

Association of brain derived neurotrophic factor (BDNF) with inflammation in psoriasis



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Submission: 31-07-2020

Revision: 09-09-2020

Publication: 01-11-2020

ABSTRACT

Background: Psoriasis is a common immune mediated chronic inflammatory disorder characterized by involvement of skin and other organ systems. Brain derived neurotrophic factor (BDNF) which has various roles in the nervous system, is also involved in cutaneous sensory innervation. Apremilast is a relatively new drug indicated for moderate-to-severe plaque psoriasis and psoriatic arthritis. **Aims and Objective:** The present study aimed to explore the BDNF levels in moderate to severe plaque psoriasis and analyse the variation in the levels, if any, in response to apremilast therapy. **Materials and Methods:** Blood samples from patients of psoriasis (n = 24), of either sex and age ≥ 18 years suitable to be prescribed apremilast as standard treatment, were taken on initial and subsequent follow up visit after two months of therapy. Sample from matched controls were also evaluated. Enzyme-linked immunosorbent assay (ELISA) kit (QUAYEE-BIO) and microplate reader (at 450 nm) were used to determine BDNF values. Sample concentrations in each plate were calculated from standard curves and dilution factors. **Results:** The BDNF values in healthy controls had a mean of 25.14 ± 14.21 ng/mL. The baseline values in the patients had a mean of 72.49 ± 9.05 ng/mL. The values in the patients after apremilast therapy had a mean of 63.60 ± 9.53 ng/mL. **Conclusion:** BDNF levels are significantly increased in patients with moderate to severe plaque psoriasis. Apremilast therapy significantly reduced the raised BDNF levels in such patients, though the reduced level was still significantly higher than the levels in normal healthy controls. Rather than being linked to any neurobehavioral component, the BDNF levels predominantly appear to be linked to the underlying inflammation in psoriasis.

Key words: Psoriasis; Brain derived neurotrophic factor; Apremilast

Access this article online

Website:

<http://nepjol.info/index.php/AJMS>

DOI: 10.3126/ajms.v11i6.30389

E-ISSN: 2091-0576

P-ISSN: 2467-9100

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INTRODUCTION

Psoriasis is a common immune mediated chronic inflammatory disorder, with world-wide prevalence of 2-3%, affecting the skin and joints.¹ In India, the prevalence of psoriasis varies from 0.44% to 2.8%.² It is characterized by excessive and abnormal and differentiation of keratinocytes resulting in chronic erythematous scaly plaques of variable sizes. The skin manifestations are often associated with psoriatic arthritis, metabolic syndrome, cardiovascular problems and numerous other comorbidities. The mood disorders such as depression and anxiety along with suicidal

tendency have also been found to be increased in psoriasis.³ The current treatment recommendations for the disease include topical therapies (e.g., emollients, salicylic acid, coal tar, anthralin, corticosteroids, vitamin D3 analogues, calcineurin inhibitors, tazarotene), phototherapy and systemic therapy (e.g., methotrexate, cyclosporine, acitretin, immunomodulatory agents) alone or in combinations.⁴ Apremilast, a relatively newer drug, is a selective inhibitor of phosphodiesterase 4 (PDE4), which blocks the pro-inflammatory cytokines involved in pathogenesis of psoriasis. The drug, approved by FDA in 2014, has also been added to the existing armamentarium of therapies to

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manage moderate-to-severe plaque psoriasis and psoriatic arthritis.⁵

Brain derived neurotrophic factor (BDNF) plays various roles in the adult nervous system, such as regulation of neuronal function, neurotransmitter release, and synaptic plasticity.⁶ It is also secreted by skin and plays a role in cutaneous sensory innervation. Some studies have shown the levels of BDNF to be low in psoriasis and the levels remained low even after complete treatment of psoriasis.⁷ It is not clear if this decrease is related to the accompanying mood disorders in this chronic disease. On the other hand, several studies showed increase of BDNF levels in inflammatory skin disorders.⁸ It has been suggested that high eosinophilia in such disorders increases the levels of BDNF and other neurotrophins.

There have not been conclusive studies on BDNF levels in psoriasis as a potential predictor of disease severity or response to therapies. To the best of our knowledge, no study has evaluated the BDNF levels in moderate to severe form of plaque psoriasis or the correlation of its levels in response to therapy. As apremilast is indicated in moderate to severe form of plaque psoriasis, we aimed to evaluate the BDNF levels in this subtype of patients and analyse the variation, if any, in response to apremilast therapy.

MATERIALS AND METHODS

Study design

It was a prospective observational study approved by the Institutional Ethics Committee vide Ref.NO.SU/SMS&R/76-A/2019/45. The aim was to evaluate the BDNF levels in patients of moderate to severe plaque psoriasis on apremilast therapy for two months. The participants were from among the patients who attended the outpatient department of Dermatology, of a tertiary care hospital in India.

