic Features: Are They Linked?

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Received: March 09, 2015; **Accepted:** March 31, 2015; **Published:** April 02, 2015

Abstract

Psoriasis is a chronic inflammatory skin disease with a high impact on quality of life. It is a psychophysiological skin disorder with several psychiatric comorbidities. Schizophrenia is the most debilitating neuropsychiatric condition and recent studies have suggested that inflammatory pathways are part of its etiopathogeny. A possible connection between psoriasis and schizophrenia, or other disorders with psychotic features, has been suggested, although the studies in this field are scarce. We decided to perform a systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), using the 5S model of evidence based on information services described by Haynes. Our aim was to analyse what has been published on this topic. Psoriasis, schizophrenia and disorders with psychotic features seem to share genetic, immune and inflammatory processes which would explain why they could be linked. Cytokine activity may modulate the Hypothalamo-Pituitary-Adrenal (HPA) and Sympathetic Adrenomedullary (SAM) axes in both cases. Anti-psychotic medication and some treatments used for psoriasis modify the complex network of cytokines involved in both psoriasis and schizophrenia/disorders with psychotic features. This could explain, for instance, the reported adverse effects of some of the drugs used to treat psoriasis and schizophrenia. Further studies are necessary to explore the etiopathogenic correlations which may be found in psoriasis and schizophrenia with potential therapeutic relevance. More studies are necessary to confirm the evidence of a higher prevalence of psoriasis in schizophrenic patients and of psychotic features in psoriasis patients as well as the mechanisms that may be responsible.

Keywords: Disorders with psychotic features; Schizophrenia; Psoriasis

Introduction

It is estimated that the prevalence of psychiatric morbidity in dermatological patients is 30-40% [1,2]. Both brain and skin are embryologically derived from the neural plate in the ectoderm and this may be relevant in understanding if they also share biochemical mechanisms. The neuro-immuno-cutaneous-endocrine model was suggested by O'Sullivan et al. [3] to explain the mind and body connection. This model explains how many inflammatory cutaneous dermatoses, such as psoriasis, are triggered or exacerbated by stress factors, including psychological stress. These conditions are called psychophysiological skin disorders [1]. This embryological and biochemical relationship between the brain and the skin could also explain the high prevalence of psychopathology in dermatological patients, such as in psoriasis. Psoriasis is a chronic inflammatory skin disease with profound negative psychosocial effects affecting approximately 2% of the population worldwide [4]. The psychiatric morbidity in psoriasis is often a more important indicator of the disability experienced by the patient than the dermatologic aspects of the disorder [2]. Although referred to less frequently, some studies found a possible connection between psoriasis and psychosis, including schizophrenia [5,6]. Schizophrenia is a polygenic, multi-factorial disorder and recent neuroanatomical, neurobiological, environmental and genetic studies have suggested that inflammatory pathways are also involved in its pathogenesis [7]. In turn, psoriasis patients exhibit numerous diseases more often than expected on the basis ofthe prevalence of the respective disease [8]. Psoriasis is considered a state of chronic systemic inflammation, where several genes and related immune processes might explain the link between psoriasis and its comorbidities [8]. Based on the information above, this systematic review sets out to analyse the literature about a possible connection between psoriasis and schizophrenia and/or disorders with psychotic features.

Methods

The systematic review protocol was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [9].

Inclusion criteria

All articles that mentioned a link between psoriasis and schizophrenia, or psoriasis and disorders with psychotic features, were analysed. We considered the articles about prevalence, etiopathogeny and clinical aspects. Only articles published in English, German, French, Spanish and Portuguese were selected. The date restrictions were between 1990 and 2015. All study designs were included.

Search strategy

The search was performed in February 2015 and followed the 5S model of evidence based on information services, described by

Citation: Ferreira BR, Pio Abreu JL and Figueiredo A. Psoriasis, Schizophrenia and Disorders with Psychotic Features: Are They Linked?. J Schizophr Res. 2015;2(1): 1006.

