

Increased Prevalence of Bipolar Disorders in Hidradenitis Suppurativa: More Than a Striking Co-existence?

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ABSTRACT **Introduction:** Hidradenitis suppurativa (HS) is a chronic inflammatory skin disorder of the hair follicle characterized by intense discharge and pain. Recently, HS intrinsic association with neuropsychiatric disorders has become a focus of attention, and bipolar disorder (BD) emerged as a relevant topic for such an association.

Objectives: This study aimed to evaluate BD prevalence among HS patients and present the HS and BD overlap patients demographics, detailed clinical characteristics with a discussion on aggravating factors.

Methods: A retrospective chart review of 247 HS outpatients (Group-1) identified nine patients with BD. The frequency of BD in HS patients is compared to psoriasis patients (Group-2) and controls (Group-3) in age- and gender-matched groups. The demographic and clinical features of the 9 patients revealing HS-BD co-existence were analyzed.

Results: BD (N = 9) was the 7th most common co-morbidity in the HS cohort. The frequency of BD is detected as 3.6% in group 1, 0.7% (N = 1) in group 2, and 0.6% (N = 1) in group 3, respectively. Group 1 demonstrated an increased prevalence of BD compared to other groups (P = 0.001). Of the 9 patients revealing HS and BD co-existence, 66.6% were active smokers, 66.6% were obese and 44.4 % had metabolic syndrome.

Conclusions: This study results reveal that the prevalence of BD in HS patients is higher than psoriasis patients and controls. The pathogenetic mechanisms underlying BD and HS co-existence needs to be investigated further.

Introduction

Hidradenitis suppurativa (HS) is a highly painful and extremely destructive, inflammatory skin disease of the hair follicle with substantial negative psychosocial impacts on patients. Many HS patients suffer from psychiatric conditions, such as depression, anxiety, impaired self-esteem, and stigmatization. Therefore, a psychiatric evaluation of HS patients is strongly recommended [1]. Through the evaluation of neuro-psychiatric disorders in HS patients, bipolar disorders (BD) have just begun to attract attention [2,3].

HS and BD are relatively common conditions affecting more than 1% of the population for each condition. The onset of these chronic, fluctuating diseases is typically in young adulthood and both are considered as leading causes of disability among young people [4-6].

A substantial proportion of BD patients report a positive family history for BD connoting the contribution of genetics; however similar to HS, the multifactorial model including gene environment interactions is accepted as the best concept to explain BD etiopathogenesis [7]. Furthermore, numerous associations have been purported between bipolar disorder and other medical co-morbidities including cardiovascular disorders, diabetes and obesity [8-11]. The higher prevalence of these medical co-morbidities in BD is principally explained via three perspectives including the adverse effects of pharmacological treatments, genetic vulnerability, and lifestyle (eg smoking, malnutrition, and sedentary life-style) [4,12].

Population-based studies were conducted to search for an intrinsic relationship between HS and BD with conflicting results [2,3,13]. Some studies reported a remarkably increased prevalence of BD among HS patients; however, others did not confirm such an association. Lithium, one of the most effective treatments for the prevention of both manic and depressive episodes is also acknowledged as an extrinsic factor to exacerbate HS lesions [14]. Additionally, similar to BD, smoking and obesity are strongly linked to HS pathogenesis (4). BD and HS are complex traits influenced by numerous common genetic variants; however, the existence of a genetic association between HS and BD has not been investigated [15,16].

Objectives

This study aimed to evaluate BD prevalence among HS patients and present the HS and BD overlap patients' demographics, detailed clinical characteristics with a discussion on aggravating factors.

Methods

The patients diagnosed and followed up in the HS outpatient clinic of Gülhane Training and Research Hospital of

the University of Health Sciences between September 2018 and November 2020 were included. The authors conducted a retrospective chart review to extract the variables of interest, including the patients demographic and clinical features (age, gender, age of onset, disease duration, Hurley stage, International Hidradenitis Suppurativa Severity Score System (IHS4), accompanying medical co-morbidities, particularly psychiatric disorders, medications). The patients in this manuscript have given informed consent to publication of their case details.