The study included the patients of psoriasis of either sex and age ≥ 18 years suitable to be prescribed apremilast as standard treatment along with age and sex matched controls. Prior written informed consent for the study was taken from the participants. Pregnant or lactating women and patients with history of substance abuse causing depressed mood (e.g., drugs, alcohol, medications), comorbid psychiatric disorders (other than mood disorders, if any) were not included in the study. Detailed medical history was noted from all the participants and physical examination was done by the Dermatologist.

Blood samples were obtained from the antecubital vein into EDTA-treated tubes. Samples were spun at 3000 g

for 15 min, and the collected plasma was stored at -80°C until analysis. Second sample collection from the patients and subsequent storage of the samples was again done on their follow up visit after two months of apremilast therapy. Sample collection was also done from normal healthy volunteers after proper informed consent. Enzyme-linked immunosorbent assay (ELISA) kit (QUAYEE-BIO) and microplate reader (at 450 nm) were used to determine BDNF values. Sample concentrations in each plate were calculated from standard curves and dilution factors.

Statistics

Sample size

Statistical considerations in an observational study for the effect of one variable on another was applied and the sample size was thus calculated with significance level at 0.05, standard deviation of the dependent variable (serum BDNF) at 3 (based on previous studies) and power at 0.8.^{7,8} The resultant sample size using the formula was 34 for effect size 1.5 and 20 for effect size 2. Thus, the present study aimed to include 30 patients. Another control group consisted of similar number of age and sex matched healthy volunteers.

Statistical analysis

All the data were collected, compiled and analysed using Excel 2016. Presentation of data was done as Mean \pm SD. Data analysis was done by one way ANOVA to compare the three different value groups of BDNF levels to find if any group was significantly more different than the other. Paired t test was done to assess the difference before and after apremilast therapy. Unpaired t test was applied to compare the patient BDNF levels with those of the normal controls. A p-value of <0.05 was considered as statistically significant.

RESULTS

Demographics

The patients included in the study had a mean age of 41 ± 7.5 years and it was statistically similar to the healthy controls which had a mean age of 41 ± 6 years. Out of the total 30 patients the number of female and male patients was 9 and 21, respectively. The analysis after second visit could be done on 24 patients (with two male patients dropping out due to adverse reactions to apremilast therapy and four male patients lost to follow up).

Observed values of BDNF in controls and patients

The BDNF baseline values (before apremilast therapy) in the patients had a mean of 72.49 ± 9.05 ng/mL. The BDNF values in treated patients (after apremilast therapy) had a mean of 63.60 ± 9.53 ng/mL. The BDNF values in healthy controls had a mean of 25.14 ± 14.21 ng/mL. The comparative details are shown in Table 1 and 2.

Controls	Patients	
	Before therapy	After therapy
52.276	71.721	66.054
29.374	88.146	76.995
9.1	86.623	69.503
15.782	72.849	65.044
4.99	73.995	65.415
34.527	77.128	72.074
49.827	74.132	56.879
8.379	76.493	65.739
39.721	68.194	54.231
32.601	76.418	73.835
10.012	62.347	59.307
26.321	65.664	51.975
13.256	75.811	65.079
38.042	43.368	33.473
36.542	73.696	65.473
41.896	67.982	62.843
14.213	77.149	68.514
21.325	80.946	73.055
9.012	64.049	61.124
26.123	66.574	52.594
14.211	76.395	75.137
45.236	72.507	52.594
11.236	77.684	71.125
19.258	69.199	68.401

Comparison of pre-treatment BDNF values of patients with the values in healthy controls (Table 1 and 3): The baseline values of BDNF levels in patients compared to the BDNF levels in the control group showed significantly more peak flow scores; the t-value was 14.5878. The difference was significant (p-value <0.00001).

Comparison of post-treatment BDNF values of patients with the values in healthy controls (Table 1 and 3): The post-treatment BDNF levels in the patients compared to the BDNF levels in the control group demonstrated more peak flow scores; the t-value was 10.77987. The difference was significant (p-value <0.00001)

Comparison of post-treatment BDNF values with the pre-treatment values in patients (Table 1 and 3): The BDNF levels of the patients after apremilast therapy, as compared to the BDNF levels before apremilast therapy, was decreased significantly (t-value: 8.308514; p<0.00001).

The serum levels of BDNF in healthy volunteers found in this study were similar to that found in earlier studies.⁹

The apremilast therapy was well tolerated by most of the participants. No serious adverse effects were reported by the patients. Diarrhoea in two patients caused them to discontinue the treatment. Four other patients were lost to follow up and we do not know the exact reason as they did not respond to the phone calls. When asked in subsequent visits, mild loose motion was reported by

BDNF levels	Mean±SD in ng/mL	p-value (by ANOVA)
Baseline values in patients	72.49±9.05	<0.0001
Post-treatment values in patients	63.60±9.53	
Healthy controls	25.14±14.21	

BDNF levels	Mean±SD in ng/mL	p-value
Baseline in patients vs healthy controls	72.49±9.05 vs. 25.14±14.21	<0.00001
Post-treatment in patients vs healthy controls	63.60±9.53 vs. 25.14±14.21	<0.00001
Pre-treatment vs Post-treatment in Patients	72.49±9.05 vs. 63.60±9.53	<0.00001

three other patients, nausea by two patients and headache by four patients but they completed the desired duration of the treatment for this study.