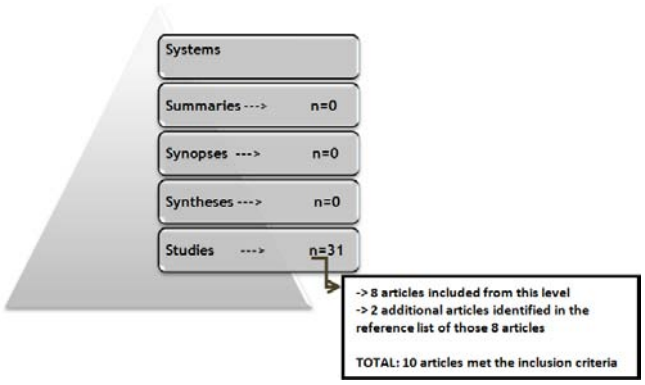

Figure 1: Flow chart of study methodology identified for this systematic review. The search strategy followed the Haynes' 5S Model of Evidence Based Information Services and resulted in 31 articles. 23 articles were excluded because they did not meet the inclusion criteria.

Haynes [10]. It is a pyramid with five levels of evidence that starts in *systems*, the top level, and goes down the pyramid to *summaries*, *synopses*, *syntheses* and *studies*. The *systems* level of evidence was not used, as it was not fully developed. Therefore, the first level used in this review was *summaries*. At this level, the search was carried out in Clinical Evidence by cross-referencing the words "psoriasis and schizophrenia" and "psoriasis and psychosis". No articles which focused on the inclusion criteria were found. At the *synopses* level of evidence, the search was conducted using the same words in the Evidence Based Medicine database, but no specific articles on that topic were retrieved. At the next level of evidence, *syntheses*, the Cochrane Library was used and again no articles were retrieved. At the *studies* level, the search in the Medical Subject Headings (MeSH) of PubMed was used to find studies that used different synonyms for the same concept. We used it to complete our systematic review. More precisely, the search strategy was the conjunction of the following terms: ("Psoriasis"[Mesh]) AND "Schizophrenia and Disorders with Psychotic Features"[Mesh]. The limits applied to this search were the studies with humans published up to 2015 in English, French, Spanish, German or Portuguese. This search gave us 31 articles.

Process of study and data collection

The titles and abstracts obtained from the search were reviewed and selected to be read in their entirety when they focused on the inclusion criteria.We also analysed and included the references of the selected articles when they met the inclusion criteria.

Data collection and analysis

Data extracted from each article that met the inclusion criteria were analysed following these parameters: the prevalence or probability of schizophrenia and disorders with psychotic features in psoriasis patients and the prevalence or probability of psoriasis in schizophrenic patients; the mechanisms which may explain the possible relationship between psoriasis and schizophrenia spectrum disorders; the medication used in the treatment of psoriasis and its psychotic adverse effects, and anti-psychotic drugs and psoriasis. Resulting from this, a total of 10 articles were included: 8 articles were identified through the Haynes' model and 2 identified in their reference list (Figure 1).

Results

The search provided 31 articles. The levels from the top of the Haynes pyramid of evidence did not retrieve articles about this topic. This shows that there is no other article which globally analyses the association that has been suggested between psoriasis and schizophrenia or disorders with psychotic features. Moreover, this points out that there is no other research that discusses those few studies that have been published on this subject.

After applying the inclusion criteria, only 8 articles from the studies level were included. We also included 2 articles after assessing the reference list. Table I exposes these articles and the characteristics of each study. Table II describes the main findings from the studies which were considered.

In the literature, there are 7 case-report studies that include a total of 10 patients. Considering the patients of the case-report studies, the range of ages was between 21 and 80. Four of those patients had an improvement of both psoriasis and psychosis with typical anti-psychotic drugs, namely haloperidol, levomepromazine and chlorpromazine. Three other patients exhibited an exacerbation of psoriasis or displayed symptoms of this skin condition shortly after the introduction of olanzapine, an atypical anti-psychotic drug. Two other patients from those identified showed an exacerbation of their psychotic symptoms shortly after the introduction of anew treatment for their psoriasis (cyclosporine and etarnecept). The last patient had a schizoaffective disorder and psoriasis. The other 3 studies given by this systematic review are: a case-control study which concludes that schizophrenic patients are at a greater risk of having psoriasis; a case-control study to determine the personality disorders found in psoriasis patients; a cross-sectional study which points out the high prevalence of psychopathology in psoriasis patients, including schizophrenic traits. More precisely, the first study belongs to Yang and Lin [5] who intended to investigate the risk of psoriasis among patients with schizophrenia compared with the general population, using a nationwide population-based dataset. They selected 47,390 patients who had been hospitalized between 1997 and 2001 for the treatment of schizophrenia and they excluded patients under the age of 18. Thereby, 46,350 patients with schizophrenia made up the study group. The comparison group was composed of 46,350 patients who were randomly extracted, one for every patient with schizophrenia, matched by age and sex. The intention was to know whether or not a patient had received a principal diagnosis of psoriasis between 2002 and 2005. This showed that the adjusted odds ratio (OR) for psoriasis was 1.21 [95% Confidence Interval (CI) 1.03–1.42, $P = 0.019$] for the patients with schizophrenia, compared with those without schizophrenia. It also showed that among the female patients sampled, the adjusted OR of having psoriasis for those with schizophrenia was 1.42 (95% CI 1.10–1.85, $P = 0.008$) compared with patients without schizophrenia. The second study mentioned above belongs to Rubino et al. [11] and reinforces the conclusions of other studies about the high scores of schizoid personality in psoriasis patients. Finally, the last study belongs to Mazzetti et al. [6], who found that 6.25% of psoriasis patients had a schizophrenic trait.