Besides, two study groups, including age- and gender-matched patients, were enrolled. These groups were composed of psoriasis patients (group-2) and patients admitted with a non-inflammatory skin disease (eg, xerosis, tinea pedis, and localized dermatitis) to the outpatient clinic of the same tertiary center (group-3).

Among the selection of the study population, all of the psoriasis patients received at least one systemic agent, including conventional drugs or biologic agents. Only the cases with missing data were excluded from the overall study population, and no additional specific exclusion criteria were used.

The authors analyzed patients revealing BD and HS co-existence, particularly for possible aggravating factors.

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III)-2001 Metabolic Syndrome Diagnosis Criteria was implemented to evaluate metabolic syndrome as it is the most cited definition for metabolic syndrome.

Statistical Analysis

Statistical analyses were performed using the Statistics Package for the Social Sciences (SPSS) for Windows version 22.0 (IBM, Armonk, NY, USA). Numerical variables were presented as mean \pm SD or median (min-max). Categorical variables were shown by number and percentage. $P < 0.05$ was considered significant in all comparisons.

This study must recruit 59 individuals for each group to have 80% power with 5% type I error level to detect clinically significant difference of 1% prevalence when the expected value in the control group is 1%.

Results

A total of 247 HS patients (group 1), consisting of 105 females and 142 males, between 14-68 years of age (mean age: 33.48 ± 11.6 years), were eligible for inclusion in the study. The mean disease duration was 7.3 ± 6.9 years (range 0-35). Of 247 patients, 186 (75,3%) and 14 (5,6%) were active and ex-smokers respectively with an average of $12,7 \pm 14,3$ (range 1-90) pack-year smoking history. The mean body mass index (BMI) was $28.6 \pm 6,8$ (min-max:14,8-85) and

Table 1. Demographic and clinical characteristics of 247 HS patients

Demographic and clinical characteristics of 247 HS patients			
Gender (female/ male)		105 / 142	
Age, years (mean±SD) (min-max)		33.48±11,6 (14-68)	
Mean disease duration, years (mean±SD) (min-max)		7.3±6,9 (0-35)	
Active smokers (%) / packet-year (mean±SD) (min-max)		75 /12.7±14.3 (1-90)	
Body mass index (mean±SD) (min-max)		28.6±6.8 (14,8-85)	
Hurley stage (N/%)		82, 33.2%	
I		81, 33.8%	
II		84, 34.0%	
III			
	N (%)		N(%)
Diabetes mellitus	31 (12.5)	Psoriasis	5 (2.0)
Hypertension	16 (6.4)	Crohn disease	4 (1.6)
Spondyloarthropathy/ arthritis	15 (6.0)	Pulmoner disease	4 (1.6)
Hyperlipidemia	12 (4.8)	Down syndrome	2 (0.8)
Familial Mediterranean Fever	10 (4.0)	Pyoderma gangrenosum	2 (0.8)
Chronic cardiac disease	10 (4.0)	Vitiligo	1 (0.4)
Bipolar disorder	9 (3.6)	Multiple sclerosis	1 (0.4)
Thyroid disease	8 (3.2)		

N = number of patients; SD = standard deviation; % percentage of patients.

33.2% (N = 82) of the patient BMI were over 30. The distribution of Hurley staging was as follows: stage I (N = 82, 33,2%), stage II (N = 81, 33,8%), and stage III (N = 84, 34%). Among 15 co-morbidities detected within the current HS cohort, BD was the 7th most common, encountered in 9 (3.6 %) patients (Table 1).

The authors reviewed psoriasis patients (group 2, N = 135) and patients without an inflammatory skin disorder (group 3, N = 152) for the presence of BD. Only one patient had BD diagnosis per group 2 (0.7%, N:1/135) and group 3 (0.6%, N:1/152).

