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Study of the Role of Stress, Depression and Anxiety in Development of Psoriasis along with Morphological and Biochemical Changes

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Abstract

Introduction: Psoriasis is a chronic, relapsing, cutaneous disease affecting about 2-3% of the world's population and presents as erythematous, indurated, scaly plaques over the skin with involvement of nails and joints in some cases. Although psoriasis is not a life threatening disease, but the quality of life is severely affected and there is still no curative treatment. Many patients also have associated stress, depression and anxiety related problems. **Aim of the study:** To study the role of stress, anxiety and depression in development of psoriasis, to study the histopathological changes in psoriatic skin biopsies and serum serotonin levels in psoriasis. **Materials and Methods:** A total of 27 cases of biopsy diagnosed psoriasis cases and 27 controls were studied for clinical presentation, microscopic findings, for stress, depression and anxiety indices. The serum serotonin levels of psoriasis cases were compared with age and gender matched non-psoriatic healthy control individuals. **Results:** The patient age ranged from 17 to 55 years and there was a male predominance with male to female ratio of 3.5:1. Psoriasis was more common in the fourth and fifth decades. Psoriasis vulgaris was the most common clinical presentation. Consistent biopsy findings in most of the cases were presence of parakeratosis, dilated capillaries, elongated rete ridges with blunted edges, hypogranulosis and regular acanthosis. All three indices showed mean value signifying a Moderate degree of perceived stress, depression and anxiety in psoriasis group. The difference between serum serotonin levels in the patient group and control group was highly significant. **Conclusion:** Psoriasis is a chronic skin disorder affecting young to middle people and is more common in males. Psoriasis vulgaris was the most common clinical presentation. Consistent biopsy findings in most of the cases were presence of parakeratosis, dilated capillaries, elongated rete ridges with blunted edges, hypogranulosis and regular acanthosis. These patients are more likely to have mild to moderate degree of perceived stress, depression and anxiety. Many patients with psoriasis have elevated serum serotonin and are also likely to have depression. Prescription of serum serotonin reuptake inhibitors (SSRIs) has to be done cautiously in these patients.

Keywords

Psoriasis, Stress, Anxiety and Depression in psoriasis, Histopathology of psoriasis, Serum serotonin in psoriasis.

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INTRODUCTION

Psoriasis is a chronic, relapsing, cutaneous disease affecting about 2-3% of the world's population and presents as erythematous, indurated, scaly plaques over the skin with involvement of nails and joints in some cases. [1] Although psoriasis is not a life-threatening disease, but the quality of life is severely affected and there is still no curative treatment. [2]

There are many factors involved in the induction and/or exacerbation of psoriasis like genetic, environmental, infections, stress, some drugs, smoking and alcohol. Together, genetic and extrinsic factors lead to abnormal keratinocyte proliferation, cutaneous inflammation, skin vessel disturbances, finally resulting in clinical features of psoriasis. [3] Because of its chronicity and visibility, psoriasis is responsible for significant distress, suffering, decrease of quality of life level and stigmatization. [4] Itching was the most common subjective symptom reported by psoriatic patients and this further contributes to lowering of psoriatic patients' well-being. [5]

Though psoriasis can be diagnosed clinically, for all new cases a skin biopsy is used as the gold-standard for diagnosis and to rule out the mimics of psoriasis.

Studies have established considerable connection of stress and mood disorders in development of psoriatic lesions. [6, 7]

Questions of causality arise when exploring the complex relationship of psoriasis and mood disorders, and studies have revealed that inflammation may serve as the common denominator linking psoriasis and depression. Conversely, many investigators have reported that psoriasis severity may fluctuate with perceived psychological distress, suggesting that psychological factors, rather than inflammation, may be the driving force behind disease exacerbation in these cases. The truth is likely a combination of both schools of thought: a bidirectional relationship between cutaneous and psychological disease manifestations with an overlapping biological mechanism associated with inflammation. [8]

Serotonin (5 hydroxytryptamines; 5-HT) is a neurotransmitter whose effect is mediated through different receptor interactions and consists of 14 subtypes. It plays an important role in cognition and memory. It is thought that any decrease in serotonin, leads to an increase in proinflammatory cytokines that propel the inflammatory process towards psoriasis. [9]

In the present study we have attempted to look at the role of stress, depression and anxiety in the causation of psoriasis, the histopathological changes in skin biopsies in psoriasis and also the serum serotonin levels in psoriasis.

