

Prevalence and Sociodemographic Profile of Lithium-induced Cutaneous Side Effects in Bipolar Affective Disorder Patients: A 1-year Prospective Observational Study in South India

B. S. Suganya Priyadharshini, I. Syed Ummar

ABSTRACT

Objectives: Objective in our study is i) To assess the prevalence and sociodemographic profile of cutaneous side effects in bipolar affective disorder patients (BPAD) on lithium. ii) To assess the course of pre-existing skin reactions, when patient is initiated on lithium therapy. **Methods:** Lithium induced cutaneous side effects were assessed at baseline and monthly for 6 months followed by every 2 months over a year. Dermatologist opinion obtained to diagnose and treat for each patient who developed cutaneous side effects. Data were analyzed in percentage. **Results:** The prevalence of lithium induced cutaneous side effects in our study is 38.46%. On analyzing the individual subtype of cutaneous lesions, acneiform eruption and hairfall were most common. The cutaneous adverse reactions on lithium are more common in early adulthood than in the late adulthood and geriatric age group and among the subtypes of skin lesion acneiform eruptions are more common among males than in females. On analyzing the course of pre-existing lesions, severe alopecia developed with pre-existing systemic lupus erythematosus. **Conclusion:** These novel finding indicate that prevalence of lithium induced cutaneous side effects continues to be high. Hence, clinician should educate the patients before initiating lithium to improve attrition rate.

Key words: Bipolar disorder, cutaneous sideeffects, Lithium

INTRODUCTION


Lithium has been used in the treatment of mood disorders for more than five decades^[1] and it has been the focus of numerous investigations for its systemic

side-effects. Although lithium is notorious to cause cutaneous lesions^[2] the literature on skin disorders secondary to lithium therapy is limited.

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Department of Psychiatry, PSG Institute of Medical Science and Research, Coimbatore, Tamil Nadu, India

Address for correspondence: Dr. B. S. Suganya Priyadharshini

Department of Psychiatry, PSG Institute of Medical Science and Research, P.O. Box No: 1664, Avinashi Road, Peelamedu, Coimbatore - 641 004, Tamil Nadu, India.

E-mail: suganyapriyadharshini@yahoo.com

Lithium is known to cause multiple cutaneous side effects, and the most common side effects are an acneiform and psoriasiform eruption.^[3] It is known to cause psoriasis and also exacerbate preexisting psoriasis. Lithium-induced psoriasis are most distressing, and it is associated with the increased risk of suicide and substance use.^[4]

It causes specific manifestations such as acneiform eruptions, seborrheic dermatitis, hyperpigmentation, and follicular keratitis. Other cutaneous manifestations includes mucosal and vaginal ulceration, edema, purpura, lupus erythematosus such as syndrome, urticaria, pretibial ulceration, dermatitis herpetiformis, eczema, exfoliative dermatitis, folliculitis, alopecia, allergic vasculitis, hidradenitis suppurativa, lichenoid stomatitis, exacerbation of Darier's disease, palmoplantar hyperkeratosis with ichthyosiform features, increased growth of wart, mycosis fungoides, and hair loss.^[5,7-9]

Lithium is also suggested to induce lupus erythematosus. Lithium-induced lupus was more common among females and among adolescence (20–40 years).^[6]

In the previous study, females showed increased incidence of cutaneous side effects compared to males. The prevalence of lithium-induced skin reactions is reported to range from 3% to 34%.^[7] In another study, the prevalence of lithium-induced skin reactions is reported to be 45%.^[8]

Lithium-induced lesions cause disturbances in the self-image and affect their social, occupational, and interpersonal functioning which may contribute to the risk of noncompliance. Even though its cutaneous side effects results in poor compliance, studies in these area are very few hence we have decided to do study with the primary aim is to find the prevalence of lithium-induced skin reactions. Our other objectives are to find the sociodemographic profile and its correlate with lithium-induced skin side effects and the course of preexisting skin reactions with lithium therapy.