The patient in group 2 was a 40-year-old male. He had been diagnosed with psoriasis 9 years ago and BP onset was noted within the following year. His BMI was 33.9 and he had never smoked before. He revealed chronic plaque psoriasis without psoriatic arthritis. His previous medical history was unremarkable. The initial treatment choice for this patient was methotrexate which was replaced by certolizumab pegol injections due to inefficacy. Psoriasis Area Severity Index [PASI] score reduced from the baseline value of 8 to 1.5 on the 6th month of certolizumab pegol treatment.

The dermatological diagnosis of the BD case in the control group was basal cell carcinoma. The prevalence of BD in the HS cohort (3.6%) was 4.5 and 6 times higher than in the psoriasis cohort (0.7%) and controls (0.6%) (P = 0.001 for Group1-2 and Group 1-3).

Table 2 exhibits the demographic and clinical characteristics of 11 patients with BD. The majority of the patients with BD were male (N=7/11). Similarly, 6/9 of the patients with HS and BP were male. Family history of HS or BD

was present in 4/9 (44.4%) of the patients with HS and BD. Totally (88.8%) 8 of the HS patients had moderate to severe HS according to the Hurley stage and IHS4 scores. The median disease duration of HS and BD was as follows, 6 (min-max:4-20, interquartile range [IQR]: 11) and 7 (min-max:2-16, IQR: 10.5) Of the HS patients, 5 were on adalimumab and 4 were on doxycycline. Of nine cases with HS and BD, 4 (44.4%) had concurrent metabolic syndrome. Most frequently used current medications for BD in HS patients were lithium (N = 5/9) and sodium valproate (N = 4/9), respectively. Of 9 HS patients, 6 had been prescribed lithium previously, and 3/6 (50%) reported exacerbations under lithium. Because of uncontrolled BD despite multiple treatments, lithium had to be continued in two of these 3 patients who described exacerbations.

Conclusions

In the current study, the prevalence of BD was 3,6 %. BD frequency was significantly higher in the HS cohort than the psoriasis cohort and control patients. Physicians dealing with HS patients are familiar with psychiatric complaints, occasionally leading to anxiety and depression [17-19]. HS substantial burden on quality of life measures has been proposed as the principal causal factor for the association of HS and psychiatric co-morbidities [19,20].

Associations between several endocrinologic, metabolic and rheumatological disorders and HS reveal that HS is more than skin deep [21]. Deciphering the interdisciplinary links is essential for HS optimal management and

Table 2 Demographic and clinical characteristics of patients with bipolar disorders in Group 1 (HS patients), Group 2 (psoriasis patients) and Group 3 (control group).

	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11
Age (years)	45	52	33	43	59	30	40	33	33	40	37
Gender	M	M	M	F	F	M	M	M	F	M	F
Family history HS/psoriasis	-	-	-	+	-	-	+	+	+	-	-
Family history BD	-	+	-	-	-	+	+	-	+	-	-
BMI	25,7	36,1	29,2	29,4	30	30,7	37,0	35,4	43,6	23,5	22,3
NCEP-ATPIII MS ^a	-	-	+	+	+	-	+	-	-	-	-
^a Waist circumference (cm)	87	94	115	98	84	115	135	122	110	-	-
^a Triglyceride (mg/dL)	225	179	430	320	175	235	391	259	194	-	-
^a HDL-c (mg/dL)	30	35	34	32	35	40	40	43	59	-	-
^a Blood pressure >130/85 mmHg	-	-	-	+	+	-	+	-	-	-	-
^a Fasting glucose (mg/dL)	89	91	188	103	95	81	121	99	73	-	-
Active smoker	+	+	+	+	-	+	+	-	-	-	+
Hurley stage	1	3	3	2	3	2	3	3	2	Current	-
IHS4 score	6	15	18	11	14	4	9	12	3	PASI:1.5	-
Duration of HS/psoriasis (years)	10	4	6	20	20	6	5	0,5	12	9	-
Duration of BD (years)	12	7	2	2	10	6	16	4	15	6	12
Current treatment-HS	Doxy	ADA, 2 years	ADA, 2 years	Doxy, surgery	ADA, 4 years	Doxy	ADA, 6 months	ADA, 6 months	Doxy	Certolizumab pegol	-
Current treatment-BD	Lithium, sodium valproate, quetiapine, bupropion	Lithium, Ziprasidone hydrochloride	Lithium, quetiapine	Trifluoperazine hydrochloride, Venlafaxine	Lithium, lamotrigine	Sodium valproate, aripiprazole	Lithium, Risperidone	Sodium valproate, fluoxetine	Sodium valproate	Sodium valproate	Lithium
Co-morbidities	-	DM, HL	-	HT, DM, spondylarthritis, FMF	HL, HT glaucoma	-	HT	Hypertriglyceridemia	-	-	-

