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Original article

Adverse Childhood Experiences and C-Reactive Protein among Adult Patients with Bipolar Disorder at Zagazig University Hospitals

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ABSTRACT

Background: Childhood trauma exposure has been associated with increase in the risk of psychiatric disorders and elevated levels of systemic inflammation. Our study will discuss the effect of adverse childhood experiences on Bipolar Disorder (BD) clinical characteristic and high sensitivity C-reactive protein (hs-CRP) level. Our aim is to to estimate the frequency of childhood trauma and its effect on bipolar disorder clinical characteristics and to assess the association between childhood trauma and serum level of hs-CRP in adult patients with bipolar disorder. **Methods:** The study included 91 bipolar patients who fulfilled the inclusion criteria. The diagnosis of BD was confirmed by Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I. Confirmation of remission was done by Young Mania Rating Scale (YMRS) or Hamilton Depression Rating Scale (HAM-D). Semi-structured Clinical Interview clinical characteristics of the disorder were performed. The World Health Organization (WHO) Adverse Childhood Experiences International Questionnaires (ACE-IQ) was used to estimate the prevalence of childhood trauma among BD subjects and then a blood sample was collected from each participant to measure the hs-CRP. **Results:** About 93.4% of the studied bipolar patients had at least 1 childhood trauma (CHT). A statistically significant difference between the studied groups is reported in some clinical characteristics, regarding the number of depressive and the total number of mood episode, the type of the first episode, the presence of psychotic features, the noncompliance to medications, the suicidal attempts and Hs-CRP level. **Conclusion:** Presence of childhood trauma in patients with BD is common. It worsens its clinical course and is associated with higher adult inflammation.

Keywords: Bipolar Disorder; Adverse childhood experiences; hs-CRP

INTRODUCTION

Bipolar disorder (BD) is a complicated disorder characterized by manic, depressive and euthymic states at both syndromal and subsyndromal levels. BD frequently disrupts mood, energy, activity, sleep, cognition, and behavior **[1]**; therefore patients struggle to maintain employment and interpersonal relationships. The mean age of onset for bipolar disorder was 18 and 20 years **[2]**. A study of veterans with BD found that a history of child abuse increased the tendency to develop post-traumatic stress disorder (PTSD), panic disorder and alcohol use disorder. The study reported that the number of major depressive episodes increased with lower SF-36 (QoL) mental scores, PTSD and alcohol use disorder and that the risk of suicide attempts due to depression increased in patients with a history of physical and sexual abuse **[3].** Furthermore, physical and sexual abuse in children were found to be associated with the early onset of BD, longer manic or depressive episodes, a rapid-cycle

course as well as a higher likelihood of suicide attempts and substance abuse **[4]**. Childhood trauma also increases the risk for physical illnesses including cardiovascular disease, diabetes and metabolic disorders **[5]**. The biological mechanisms underlying the link between trauma and poor health are not well understood, but there is evidence that inflammation may play a key role **[6]**. Evidence from animal models and from experimental human research suggests that elevated inflammation is a causal factor that promotes psychiatric symptoms rather than a mere correlate of the disorder **[7]**. Chronic low-grade inflammation is also an established risk factor for physical diseases that are associated with trauma exposure, including cardiovascular disease and autoimmune disorders **[8]**. Both childhood trauma and specific types of adulthood trauma exposure have been associated with elevated levels of systemic inflammation. Childhood maltreatment has been linked with elevated levels of high sensitivity C-reactive protein (hs-CRP) **[9]**. The hs-CRP is the most widely evaluated biomarker in the quest for an ideal biomarker for global cardiovascular disease (CVD) risk prediction **[10]** so we chose hs-CRP because it is thought to be one of the most reliable indicators of inflammation and recently has been endorsed as an adjunct to traditional risk factor screening for cardiovascular disease by the Centers for Disease Control and Prevention and the American Heart Association. The aim of this study was to estimate the frequency of childhood trauma and its effect on bipolar disorder clinical characteristics and to assess the association between childhood trauma and serum level of hs-CRP in adult patients with bipolar disorder.

METHODS

The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

This study is a cross-sectional study. It was done at the Psychiatry department during the period from August 1st, 2017 to November 30th, 2018. Ninty one Euthymic patients from both sexes, in the age group from 18-40 years old with DSM-5 diagnosis of bipolar disorder were selected by simple random sampling. They fulfilled the inclusion criteria, from the bipolar patients who came for follow up and to receive their medications from psychiatry outpatient clinic. Excluded patients are those who had current depressive or manic episodes, clinically significant medical condition that might have a psychiatric manifestation, acute or chronic infection /inflammation and patients who had a history of trauma or surgical intervention in the preceding 6 months.