AIM OF THE STUDY

To study the role of stress, anxiety and depression in development of psoriasis, to study the histopathological changes in psoriatic skin biopsies and serum serotonin levels in psoriasis.

MATERIALS AND METHODS

No ethical issues were involved in the study. Written consent was taken from all the participants. This was a prospective, hospital-based study done in the Department of Pathology at Subharti Medical College, Meerut, Uttar Pradesh, India, which is a tertiary care centre. The study period was of one year from October 2017 to October 2018.

Patients coming to the dermatology out-patient department (OPD) with the clinical diagnosis of Psoriasis or suspected psoriasis were the main focus of this study. Skin biopsies were done by the dermatologist from representative skin lesions. Punch or incisional biopsy were done and were immediately put in 10% buffered neutral formalin for fixation. Then they were submitted to the department of pathology for histopathological processing. After adequate fixation the tissue specimens were processed by routine histopathological methods. Then the sections were cut at five-micron thickness and were stained with routine haematoxylin and eosin stain. The stained sections were observed under light microscope and the histopathological findings were noted.

For those cases that were diagnosed as psoriasis on skin biopsies; when the patients came to collect the reports, they were informed about this study and were asked about their willingness to participate in the study. Written informed consent was taken from the participants.

Next, all the participants were interviewed by the principal investigator regarding the clinical details and symptomatology with special reference to PASI score. The principal investigator in person administered three questionnaire based tests to the participants to assess the Stress, Anxiety and Depression. The various scores used were Perceived Stress Scale (PSS), Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-S).

A total of 27 patients with psoriasis were studied for the three scores and their biopsy findings were observed. Venous blood samples taken from antecubital area of the arm were collected from all the patients for serum serotonin and were analyzed using the ELISA method. Age and gender matched blood samples from healthy adults were also collected from our blood bank and these were considered as the control samples.

The control cases were also administered the questionnaires for PSS, HAM-D and HAM-A.

Inclusion criteria:

1. All new cases of psoriasis
2. Both genders and all age groups
3. Histopathologically proven cases of Psoriasis

Exclusion criteria:

1. Clinically suspected but biopsy negative cases were excluded
2. Cases with inadequate biopsy material
3. Patients already on antidepressants were excluded.

Perceived Stress Scale (PSS): [10] The Perceived Stress Scale (PSS) is the most widely used psychological instrument for measuring the perception of stress. It is a measure of the degree to which situations in one's life are appraised as stressful. The scale also includes a number of direct queries about current levels of experienced stress. The PSS was designed for use in community samples. The items are easy to understand, and the response alternatives are simple to grasp. Moreover, the questions are of a general nature and hence are relatively free of content specific to any subpopulation group. The questions in the PSS ask about feelings and thoughts during the last month.

Individual scores on the PSS can range from 0 to 40 with higher scores indicating higher perceived stress. Scores ranging from 0-13 are considered low stress. Scores ranging from 14-26 are considered moderate stress and scores ranging from 27-40 are considered high perceived stress.

Hamilton Depression Rating Scale (HDRS): [11] The HDRS (also known as the Ham-D) is the most widely used clinician-administered depression assessment scale. The original version contains 17 items (HDRS17) pertaining to symptoms of depression experienced over the past week. The HDRS was originally developed for hospital inpatients, thus the emphasis on melancholic and physical symptoms of depression. A score of 0–7 is generally accepted to be within the normal range (or in clinical remission), while a score of 20 or higher (indicating at least moderate severity) is usually required for entry into a clinical trial.

Hamilton Anxiety Rating Scale (HAM-A): [12] The HAM-A was one of the first rating scales developed to measure the severity of anxiety symptoms and is still widely used today in both clinical and research settings. The scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). The HAM-A does not provide any standardized probe questions. Despite this, the reported levels of inter-rater reliability for the scale are acceptable.