With regard to the explanation for a possible relationship between psoriasis and schizophrenia and/or disorders with psychotic features, several reasons have been suggested. Yang and Lin [5] mention that

Table I: Characteristics of the studies included in the systematic review.

Title	Article	Year of publication	Type of article/ study design	Patients	Data collection
Increased risk of psoriasis among patients with schizophrenia: a nationwide population-based study	[5]	2012	Case-control	Study group: 46,350 adult patients with schizophrenia who had been hospitalized between 1997 and 2001 for the treatment of schizophrenia. Comparison group: randomly extracted, 46,350 patients.	Study identified through the Haynes pyramid of evidence
Exacerbation of paranoid schizophrenia in a psoriatic patient after treatment with cyclosporine A, but not with etanercept	[14]	2007	Case-report	A 44-year-old man undergoing cyclosporine therapy for treatment of generalized plaque psoriasis.	Study identified through the Haynes pyramid of evidence
Etanercept, anticytokines and mania	[13]	2005	Case-report	A 21-year-old female patient with a manic episode with psychotic symptoms and psoriatic arthritis.	Study identified in the reference list of the article: *"Exacerbation of paranoid schizophrenia in a psoriatic patient after treatment with cyclosporine A, but not with etanercept"*
Psoriasis during therapy with olanzapine	[15]	2003	Case-report	Two cases of psoriasis in patients treated with olanzapine.	Study identified through the Haynes pyramid of evidence
Exacerbation of chronic large plaque psoriasis associated with Olanzepine therapy	[16]	2000	Case-report	A 52-year-old Caribbean woman with a prolonged history of schizophrenia associated with severe psoriasis.	Study identified through the Haynes pyramid of evidence
Schizophrenia associated with psoriasis vulgaris: three case reports	[12]	2000	Case-report	Three cases that developed schizophrenia and psoriasis vulgaris.	Study identified through the Haynes pyramid of evidence
Personality disorders and psychiatric symptoms in psoriasis	[11]	1995	Case-control	–	Study identified through the Haynes pyramid of evidence
Psoriasis, stress and psychiatry: psychodynamic characteristics of stressors	[6]	1994	Cross-sectional	80 in-patients	Study identified through the Haynes pyramid of evidence
Annular pustular psoriasis associated with affective psychosis	[28]	1990	Case-report	An 80-year-old man with annular pustular psoriasis and manic episodes.	Study identified in the reference list of the article: *"Schizophrenia associated with psoriasis vulgaris: three case reports"*
Mood-dependent fluctuations in the severity of dyskinesia and psoriasis vulgaris in a patient with schizoaffective disorder: possible role of melatonin	[29]	1990	Case-report	A 28-year-old female patient with schizoaffective disorder associated with psoriasis vulgaris and tardive dyskinesia.	Study identified through the Haynes pyramid of evidence

one explanation for the positive association between schizophrenia and psoriasis is related to inflammatory processes. They also note that many studies have confirmed that PSORS1 on chromosome 6p21.3 is a major locus for psoriasis susceptibility. Interestingly, there is also evidence that schizophrenia may be linked with chromosome 6p22–24, which is not too distant from PSORS1. Miyaoka et al. [12] pointed out that there might be a genetic susceptibility to psoriasis vulgaris and schizophrenia located on chromosome 6p as well. In addition, they also mentioned in their study that they could obtain the consent to examine the HLA type from only one of the three patients and HLA-Cw7 was present in that schizophrenic patient. HLA-Cw7 is also associated with psoriasis vulgaris. Moreover, those authors focused the elevation of phospholipase A2 activity in both psoriasis and schizophrenia too.