DISCUSSION

The results of this study showed that BDNF levels are significantly higher in psoriasis patients, both before and after apremilast therapy, as compared to the healthy individuals. There are few studies evaluating the BDNF levels in psoriasis patients. Brunoni et al (2015) found the BDNF levels to be lower in psoriasis patients which is in contrast with our results.⁷ The present study had only included the patients with moderate to severe plaque psoriasis whereas the earlier study had all variants of psoriasis with different severity levels. This variation in the patients of two studies may have contributed to the different BDNF levels. We could not find any other earlier study on the variation of BDNF levels, particularly in the moderate to severe cases of plaque psoriasis variants.

Raap et al (2005) showed that patients with atopic dermatitis had significantly higher levels of BDNF than the normal individuals.¹⁰ It was proposed that the rise in BDNF levels in atopic dermatitis patients could be mediated by an increased release of BDNF from eosinophils in these patients.¹⁰ There was also an increased expression of BDNF receptors in those patients and the study pointed to a complex response in terms of cytokines levels in chronic inflammatory skin disorder.¹⁰ Additionally, it was found that BDNF levels are increased in serum and diseased skin of patients with chronic spontaneous urticaria suggesting that BDNF has a role in pathophysiology of chronic inflammatory skin disease.⁸

Several studies have documented the active and important role of eosinophils in different kinds of inflammatory skin disorders. It was shown that severe forms of psoriasis were associated with peripheral blood eosinophilia.¹¹ These findings suggest that eosinophils may have significant roles in the pathogenesis of severe types of psoriasis. Eosinophils are proinflammatory cells that play important role in the pathogenesis of various inflammatory diseases. However, their impact has not been explored in detail in the context of psoriasis. In a pre-clinical study, it found that eosinophils accelerate psoriatic inflammation by supporting inflammatory microenvironments, leading to the activation and infiltration of neutrophils.¹² Additionally, it was shown that the underlying anti-psoriatic mechanisms of cyclosporine A was linked to lowering the number of blood eosinophils.¹³ It can be inferred from these studies that pruritus in psoriasis is coupled to disease severity. Eosinophils may play important role in severe types of psoriasis and are also linked to increased BDNF levels. Thus, in our study, with patients of moderate to severe plaque psoriasis, this could be one of the probable reasons for increased BDNF levels in this subset of patients. Future studies in this subgroup of patients with larger number of participants are needed to give us further insights.

None of the patients included in this study had major depressive disorder and were in no need of anti-depressants. One of the initial assumptions that psoriasis patients may have decreased BDNF levels due to underlying affective component did not translate to our study. Probably the actual disease process in the moderate to severe stage of disease and the inflammatory response to the underlying pathophysiology played more important role than any undercurrent of mood modulation in influencing the BDNF levels.

Following apremilast therapy for two months, the BDNF levels were significantly reduced but still were significantly higher than the healthy controls. Apremilast caused symptomatic relief in majority of the patients but the BDNF levels linked to the underlying pathophysiology of the disease remained higher than normal. As psoriasis is a chronic disease, it appears that the underlying reactive changes in body, though decreased significantly as compared to the baseline before therapy, are not altered to the level of normalcy.

One of the adverse effects of apremilast is depression, seen in less than 1% of patients treated for a prolonged duration of more than 4 months.¹⁴ Major Depressive disorder is associated with decrease in BDNF levels.¹⁵ The two months treatment regimen in our study, is unlikely to contribute to changes in BDNF levels due to depression. The decreased BDNF levels is more likely related to the

decrease in severity of the psoriasis symptoms, which was still higher than normal as the underlying pathology had not been cured.

Limitations

In spite of the observed statistically significant differences in the BDNF levels between the groups, the number of patients and the duration of therapy of this study could be a limiting factor. Larger studies with prolonged duration of therapy can further highlight the findings and shortcomings of the present study.

CONCLUSION

BDNF levels are significantly raised in patients of moderate to severe plaque psoriasis. Apremilast therapy significantly reduced the BDNF levels in such patients. The decrease in BDNF levels in response to therapy is more likely related to the decreased inflammatory symptoms.

Take away messages

The results of this study suggest that BDNF levels do not seem to be linked to underlying neurobehavioral affective component, if any, of moderate to severe form of plaque psoriasis. Rather, it is the inflammatory component of the disease which seems to influence the BDNF levels.

ACKNOWLEDGEMENT

None.

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Source of funding: ELISA kit was sponsored by Sharda University, **Conflict of Interest:** None