Scoring: Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0–56, where < 17 indicates mild severity, 18–24 mild to moderate severity and 25–30 moderate to severe.

Psoriasis Area Severity Index (PASI): Psoriasis Area and Severity Index (PASI) [13] is the most widely used tool for the measurement of severity of psoriasis. PASI combines the assessment of the severity of lesions and the area affected into a single score in the range 0 (no disease) to 72 (maximal disease)

The body is divided into four sections (head (H) (10% of a person's skin); arms (A) (20%); trunk (T) (30%); legs (L) (40%)). Each of these areas is scored by itself, and then the four scores are combined into the final PASI. For each section, the percent of area of skin involved, is estimated and then transformed into a grade from 0 to 6:

1. 0% of involved area
2. < 10% of involved area
3. 10–29% of involved area
4. 30–49% of involved area
5. 50–69% of involved area
6. 70–89% of involved area
7. 90–100% of involved area

Within each area, the severity is estimated by three clinical signs: erythema (redness), induration (thickness) and desquamation (scaling). Severity parameters are measured on a scale of 0 to 4, from none to maximum.

The sum of all three severity parameters is then calculated for each section of skin, multiplied by the area score for that area and multiplied by weight of respective section (0.1 for head, 0.2 for arms, 0.3 for body and 0.4 for legs).

PASI is widely used in clinical trials of therapies to treat psoriasis. Although absolute PASI score is often used to define entry into a trial, it is response to treatment that is important to measure efficacy and outcomes. This is usually presented as a percentage response rate, e.g., PASI 50, PASI 75, PASI 90, PASI 100.

Statistical analysis is depicted as percent, mean values, standard deviations and p-values.

OBSERVATIONS AND RESULTS

A total of 27 patients were studied for histological features, for stress, depression, anxiety indices and for serum serotonin levels in biopsy diagnosed cases of psoriasis.

There was a male predominance and the male to female ratio was 3.5:1 (21 male patients and 6 female patients). The patient age ranged from 17 years to 55 years.

Based on clinical presentation, Psoriasis vulgaris was the commonest type 22 (81.4%) cases followed by the maculopapular variety 4 (14.8%) cases and least common was the erythrodermic type 1 (3.7%) case.

Table 1 Age-wise distribution of cases

Age (in years)	No. of cases	Percent (%)
10-20	3	11.1%
21-30	3	11.1%
31-40	10	37%
41-50	10	37%
51-60	1	3.7%
Total	27	100%

Most (74%) of the patients were in the 31 to 50 years age groups.

Table 2 Comparison of subject and control characteristics

Characteristics		Cases	Controls	P value
Gender	Males	21	23	NS
	Females	6	4	NS
Age (in years) Mean +/- SD		37 (+/- 9.5)	36 (+/- 7.5)	NS
Family history	Present	6 (22.2%)	-	S*
	Absent	21 (77.7%)	27 (100%)	
Type of psoriasis	Type I	16 (59.2%)	-	-
	Type II	11 (40.8%)	-	-
PASI	Mild	12 (44.4%)	-	-
	Moderate	10 (37%)	-	-
	Severe	4 (14.8%)	-	-
Clinical type of psoriasis	Psoriasis vulgaris	22 (81.4%)	-	-
	Maculopapular	4 (14.8%)	-	-
	Eythrodermic	1 (3.7%)	-	-

PASI: Psoriasis area severity index. P value <0.05 is significant; NS: Not significant; S*: Significant

Type I psoriasis occurs before age 40 and type II occurs after age 40. In our study Type I was more common (16/27 cases, 59.2%) than Type II (11/27 cases, 40.8%).

Clinically, psoriasis vulgaris was the most common presentation and was seen in 81.4% patients.