MATERIALS AND METHODS

Study design

This is a prospective observational study done in bipolar affective disorder patients who came to our psychiatry department. A total of 52 bipolar affective disorder patients were recruited both from in- and out-patient settings by convenient sampling. The study protocol was explained to the participants, and a written informed consent was obtained from the patient. If patient could not consent, it was obtained from the family member and later from the patient when he/she could consent. The study was approved

by Institutional Human Ethics Committee with the reference number 14/147.

Participants

Men and women aged 18–65 years with the primary diagnosis of bipolar affective disorder who were either newly initiated or already on lithium therapy were eligible for the study. Diagnosis of bipolar affective disorder was made by a qualified psychiatrist based on the International Classification of Disease criteria.

Patient on other mood stabilizers and on other medication known to cause cutaneous reactions other than antipsychotics were excluded from the study.

Assessments

Initial assessment

We designed a semi-structured pro forma and dermatological assessment sheet which were used for the initial assessment. It included sociodemographic details of the patient such as age, sex, socioeconomic status and education, details of history of skin lesions, and family history of skin lesion. We arbitrarily divided age group into early adulthood <40 years, late adulthood between 40 and 60 years and more than 60 years. All the patients were asked for the presence of skin lesions currently and in the past through history and by complete physical examination. Semi-structured dermatological assessment sheet includes the details about the type of skin lesions and questionnaire covering the details of skin lesions and its relationship to treatment lithium. These patients were examined by the dermatologist and diagnosis was made. The dermatologist would also determine that the lesion was related to the drug lithium. Necessary treatment for the concerned dermatological diagnosis was given by the dermatologist.

Follow-up assessment

We did follow-up assessments monthly for 6 months and thereafter every 2 months for a year. During each follow-up, patients were examined for the presence of skin lesions. Follow-up assessment was done using semi-structured pro forma which included the course of individual skin lesions and preexisting skin lesions as persisted, remitted or exacerbated, and for the presence of new lesions. If the patient develops any new lesions dermatologist opinion was sought each time and they were given required medications. If the patient missed a follow-up, they were contacted over phone and enquired for the presence of any skin lesions and its course both from the patient and the caregiver. Even if they did not come for follow-up, they were included in the study.

Statistical analyses

The prevalence of cumulative subtype of cutaneous lesions and total prevalence of cutaneous lesions were calculated.

Table 1: Baseline sociodemographic details of the sample study

Variables	Number of patients (%)
Age (years)	
<40	31 (59.6)
40-60	18 (34.6)
>60	3 (5.8)
Gender	
Female	25 (48.1)
Male	27 (51.9)
Socioeconomic status	
Upper middle	49 (94.2)
Lower middle	3 (5.8)
Education	
Illiterate	15 (28.8)
Mid school	30 (57.7)
High school	7 (13.5)
Postgraduate	0

The prevalence of individual lesions is compared with the age and gender.

RESULTS

General characteristics of study sample

In the study sample, the majority were in the age group of <40 years (59.6%), those between 40 and 60 years are 34.6%. Gender distribution was almost equal where females are 48.1% and males are 51.9%. The majority were from upper middle socioeconomic status (94.2%) as per modified Kuppusamy scale and 57.7% had finished their mid school level [Table 1].

Analysis of cumulative prevalence of cutaneous lesion during 1-year follow-ups

The prevalence of lithium-induced skin reactions in our study was 38.46%. On analyzing the cumulative prevalence, acneiform eruption peaked during the 2nd month ($n = 11/52$), and it abated at the end of 1 year. Hair fall had peaked at the 4th month ($n = 6/52$) later has gradually came down and again increased at the end of 1 year. Hyperpigmentation occurred from the 3rd month; it peaked in the 5th month and persisted throughout the study. Only one patient had developed seborrheic dermatitis during 1st month, but it abated in between for 4 months with dermatological treatment and reappeared during 8th month and persisted till the end of the study.