Ethical committee approval and written informed consent were obtained. The Psychometric assessments that were done by a psychiatrist were:

Phase 1:

a) General Medical Examination:

General medical examination of patients was done to exclude the presence of severe physical disorders, inflammation or Organic brain disease.

b) Structured Clinical Interview for DSM-IV Axis I Disorders **(SCID-I) [11]** was applied to confirm diagnosis of bipolar disorder.

c) Hamilton Depression Rating Scale **(HAM-D)** (less than 8) **[12]** and the Young Mania Rating Scale **(YMRS)** (less than7) **[13]** were completed to confirm the remission in order to exclude the presence of current manic or depressive symptoms.

Hamilton Depression Rating Scale (HDRS) is a multiple item questionnaire used to provide an indication of depression and as a guide to evaluate recovery. The questionnaire is designed for adults and is used to rate the severity of their depression by probing mood, feelings of guilt, suicide ideation, insomnia, agitation or retardation, anxiety, weight loss, and somatic symptoms. The patient is rated by a clinician on 17 items scored either on a 3-point or 5-point Likert-type scale **[12].**

Young Mania Rating Scale is 11-item measure that uses the subjective report of mental phenomena and clinical observations to rate behaviours associated with mania. Seven items (elated mood, increased motor activity, sexual interest, sleep, language, appearance, insight) are

scored 0–4 based on the severity and the remaining four items (irritability, rate or amount of speech, delusional/ grandiose thought content, and severe aggressive or uncontrollable behaviour) are scored 0–8, as characteristic features of manic episodes **[13]**.

d) Collection of clinical data of patients was done by a semi-structured questionnaire, specifically developed for this study. It included: age of onset of the disorder, duration of the disorder, type of the first episode, substance use and compliance on treatment, the presence of psychotic features, history of suicide and family history of psychiatric.

e) Assessment of Adverse Childhood Experiences was done by using of Adverse Childhood Experiences International Questionnaires (ACE-IQ) **[14]**.

An anonymous self-report questionnaire was used to collect data. It contains eight domains: marriage and family demographics, protection, neglect, household dysfunction, abuse (emotional, physical, and sexual), peer violence, community violence, and collective violence The ACE-IQ questionnaire was approved by the research team, checked for internal validity, and posted on the WHO website: http://www.who.int/violence injury prevention/violence/activities/adverse childhood experiences/en/index.html. To calculate the ACE score using the binary version: If the participant answered in the affirmative (whether with once, a few times, or many times) then that counts as a yes, and so that response should be circled, and a 1 placed in the final column. Once completed you will get an answer from 0 to 13**[14]**. The questionnaire was translated into Arabic, back-translated (into English), and modified for cultural adaptability **[15]**.

f) A blood sample was collected from all participants to measure hs-CRP.

Phase 2:

After the clinical assessment, participants were divided into 4 groups :The 'bipolar disorder without CHT group and bipolar with CHT (3 subgroups 1, 2, ≥3 ACE) regarding their ACE-IQ total scores groups .

Phase 3:

Clinical variables and hs-CRP level were compared between bipolar patients without CHT and bipolar patients with 1, 2 and, ≥ 3 ACE.

Statistical Analysis:

After data collection, data were coded, entered and analyzed using SPSS (Statistical Package for Social Science) version 25. Qualitative data were presented as frequencies and percentages. Quantitative data were presented as mean, standard deviations and median. Qualitative independent variables were compared using chi-square test while quantitative data of multiple independent groups were compared using analysis of variance (ANOVA test) for normally distributed data and Kuskal-Wallis test for none normally distributed data. Correlation coefficient was used to assess the strength and direction of correlation between different quantitative variables. P value (≤ 0.05) was considered statistically significant difference.