Table 3 Histopathological changes in biopsy specimens

Serial number	Histological findings	No. of cases	Percent (%)
1	Hyperkeratosis	26	96.2%
2	Parakeratosis	24	88.8%
3	Acanthosis	25	92.5%
4	Elongation and blunting of rete ridges	26	96.2%
5	Suprapapillary thinning	18	66.6%
6	Absence of granular layer	24	88.8%
7	Spongiosis	8	29.6%
8	Munro micro abscess	9	33.3%
9	Kogoj abscess	5	18.5%
10	Intraepidermal neutrophilic exocytosis	7	25.9%

On histopathology, hyperkeratosis, acanthosis, elongated rete ridges and hypogranulosis were common and consistent findings in most of the cases.

Table 4 Causes for stress in cases of psoriasis

Reasons for stress	No. of cases	Percent (%)
Financial problems	11	40.7%
Family problems	13	48.1%
Loss of dear one	1	3.7%
Loneliness	1	3.7%
Forced withdrawal from school education	1	3.7%
Total	27	100%

Normal serum serotonin levels are 70-270 ng/ml.
HS*: Highly significant

Table 5 Stress index, depression index and anxiety index in psoriasis cases

Serial number	Stress index (PSS) (0-13: Low stress 14-26: Moderate stress 27-40: High stress)	Depression index (HAMD) (0–7 within the normal range/or in clinical remission 7-17: Mild depression 18-24: Moderate depression >25: Severe depression)	Anxiety index (HAMA) (< 17: Mild 18–24 Moderate 25–30 Severe)
1	25	22	21
2	24	27	27
3	25	23	14
4	35	11	06
5	34	36	26
6	31	30	33
7	20	07	10
8	13	29	22
9	32	19	16
10	29	25	25
11	26	21	22
12	23	27	22
13	25	26	20
14	22	25	20
15	38	34	22
16	27	21	19
17	15	25	26
18	34	23	21
19	33	24	21
20	10	24	22
21	23	23	17
22	22	23	20
23	14	25	22
24	18	20	20
25	30	24	20
26	13	27	23
27	20	27	24
Mean	24.4 (+/-7)	24 (+/- 7.2)	20.7 (+/-6.7)

All three indices showed mean value signifying Moderate degree of perceived stress, depression and anxiety.

Table 6 Stress index, depression index and anxiety index in controls

Serial number	Stress index (PSS) (0-13: Low stress 14-26: Moderate stress 27-40: High stress)	Depression index (HAM-D) (0–7 within the normal range/or in clinical remission 7-17: Mild depression 18-24: Moderate depression >25: Severe depression)	Anxiety index (HAM-A) (< 17: Mild 18–24 Moderate 25–30 Severe)
1	20	17	10
2	16	03	3
3	20	11	10
4	10	0	2
5	13	0	4
6	17	1	4
7	25	3	2
8	29	3	1
9	11	2	3
10	11	1	2
11	11	0	1
12	17	2	3
13	16	4	1
14	11	7	1
15	12	1	12
16	20	03	07
17	18	1	0
18	20	0	3
19	17	0	12
20	17	2	12
21	17	2	12
22	05	2	2
23	06	0	4
24	08	0	2
25	15	2	12
26	16	9	7
27	17	11	7
Mean	15.3 (+/-6)	3.2 (+4.2)	5.1 (+/-3)

Table 7 Comparison of serum serotonin levels, stress index, depression index and anxiety index between psoriasis and non-psoriasis control group

Variable	Mean +/- SD Psoriasis	Mean +/- SD Non-Psoriasis	Mean difference	95% CI	P value
Serum serotonin level (ng/ml)	605.4 +/- 151.3	407.9 +/- 101.9	197.5	267.9 to 127.0 (DF=52)	<0.0001 HS*
Serum serotonin level (ng/ml) Excluding four highest values	496.05 +/- 124	117.8 +/- 29.4	378.2	431.7 to 324.6 (DF= 44)	<0.0001 HS*
Stress index	24.4 (+/-7)	15.3 (+/-6)	9.1	12.6 to 5.5 (DF= 52)	<0.0001 HS*
Depression index	24 (+/- 7.2)	3.2 (+/-4.2)	20.8	24.0 to 17.5 (DF= 52)	<0.0001 HS*
Anxiety index	20.7 (+/-6.7)	5.1 (+/-3)	15.6	18.4 to 12.7 (DF= 52)	<0.0001 HS*