Kaufman [13] highlights the relationship between the levels of TNF-alfa and several pathologies, namely psoriasis and manic episodes with psychotic features. In turn, Di Nuzzo et al. [14] pointed out in their article that IL-2 plays a role in both psoriasis and schizophrenia and that some drugs used in the treatment of psoriasis reduce the levels of IL-2. This is the case of cyclosporine.

Latini and Carducci [15] and Ascari-Raccagni et al. [16] pointed out the possible higher risk of exacerbating or starting psoriasis after the introduction of olanzapine to treat a comorbid psychosis.

Discussion

This systematic research showed that little has been written about the relationship between psoriasis and schizophrenia or disorders with psychotic features. There is no other systematic review about this topic. We consider that the relationship between psoriasis and schizophrenia or disorders with psychotic features should be more deeply analysed. It is important to read and compare what has been published in order to understand whether or not this matter may have clinical relevance that requires further research. There are several topics which should be discussed regarding this theme. First of all, the definition of the kind of psychosis is not always clear in all the case-reports on this topic. Moreover, that definition is not always rigorous in clinical practice and this could influence the number of reported cases. On the other hand, an imprecise description of the psychiatric diagnosis may difficult a rigorous analysis about a possible link with psoriasis and the own subtleties of each comorbidity. However, according to the results of this systematic review, there is some evidence of a relationship between schizophrenia and/or disorders with psychotic features and psoriasis. For example, Yang and Lin [5], carried out a case-control study which concluded that schizophrenic patients have a higher probability of having a diagnosis of psoriasis. Other studies highlight that psoriasis patients have a higher risk of having schizophrenic traits [6,17,18].

Table II: Description of the main findings of the studies.

Article	Main findings	
[5]	Patients with schizophrenia had 1.2-fold higher risk of psoriasis. The risk of psoriasis was significantly increased (1.4 times) among women with schizophrenia.	
[14]	**Patient:** a 44-year-old man with generalized plaque psoriasis (from the age of 31) and paranoid schizophrenia (diagnosed at the age of 23).	Cyclosporine therapy exacerbated psychotic symptoms within a few weeks after its introduction. These symptoms disappeared a few days after discontinuation of cyclosporine.
[13]	**Patient:** a 21-year-old female patient with a maniac episode with psychotic symptoms and psoriatic arthritis.	The patient developed a manic episode with psychotic symptoms shortly after introducing etanercept to treat her psoriatic arthritis.
[15]	**Patient:** a 38-year-old male patient with psychosis and mild psoriasis (psoriasis was diagnosed at the age of 14).	He had a worsening of his pre-existing mild psoriasis two weeks after the first introduction of olanzapine treatment and 15 days after the reintroduction of that anti-psychotic drug for the second time.
	Patient: a 28-year-old male patient with psychosis (diagnosed at the age of 22).	His psoriasis started for the first time 20 days after starting olanzapine treatment. He had no previous personal history of psoriasis. His father had the disease.
[16]	**Patient:** a 52-year-old female patient with schizophrenia and severe psoriasis (schizophrenia diagnosed at the age of 21 and psoriasis at the age of 40).	Olanzapine proved to be very active in improving the subject's psychiatric condition. However, after 2 weeks of treatment there was a dramatic worsening of her psoriasis with larger plaques on the trunk, massive scalp involvement and for the first time lesions on the palms and soles.
[12]	**Patient:** a 39-year-old male patient with schizophrenia and psoriasis vulgaris (both diagnosed at the age of 29).	Both schizophrenia and psoriasis were well controlled by low dose neuroleptics. In the clinical course, anti-psychotic medication (haloperidol) did not exacerbate but rather helped his psoriasis.
	Patient: a 40-year-old male patient with schizophrenia and psoriasis vulgaris (both diagnosed at the age of 25).	In the clinical course, anti-psychotic medication (haloperidol) did not exacerbate but helped his psoriasis.
	Patient: a 56-year-old female patient with schizophrenia and psoriasis vulgaris (schizophrenia diagnosed at the age of 21 and psoriasis at the age of 40).	In the clinical course, anti-psychotic medication did not exacerbate but helped his psoriasis (levomepromazine in this case).
[11]	High scores of schizoid personality in psoriasis patients.	
[6]	There is a high prevalence of psychic disorders in psoriasis patients. 6.25% of psoriasis patients had a schizophrenic trait.	
[28]	**Patient:** an 80-year-old man with annular pustular psoriasis and manic episodes.	Exacerbations of his annular pustular psoriasis followed manic episodes. The use of chlorpromazine led to a remission of both conditions.
[29]	**Patient:** a 28-year-old female patient with schizoaffective disorder and psoriasis.	The exacerbation of depression symptoms occurred at the same time as the worsening of her psoriatic lesions. The improvement of depression symptoms correlated with the regression of the psoriatic lesions.