Ada = adalimumab; BD = bipolar disorders; BMI = body mass index; doxy = doxycycline; F = female; M = male; P = patient; P1-P9 = hidradenitis suppurativa; P10 = psoriasis; P11 = basal cell carcinoma
^a NCEP-ATPIII MS: Presence of at least 3 of the 5 items marked.

determining novel treatment strategies. In this study, the HS patients with BD were analyzed in detail for the presence of common predisposing factors. Of these 9 patients, 4 (44.4%) had metabolic syndrome (Table 2). Three (33.3%) patients were overweight, and 6 (66.6%) patients BMI were over 30. Furthermore, 6 (66.6%) of them were active smokers. These findings suggest the contribution of extrinsic factors to the HS-BD co-existence. Among psychiatric research, genome wide association studies (GWAS) have introduced interesting perspectives on the intricate relationship of psychiatric disorders with concurrent co-morbidities, especially obesity and metabolic syndrome [22].

On the other hand, more recently, HS and neuropsychiatric disorders' possible intrinsic relationship has become a focus of attention. Genetic studies point out shared pathogenesis for HS and Alzheimer disease (AD), both revealing mutations within the adjacent parts of the gamma-secretase gene [23]. However, population-based studies do not detect an increased risk of AD in HS patients [[24,25]. This is not surprising considering the relatively younger age of HS patients.

BD increased prevalence among HS patients emerged as another relevant topic to search for an intrinsic relationship. For the 9 patients revealing HS-BD co-existence, 4 (44.4%) had a positive family history for HS and 4 (44.4%) had a positive family history for BD. Only two (22.2%) patients reported a positive family history for both BD and HS.

Scarce data exist on the co-existence of HS and BD. Initially, Tzur Bitan et al. reported a sevenfold increase in the prevalence of BD among HS patients (0.7%, 29 of 4,191) compared with controls (0.1%) in a nationwide population-based study [2]. In another large cohort, BD prevalence in HS was 0.6% (9 of 1,411 HS patients) [3]. BD frequency in HS is relatively lower in these two studies compared to the current research [2,3]. On the contrary, a Finnish nationwide registry study indicated a higher figure of 3.1% in HS patients, similar to the current study results [4]. The apparent differences between these studies reveal the requirement of an additional evaluation for the study region baseline characteristics. Studies related to BD in Turkey have exhibited a similar prevalence to those in other countries [26,27]. Turkey is considered one of the countries with the lowest prevalence of mental disorders [28]. Geographic location cannot explain BD increased prevalence in the current study. Instead, it may be related to our department characteristics as a referral center with higher awareness and clinical experience for HS patients.

Lithium effect on HS is possibly patho-physiologically related to acneiform eruption induction [2]. Benhadou et al detected exacerbations in eight of nine HS patients who were prescribed lithium for BD. Lithium was suggested as the potential cause for the initiation and worsening of HS

lesions in 25% and 75% of the patients [2]. In the current study, six of nine BD patients with a history of lithium use experienced HS exacerbations. Accordingly, a key question for the physicians encountering HS and BD co-existence is as follows: should lithium be avoided in these cases even in the earliest stages of HS to prevent HS progression? The correct response relies on each patient's individual features and the interdisciplinary interactions. Considering other treatment options may be more appropriate, if not, indeed required for BD management. However, in the current cohort, three cases never used lithium. Additionally, six cases defined HS onset before or concurrent with BD diagnosis, highlighting additional factors' contribution.