RESULTS

In our study, authors have found that 93.4% of the studied bipolar patients had at least 1 childhood trauma (CHT), and (63.7%) of them had a score of ≥3 traumas. In addition, 18.7% and 11.0% had ACE score of 2 and 1 respectively. While (6.6%) of the studied group had bipolar disorder without CHT **(Table 1).** There was a highly statistically significant difference between bipolar patients without CHT group and groups of bipolar patients with CHT of 1, 2 and ≥ 3 ACE, regarding the number of depressive episodes and the number of the total episode. In which, the number of depressive episodes in group of bipolar patients with CHT of ≥ 3 (with median 3.5) was statistically significantly different with other groups and number of total episodes in this group (with median 6) was statistically significant different with bipolar patients without CHT group, regarding hs-CRP level, there were highly statistically significant differences in hs-CRP levels when compared between bipolar patients without CHT group and bipolar patients with CHT of 1, 2, ≥ 3 ACE groups. hs-CRP levels were statistically significant higher in patients with CHT ≥ 3 ACE group with median (5.1) in comparison with other groups (table2). There was a highly statistically significant difference between bipolar patients without CHT group and bipolar patients with CHT of 1, 2 and ≥ 3 ACE

groups regarding the type of the first episode. In which, type of the first episode was more frequently manic in bipolar patients without CHT group, bipolar patients with 1 ACE group, and bipolar patients with 2 CHT group (100%, 100% & 88.2%) and more depressive in the group of ≥ 3 ACE (77.6%). Also, there was a highly statistically significant difference between all groups regarding the presence of psychotic features during episodes, noncompliance to medications in between episodes and more frequent suicidal attempts than other groups (table3). Also in our study, there was a significant positive correlation between hs-CRP level and ACE total score, number of depressive episodes, number of total mood episodes and number of hospitalization and a statistical significant correlation between ACE total score and higher depressive episodes (r=0.435, p=<0.001) & higher number of total episodes(r= 0.289, p = <0.005). While there was a statistically significant correlation between early age at onset and ACE total score (r= -0.231, p= 0.028) (table4).

Table 1. Frequency of bipolar disorder with childhood trauma (CHT) according to the total score of Adverse Childhood Experience (ACE) scale and bipolar disorder without Childhood trauma (CHT) among the studied group:

Variable	Bipolar patients (No=91)	
	No.	%
Bipolar disorder Without CHT	6	6.6
Bipolar disorder With CHT	85	93.4
ACE total score = 1	10	11.0
ACE total score = 2	17	18.7
ACE total score = ≥3	58	63.7

Table 2 Comparison between bipolar patients without childhood trauma (CHT) and bipolar patients with CHT of 1, 2 and ≥ 3 score on Adverse Childhood Experience (ACE) scale regarding clinical data and High sensitivity C-Reactive protein (Hs-CRP) level.

variable	Bipolar patients (No=91)				F /KW	p.value
	Without CHT (No.=6) Mean±SD median	With 1 CHT (No.= 10) Mean±SD	With 2 CHT (No.= 17) Mean±SD	With ≥3 CHT (No.= 58) Mean±SD		
Age of onset of bipolar disorder (years)	24.8±3.8	23.6±5.6	20.8±3.8	20.8±6.1	F=1.527	0.213
Duration of bipolar disorder (years)	5.7±1.5 (5)	8.9±5.6 (11)	9.7±6.8 (10)	9.8±7.1 (10)	KW=1.971	0.578
Number of manic episodes	2.3±0.8 (2.5)	2.7±1.4 (3)	2.9±1.7 (2)	2.7±1.5 (2)	KW=0.291	0.962
Number of depressive episodes	0.7±0.5d (1)	1.5±1.2d (1.5)	2.1±2.4d (1)	3.7±2.5abc (3.5)	KW=19.532	<0.001**
Number of total episodes	3±0.9d (3)	4.2±1.6 (5)	5±3.6 (4)	6.3±3.6a (6)	KW=9.028	0.029*
Number of hospitalization	2.33±3.1 (1)	1.9±3.4 (0)	2.6±2.9 (2)	3.4±3 (2)	KW=6.563	0.087
Hs-CRP(1-5) mg/L	1.4±0.5 d (1.315)	1.8±0.6 d (1.795)	2.5±1.5 d (2.11)	5.3±3.8 abc (5.155)	KW=26.169	<0.001**

MW=Mann-Whitnny U test KW=Kruskal Wallis test * = Significant (P < 0.05). **= Highly Significant (P < 0.001). a = significant with group Without CHT b= significant with 1 CHT
c= significant with 2 CHT d= significant with ≥3 CHT

Table 3. Comparison between bipolar patients without childhood trauma (CHT) and bipolar patients with CHT of 1, 2, ≥ 3 score on Adverse Childhood Experience (ACE) scale regarding clinical data.