Lithium-induced ulcer ($n = 1/52$) developed during the 1st month, and it persisted throughout. It developed in the right index and middle fingers with multiple ulcers gradually it has increased its size and number. But after the end of the study, lithium was stopped and was changed over to other mood stabilizers.

Combined lesions such as acne with hair fall, acne with hyperpigmentation, and acne with seborrheic dermatitis had occurred. One patient developed acne with hair fall and acne with hyperpigmentation, they cleared up at the end of the study. As shown in Table 2, one patient had acne with seborrheic dermatitis waned off for a month and reappeared.

Prevalence of cutaneous lesions among various age groups

Acneiform eruptions ($n = 11/52$) and hyperpigmentation ($n = 2/52$) are common in early adulthood, whereas lithium-induced ulcer ($n = 1/52$) seen in late adulthood. Hair fall is equal in both early and late adulthood (5.7%). In geriatrics, 1.9% developed acneiform eruptions with hyperpigmentation [Table 3].

Gender difference in the prevalence of cutaneous skin lesions

15.2% ($n = 8/52$) of males and 11.4% ($n = 6/52$) females had developed acneiform eruptions, whereas 3.8% males and 7.6% females developed hair fall. Seborrheic dermatitis occurred in males and lithium-induced ulcer in females. Hyperpigmentation has seen in 3.8% males and 1.9% females.

About 3.8% of females had developed acneiform eruption with hair fall whereas acneiform eruption with hyperpigmentation (3.8%) and seborrheic dermatitis (1.9%) occurred in males [Table 4].

Course of preexisting skin reaction

Three patients had preexisting skin lesions, of which one had tinea during initial assessment which gradually subsided with treatment during 3rd month, and one had candidiasis improved and remitted in the 4th month.

One patient had systemic lupus erythematosus, developed severe hair fall at a 2nd month, and they stopped treatment with lithium therapy on their own at the end of 3rd month.

Drop outs

After recruitment of 52 patients, 10 were dropped out at the end of the study. Of which five were dropped out because of poor compliance. One dropped out due to lithium toxicity. One dropped out at the end of the 3rd month due to persistent vomiting, and he was changed over to another mood stabilizer. One dropped out at the end of 5th month due to nonaffordability to do routine serum lithium level. One dropped out due to severe hair fall.

DISCUSSION

In this study, the mean age was 38.6 years and most common age group was early adulthood (18–40 years).

Table 2: Prevalence of cumulative subtype of skin lesions

Type of skin lesion	Initial assessment Initial (%)	Follow ups 1 1 st month (%)	Follow ups 2 2 nd month (%)	Follow ups 3 3 rd month (%)	Follow ups 4 4 th month (%)	Follow ups 5 5 th month (%)	Follow ups 6 6 th month (%)	Follow ups 7 8 th month (%)	Follow ups 8 10 th month (%)	Follow ups 9 12 th month (%)
Acneiform eruption	13.3	19	20	17.3	13.3	7.6	11.5	9.6	5.8	1.9
Hair fall	1.9	3.8	7.7	7.7	11.4	9.5	7.7	7.7	7.7	13.3
Seborrheic dermatitis	0	1.9	1.9	0	0	0	0	1.9	1.9	1.9
Hyperpigmentation	0	0	0	1.9	1.9	3.8	3.8	3.8	3.8	3.8
Acne and hyperpigmentation	1.9	1.9	1.9	1.9	0	0	0	0	0	0
Lithium-induced ulcer	0	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9
Acne and hair fall	0	1.9	1.9	0	0	0	0	0	0	0
Acne and seborrheic dermatitis	0	0	0	0	1.9	1.9	0	1.9	1.9	1.9

Our sample had an equal gender distribution. Most were in the upper middle socioeconomic status and had completed up to middle school education.