Some immunological studies have highlighted the increased level of tumor necrosis factor-alpha (TNF)- α , soluble interleukin (IL)-2 receptor, soluble TNF receptor 1 (TNFR1), IL-26 and IL-6 levels in BD, just as HS [2,8,29]. HS is distinguished among other inflammatory skin diseases related to the substantially increased cytokine burden [30]. Thus, the CNS effects of the altered cytokine pattern may be more pronounced compared to other inflammatory skin diseases. Upon study design, to search for the confounding role of chronic inflammation on BD, the authors selected the age- and gender-matched controls from psoriasis patients, the prototypic chronic inflammatory skin disease which is also linked to metabolic syndrome and obesity [31]. Moreover, another control group was assigned among outpatients without a chronic inflammatory skin and/or systemic disease. The results of the study pointed out an increased prevalence of BD in only HS patients but not psoriasis patients compared to that of the control group.

The association between the inflammatory cytokines and BD warrants further investigation related to both diagnostic and also possible therapeutic insights. Due to the shared immunologic pathways, a single immunomodulatory drug has the potential to relieve both HS and BD symptoms. While the anhedonia symptoms of the patients with bipolar I/II depression improved significantly under infliximab [32], no clinical improvement was evident in resistant depression with infliximab in two other placebo-controlled clinical trials [33,34]. Even if there is no clinical benefit, a considerable reduction in highly sensitive C-reactive, TNFR1, and nuclear factor-kappa B (NF- κ B) proteins were remarkable for bipolar depression [34,35].

Currently, the only FDA-approved treatment for HS is adalimumab [1]. Although the direct efficacy of adalimumab on BD has not been reported, the available data from Crohn disease, rheumatoid arthritis, and ankylosing spondylitis cohorts receiving adalimumab report lower depression scores, improvement in somatic symptoms, and mental scores amelioration [36]. In the current study, 5/9 patients with BD and HS have been taking adalimumab for 6 months

to 4 years. Authors observations for these 5 patients upon physician-patient interactions can be reported as a remarkable improvement for both diseases during adalimumab treatment, but without any objective assessments for BD. However, attributing all improvements to adalimumab in BD does not seem appropriate as all five patients have continued psychiatric drugs simultaneously for the treatment of BD (Table 2). Additionally, the improvement of underlying disease severity and quality of life measures under adalimumab treatment will undoubtedly affect BD positively.

The current study period comprises the pandemic period. Therefore, the results of the study offered the chance to observe the disease course of COVID-19 in HS patients, apart from revealing the frequency of BD in HS patients. Although the course of COVID-19 in HS patients was not an outcome measure for this study, the authors observations are the line with the findings of the recent report by Dewigne et al and support that the prevalence of COVID-19 is not higher in HS patients, despite the many accompanying medical comorbidities and risk factors in HS [37]. During the period of this study, only 1 patient in our HS study group (N = 247) died in the intensive care unit due to COVID-19. This case had concomitant rheumatoid arthritis and familial Mediterranean fever and was under 6-month certolizumab pegol treatment for HS.

The small sample size and the retrospective nature were the major limitations of the current study. Since our center is a referral tertiary healthcare institution with special HS outpatient clinic, this affects the generalizability of our results. However, from a deductive perspective, we believe that this case series will complement the available nationwide surveys on this relatively novel subject to provide essential insights.

The current retrospective analysis results verify that the prevalence of BD in HS patients is higher than psoriasis patients and controls. Another factor to keep in mind is that the real-life prevalence of BD in HS could be higher than expected due to the underdiagnosis of HS. Different aspects of this co-existence need to be elucidated in the future with an ideal treatment strategy to prevent these patients from lithium-induced exacerbations. A detailed understanding of the common immunologic and possibly genetic alterations in both diseases seems crucial in identifying a targeted therapy or optimal treatment combination in patients with BD and HS.

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