variable	Bipolar patients (No=91)								X^2 Test	p-value
	Without CHT (No.=6)		With 1 CHT (No.=10)		With 2 CHT (No.=17)		With ≥3 CHT (No.= 58)			
	No.	%	No.	%	No.	%	No.	%		
Type of first episode										
Depressive	0	0.0	0	0	2	11.8	45	77.6	43.545	<0.001**
Manic	6	100.0	10	100.0	15	88.2	13	22.4		
Presence of Psychotic features during mood episodes	1	16.7	6	60.0	16	94.1	54	93.1	30.324	<0.001**
Frequency of hospitalization	4	66.6	6	60.0	16	94.1	49	84.5	38.558	0.099
Non Compliance to medications in between mood episodes	0	0.0	4	40.0	12	70.6	49	84.5	24.689	<0.001**
Frequency of suicidal attempts	0	0.0	1	10.0	9	52.9	45	77.6	27.339	<0.001**
Family history of psychiatric disorders	1	16.7	5	50.0	5	29.4	34	58.6	7.263	0.064
Substance Use	1	16.7	3	30.0	5	29.4	20	34.5	0.885	0.829

Table 4. Correlation between Severity of Childhood trauma (CHT) as reflected by a total score of Adverse Childhood Experience (ACE), high sensitivity C-reactive protein (Hs-CRP) and Clinical data of studied group.

Variable	ACE total score		Hs-CRP	
	r	p. value	r	p.p. value
Age	-0.094	0.376	-0.069	0.518
ACE total score			0.58	<0.001**
Age of Onset of bipolar disorder (years)	-0.231	0.028*	-0.165	0.118
Duration of bipolar disorder (years)	0.083	0.431	0.073	0.489
No. of manic episodes	0.017	0.877	-0.055	0.604
No. of depressive episodes	0.435	<0.001**	0.327	0.002*
No. of total episodes	0.289	0.005*	0.211	0.045*
No. of hospitalization	0.172	0.104	0.593	<0.001**

** = Significant (P < 0.05). **= Highly Significant (P < 0.001).*

DISCUSSION

The presence of childhood trauma (CHT) and Bipolar Disorder (BD) had been widely discussed, it was commonly associated and the presence of CHT in BD subjects turns the BD clinical course into a more severe one.

In the current study, Ninety-three (93.4%) of bipolar patients had at least 1 type of childhood trauma (CHT). (63.7%) of them had 3 or more types of trauma. In addition, (18.7%) and (11.0%) had 2 and 1 trauma respectively, while (6.6%) of patients had bipolar disorder without CHT. These frequencies of CHT were in line with previous studies. The frequency of childhood trauma in bipolar patients varied across the

studies: 61.2% **[16]**, 49% **[17]**, 54.4% **[18]**, 51% **[19]**, 48.3% **[20]**, 61.4% **[21]** and 33.3% **[22].** The different countries and cultures with the different methodology used to detect CHT with bipolar disorder in previous studies, variations in sample sizes and sample selection may be reasons for this variance of the prevalence of CHT among the studies. Also in traditional Egyptian culture, parents have absolute authority over their children, and physical abuse was considered to be a legitimate way of discipline. Such beliefs may remain in some conservative families.

At the current study, it was found that patients with CHT had an earlier age of onset of bipolar disorder than patients without CHT. Also, we found that bipolar patients with ≥ 3 ACE had an earlier age of onset of bipolar disorder than patients without CHT and patients with 1 or 2 ACE. This finding is consistent with previous reports **[19,22,24-26]** which also described an earlier age of onset of BD in the patients with CHT.

Our study showed that bipolar patients with CHT showed a longer duration of bipolar disorder than patients without CHT but this difference was not significant. This finding is in line with a study that demonstrated that there was no statistically significant difference between bipolar patients with or without CHT regarding the duration of bipolar disorder % **[16].** While physical and sexual abuse in children were found to be associated with the early onset and longer duration of BD in another study **[27].**

At this study, the number of depressive episodes and the total number of mood episodes (manic and depressive) were significantly higher in patients with CHT than patients without CHT which indicated the increased severity of the bipolar disorder in patients with CHT. Also, we found a more ACE total score, a higher frequency of depressive episodes and total mood episodes. These findings are consistent with findings of **[25,28]** who reported a higher number of lifetime mood episodes in the bipolar patient with CHT. Also, ***Erten*** **[29]** showed that patients who had childhood trauma had higher frequencies of depressive and total mood episodes **[16]** and Nolen concluded that a trauma history was associated with an increased number of BD episodes.