The prevalence of lithium-induced cutaneous side effects in our study was 38.46% which is comparable to the prevalence reported by Sarantidis and Waters and Chan *et al.* Acneiform eruptions and hair fall are most common lesion in our study whereas study by Sarantidis and Waters showed acneiform eruption and psoriasis as the most common secondary cutaneous lesions. The incidence of hyperpigmentation was found significant in our study compared to previous studies.

The course of acneiform eruption showed that the lesions were more during the initial period of follow-ups and gradually improved on treatment with topical retinoids.^[10-12] The patient did not have the classical type of distribution but occurred over the extremities (mostly in the back of the shoulders) as reported in previous studies by Jennis and Kerbs *et al.*

Hyperpigmentation, hair fall and seborrheic dermatitis coexist with acneiform eruptions during the course. Seborrheic dermatitis has reduced along the course with treatment but reappears on discontinuation of treatment for the same but when compared with the previous study by Dreno *et al.* where lithium is used as the treatment for seborrheic dermatitis.

In this study, one patient had developed lithium-induced ulcers. She developed multiple small pustular ulcers over the index and middle fingers which was found to be most distressing for the patient. Even with dermatological treatment using topical applications patient continued to have repeated pustular ulcers in hands with fissure.

The cutaneous adverse reactions on lithium are more common in early adulthood than in the late adulthood and geriatric age group and among the subtypes of skin lesion acneiform eruptions are more common among males than in females which is supported by previous study by Chan *et al.* Acneiform eruptions coexists with hair fall and is more common among females. An acneiform eruption with hyperpigmentation is more common among males.

Patient with pre-existing severe skin reactions are prone for new skin reaction and may contribute to poor attrition. Interestingly, patients with milder skin reactions like tinea and candidiasis improved over the course of time. But patient with systemic lupus erythematosus developed severe hairfall, resulting in dropout, which is supported by the previous study.^[13,14]

The strength of our study is prospective study, and the recruited patients are studied at multiple intervals for a

Table 3: Percentage of cutaneous skin lesion among various age groups

Age (years)	Acneiform Eruption (%)	Hair fall (%)	Seborrheic dermatitis (%)	Hyperpigmentation (%)	Lithium induced ulcers (%)	Acne, hyperpigmentation (%)	Acne, hair fall (%)	Acne, seborrheic dermatitis (%)
Early adulthood (<40)	20	5.7	1.9	3.8	0	0	1.9	1.9
Late adulthood (40-60)	3.8	5.7	0	1.9	1.9	0	1.9	0
Geriatrics (>60)	1.9	0	0	1.9	0	1.9	1.9	0

Table 4: Gender difference in prevalence of cutaneous skin lesions

Age	Acneiform eruption (%)	Hair fall (%)	Seborrheic dermatitis (%)	Hyperpigmentation (%)	Lithium-induced ulcers (%)	Acne, hyperpigmentation (%)	Acne, hair fall (%)	Acne, seborrheic dermatitis (%)
Female	11.4	7.6	0	1.9	1.9	0	3.8	0
Male	15.2	3.8	1.9	3.8	0	3.8	0	1.9

long duration. Dermatologist opinion obtained for each patient who developed lesions during each follow-up.

Our limitations are small sample size to be generalized. Few patients were on lithium with psychotropic medications which would also contribute to the skin lesions. We had taken convenience sampling. A single dermatologist assessing all the cohorts would have made the study better, and it was not possible due to practical reasons. Naranjo scale which is used to assess the association between the drugs-induced reaction and drug is not used in our study. No blinding was done for the primary therapist nor for the dermatologist, and we followed the patients through telephonic calls which may not be correct as direct observation.

CONCLUSION

The prevalence of lithium-induced cutaneous lesions continuous to be high. Clinician should educate the patient before initiating lithium to improve the attrition rate. Physician need not be apprehensive about changing to other mood stabilizers as lithium-induced skin reactions could be managed with dermatological treatment. Physician should also be cautious in starting lithium in selective cohort of sample.

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Conflicts of interest

There are no conflicts of interest.

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