Normal serum serotonin levels are 70-270 ng/ml.
HS*: Highly significant

DISCUSSION

Psoriasis is a common, relapsing, multifactorial cutaneous condition having chronic inflammation and hyper proliferation of keratinocytes as main pathogenetic mechanisms. [14] It is considered to be immune T-cell mediated inflammatory dermatoses

characterized by epidermal hyperplasia, neoangiogenesis of dermal vessels and marked acceleration of epidermal turnover. [15]

Bedi et al [16] (n=530) have reported 2.8% and Kaur et al [17] (n=1220) have reported 2.3% prevalence of psoriasis for patients visiting Dermatology outpatients. In our study, the prevalence of psoriasis was 2.5% which compares well with the above studies.

In our study the patient age ranged from 17 years to 55 years with mean age being 37 years and the male to female ratio was 3.5:1. Various studies have reported similar gender ratios of 2.4:1 and 2.03:1. [16, 17]

Most (74%) of our patients were in the 31 to 50 years age groups. Bedi et al [16] and Wardhana et al [9] have also reported similar age groups for psoriasis.

Henseler and Christopher [18] studied 2147 patients and observed two clinical presentations of Psoriasis and called them as Type I and Type II depending on the age of onset. Type I is more common and accounts for almost 75% cases. Type I has a strong positive family history, more severe disease and is more likely to have HLA-Cw6 associations. Type II is relatively uncommon and occurs after 40 years age and has strong HLA-B27 associations. [19] In our study, Type I was more common (16/27 cases, 59.2%) than Type II (11/27 cases, 40.8%). Wardhana et al [9] also observed 70% type I and 30% of Type II psoriasis in their study.

In our study, family history of psoriasis was present in 22.2% cases, whereas, in the control group it was not seen in any of the subjects. Wardhana et al [9] observed positive family history in 72% of their cases. This could be because of the more number of type I cases in their study which are known to have strong family history.

In our study the mild and moderate PASI score cases were more 22 (81.4%) as compared to severe PASI score. Wardhana et al [9] also observed that 78% of their cases fell in the mild and moderate PASI score. PASI is widely used in clinical trials of therapies to treat psoriasis. Although absolute PASI score is often used to define entry into a trial, it is response to treatment that is important to measure efficacy and outcomes. This is usually presented as a percentage response rate; e.g., PASI 50, PASI 75, PASI 90, PASI 100.

In the present study, clinically, psoriasis vulgaris was the most common presentation and was seen in 81.4% patients. According to a few Indian studies [16, 17] Chronic plaque type psoriasis /Psoriasis vulgaris (90% and 93%) were the most common clinical phenotype. Our findings compare well with the above studies.

On histopathology, hyperkeratosis, acanthosis, elongated rete ridges and hypogranulosis were common and consistent findings in most of the cases in our study. Arora D et al [20] in their study observed parakeratosis in all of their patients. Various workers (Bai et al and Park et al) [21, 22] in their respective studies have observed parakeratosis as an important and consistent biopsy finding whereas in our study parakeratosis was found in 88.8% cases. In our study, hyperkeratosis was seen in 96.2% cases. Similar finding of 89% was observed by Abdu NN et al. [23]

Stress is a well-known trigger factor in the appearance or exacerbation of psoriasis. It is associated with physical disability, emotional distress, discomfort and social stigmatization. [24] Psoriatic patients experience high levels of internalized stigma which is adoption of negative attitudes and stereotypes of the society regarding a person's illness. It causes decreased self-esteem and life-satisfaction, increased depression, suicidal tendency, and difficulty in coping with the illness. [25]

In our study effort was made to elicit the reason for stress in the patients and most common reasons observed were of financial problems and conflict with a family member affecting interpersonal relationships. These two were the most common trigger factors and were seen in 88.8% cases.