This study demonstrated that there were statistically significant higher levels of hs-CRP levels in patients with CHT than patients without CHT and there was a highly statistically significant increase in levels of hs-CRP in patients with CHT with an increased number of ACE. In line with prior work, we found that the presence and exposure to multiple childhood trauma were significantly associated with higher levels of hs-CRP **[9,30].** In a large, prospective British birth cohort design it was found that having an ACE score of 2 or more was significantly associated with raised CRP level **[31]**. A significant difference in hs-CRP was observed among the groups: patients without childhood abuse had the lowest hs-CRP, and patients with three types of abuse had the highest hs-CRP **[32]**.

This study found the frequency of psychotic features with mood episodes was significantly higher in patients with CHT than bipolar patients without CHT as well as more increase in the number of trauma exposure, more frequency of psychotic features. This was an expected finding as the presence of CHT increases the severity of episodes and consequently, psychotic features may be present. Higher comorbidity of substance use in patients with CHT may be also responsible for such finding. Several studies found that patients reporting psychotic symptoms were more likely to have been abused in childhood **[33,34].**

In line with our findings, other studies **[35,36]** showed significant associations were found between childhood abuse and auditory hallucinations.

At this study, bipolar patients with CHT were more frequently non-compliant to their medications in between mood episodes compared to patients without CHT and frequency of non-compliance increased with the more ACE total score. This finding was expected as patients with CHT cannot adhere to their medications schedule as they had more severity of bipolar disorder thus

increasing the relapse of mood episodes and the risk of functional deterioration. A study also demonstrated that patients with bipolar disorder and childhood trauma had a lower functional level and poorer engagement with treatment **[37]**.

Our results showed that patients with ≥3 ACE and patients with 2 ACE had a higher frequency of suicidal attempts compared to patients with only 1 ACE and bipolar patients without CHT and these differences are statistically significant**.** This finding is consistent with other studies that indicated childhood trauma can be strongly associated with suicidality in patients with BD **[23,38].**

Also, other studies **[16,21,39]** found a significant association between an increasing number of childhood abuse forms and the presence of a lifetime suicide

In this study, there was a significant positive correlation between Hs-CRP level and ACE total score, number of depressive episodes, number of total mood episodes and number of hospitalization and a statistically significant correlation between ACE total score and higher depressive episodes & higher number of total episodes. While there was a statistically significant correlation between early age at onset and ACE total score.

This finding is similar to a study **[16]** that found a correlation between early age at onset and Childhood Trauma Questionnaire (CTQ) total score. For Russo, childhood trauma in bipolar disorder patients is correlated to an earlier age of onset, longer duration of illness and higher depressive episodes **[40].** Also, it is consistent with ***Wium-Andersen et al***. **[41]** who examined CRP levels in 73131 patients; their results indicated that increased CRP levels were associated with increasing number of depressive episodes and risk for hospitalization**.** Our results support studies that showed a number of childhood adversities and the total number of adverse childhood events were significantly correlated with elevated levels of hs-CRP **[9,42].**

Limitations

The sample size of the study was small, especially when dividing into groups; Data on childhood trauma were derived from a retrospective self-report questionnaire without independent corroboration. Therefore, the reports may reflect memory biases of the patients or heightened sensitivities to parental failures. There was no healthy control group in this study, and such reports among the general population may get similar results found in the patients with BD. The requirement of euthymia for inclusion in the study might exclude patients with acute episode who may also have childhood trauma so our results cannot be generalized to all patients with bipolar disorder.

CONCLUSION

Childhood trauma is experienced by a significant number of patients in this sample, and it was associated with more depressive and total mood episodes, more frequent psychotic features during mood episodes, non- compliance to medications, and more suicidal attempts Experiencing childhood trauma is associated with higher adult inflammation, which might have consequences for chronic diseases, such as ischemic heart diseases and cancer. Our study suggests that childhood trauma needs more attention in psychiatric clinical practice and scientific research. Suicide risk in patients with mental disorders who have experienced childhood trauma should be assessed. Also, It is necessary to educate the public about the definition and harm of childhood abuse and neglect, as well as the importance of social support for patients with mental disorders.

Declaration of interest

The authors report no conflicts of interest. The authors are responsible for the content and writing of the paper.

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