Rubino et al. [11] corroborated the conclusions of previous studies which mentioned that psoriasis patients also have high scores of schizoid character. The main characteristics of schizoid character are social isolation, intimacy avoidance and restricted affections. Although for a long time it has been considered that a schizoid character was related to schizophrenia, this is not true. Nevertheless, schizoids may be more susceptible to psychosis. This personality shares with schizophrenia, although with its own subtleties, the problem of the distinction between the "self" and the "other" [19].

Concerning the etiopathogeny, this systematic review leads to the following conclusions. Schizophrenia is the most debilitating neuropsychiatric disorder and there is considerable evidence of changes in the immune system. It is a heterogeneous syndrome and immune changes may thus be another neuropathogenic mechanism among many already described [20]. On the other hand, the immune pathways that become activated in psoriasis represent modifications of the immune pathways in normal human skin. The causal relationship between psoriasis and comorbidities is not fully understood, but shared genetic risks, common environmental factors, or inflammatory pathways may provide the links. The genetic modifications may be inherited from the parents or may reflect environmental conditions affecting patients during pregnancy or their immediate progenitors. Several studies have shown that a dysregulation of the Hypothalamic–Pituitary–Adrenal (HPA) axis is assumed to be involved in the stress induced exacerbation of chronic inflammatory diseases by leading to an upregulation of proinflammatory cytokines [21,22]. This dysregulation includes both central and peripheral skin HPA axes activity [21,23,24]. Other studies have suggested that prenatal and perinatal infections could disrupt fetal neurodevelopmental processes, leading to long-lasting brain changes and increasing the risk of psychotic disturbances in early adulthood [20,25]. In this scenario, altered levels of IL-1 and IL-6 could influence the release of hormones by the hypothalamic-pituitary-adrenal axis, contributing to changes in monoamine neurotransmission in schizophrenic patients [20,26]. From the foregoing we may say that infection and inflammation may trigger pathological mechanisms that result in proneness to psychosis and psychophysiological cutaneous diseases such as psoriasis. Anti-psychotic medication alters immune parameters and this may explain the cutaneous changes found in psychotic patients shortly after they have started the antipsychotic drugs, as mentioned in Table II. On the other hand, the psychotic adverse effects caused by cyclosporine could be understood considering its effect on IL-2, a cytokine with an important role in the etiopathogeny of both schizophrenia and psoriasis [14]. To sum up, the reasons for the comorbidity psoriasis and schizophrenia/disorders with psychotic features could involve genetic susceptibility, such as that involving the chromosome 6p [5,27], immune and inflammatory processes.

Priorities of future research include more studies of the prevalence of psoriasis in schizophrenic patients and of schizophrenia or disorders with psychotic features in psoriasis in order to confirm and/or increase the evidence of the higher risk already mentioned. Besides, it would be interesting to explore the biochemical mechanisms which could explain the adverse effects of olanzapine, namely the probability of dermatologic problems. Moreover, it would

be important to analyse the probability of dermatologic side effects after the introduction of a typical or an atypical antipsychotic drug and the underlying reasons for this. Finally, the role of chronic stress and inflammatory or immune processes in the etiopathogeny of both psoriasis and psychiatric conditions, such as schizophrenia and other disorders with psychotic features, should be explored. Perhaps a deeper understanding of this topic could also have therapeutic relevance, considering the subtleties of the immune and inflammatory processes involved in each or both conditions.

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J Schizophr Res - Volume 2 Issue 1 - 2015
ISSN : 2471-0148 | www.austinpublishinggroup.com

Citation: Ferreira BR, Pio Abreu JL and Figueiredo A. Psoriasis, Schizophrenia and Disorders with Psychotic Features: Are They Linked?. J Schizophr Res. 2015;2(1): 1006.