In our study, the stress index, depression index and anxiety index all three were elevated in all the patients variably and the mean scores for all three parameters were in the “Moderate category”. The control cases were also administered the questionnaires and showed depression and anxiety scores within normal range, ie. as expected there were no depression or anxiety elements in the healthy blood donors and statistically the difference was highly significant between these scores in psoriasis and control subjects.

There were quite a few number of controls in whom the PSS score for stress was high and the mean of all controls was 15.3, ie, of moderate stress. This could be explained by the fact that many donors were replacement donors with their family member or friend being admitted in the hospital at that point in time and hence, could be having stress and the higher PSS score.

Gaikwad et al [26] (n=43) observed that psoriasis affected the social interactions, reduced work efficiency and caused distress at work place in more than half of their patients. They also found that in two third patient’s psoriasis had affected their interpersonal relationship leading to stress in home environment and that 67% of the patients had psychiatric comorbidity. Matoo et al [27] (n=103)

observed depressive episodes in 22% of their psoriatic study population.

The scoring for perceived stress, depression and anxiety takes into account the thoughts and feelings of the patients only for the preceding one month. Some of our patients had a longer history of symptoms which were over one-month duration. So by the time the questionnaires were administered it had crossed the one month for some of the patients. In such cases it cannot be said whether stress, depression and anxiety had actually triggered the psoriasis or they happened to be the result of the disease process.

Stress reaction in patients with psoriasis is probably mediated by the hypothalamic-pituitary-adrenal relationship causing release of adrenal hormones. Serotonin (5-hydroxytryptamine 5-HT) is a neurotransmitter that is a vasoactive amine which is stored in the blood by platelets and is released at sites of inflammation. It is well documented that stress and stress related hormones lead to increased serotonin synthesis. [28]

Serotonin has importance in the cascade that regulates T cell function. Optimal stimulation of T cell function is dependent on presence of serotonin. [29] Serotonin, or hormonal actions on serotonin and serotonin receptors, may have a role in psoriasis.

In our study, the mean serum serotonin value in psoriatic group was 605.4 ng/ml (+/- 151.3 SD) and in the control group it was 407.9 ng/ml (+/- 101.9 SD). In our laboratory the normal reference range for serum serotonin is 70-270 ng/ml. We found serum serotonin to be elevated in both the groups and the difference between the two groups was highly significant, p value <0.0001. This could be due to the fact that four of our psoriatic patients had very high serum serotonin levels (1234.80, 1318.69, 1262.38, 1122.36 ng/ml) If these four values were excluded then the serum serotonin mean value was 496.05 ng/ml

Correspondingly if the highest four values of serum serotonin (912.68, 777.01, 528.85, 492.21) from control group were excluded then the mean of control group would be 117.8 ng/ml and the difference between the two groups was highly significant. With or without excluding the highest four values the difference between psoriatic and control groups for serum serotonin was statistically highly significant (Table 6).

Serum serotonin reuptake inhibitors (SSRIs) are many times used in the treatment of depression. Low levels of serotonin in the brain may cause depression, anxiety and sleeping disorders for which serum serotonin reuptake inhibitors (SSRIs) may be prescribed. SSRIs are the most commonly used antidepressants and are generally given for severe depression. They are also known to have anti-inflammatory effects by way of inhibiting interleukin 6. [30] It is possible that for a subset of patients who already have elevated serum serotonin, the prescribed SSRIs may cause adverse effects. We recommend testing the serum serotonin of patients before prescribing SSRIs.

The limitations of this study were that the sample size was small. There was a recall bias in some of the patients for the duration of psoriatic lesions. Larger studies can examine and substantiate our findings.

CONCLUSION

Psoriasis is a chronic skin disorder affecting young to middle age people and is more common in males. Psoriasis vulgaris is the most common clinical presentation. Consistent biopsy findings in most of the cases are presence of parakeratosis, dilated capillaries, elongated rete ridges with blunted edges, hypogranulosis and regular acanthosis. These patients are more likely to have mild to moderate degree of perceived stress, depression and anxiety. Many patients with psoriasis have elevated serum serotonin and are also likely to have depression. Prescription of serum serotonin reuptake inhibitors (SSRIs) has to be done cautiously in these patients.

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