Childhood adversities in patients with fibromyalgia: are they related to comorbid lifetime major depression?

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ABSTRACT

Objective. *Fibromyalgia (FM) is a syndrome of unknown aetiology that is frequently associated with depressive disorders, and childhood adversities (including maltreatment and parental loss) are frequently described in subjects with FM and depression. The aim of this study was to investigate the extent to which the high percentage of childhood adversities reported by patients with FM is related to FM itself or to a comorbid lifetime depressive disorder.*

Methods. *Ninety-four consecutive FM patients were assessed for lifetime major depression using the DSM-IV-SCID-CV interview. Childhood maltreatment was investigated using the Childhood Trauma Questionnaire, and information relating to parental death or separation before the age of 18 years was collected by means of a semi-structured interview. The Zung Self-Rating Depression Scale, used as a quantitative measure of depressive symptoms, and the childhood adversity assessment were recorded at the same time.*

Results. *Sixty of the 94 FM patients (63.8%) were diagnosed as having a lifetime major depressive disorder. There were no significant associations between childhood parental loss, the presence/level of maltreatment, the occurrence of a lifetime major depression episode, and the Zung Self-Rating Depression Scale scores.*

Conclusion. *The results of this study suggest that there is no association between childhood adversities and comorbid lifetime major depression in patients with FM. As it would be helpful to prevent the development of FM because of the high cost and limited efficacy of therapeutic interventions, childhood adversities may offer targets for primary prevention.*

Introduction

The aetiological causes and underlying pathogenetic mechanisms of fibromyalgia (FM), which is characterised by chronic widespread pain, fatigue, sleep disturbances and comorbid depressive and anxiety disorders, have not yet been clarified but it has been suggested that adverse life events may be involved in its development. Published studies have consistently shown an association between exposure to the adversities of life and FM, and a recent meta-analysis found that people who report experiencing a trauma during life are 2.52 times more likely to have FM regardless of the type of trauma (1).

Particular attention has been drawn to adverse events occurring during childhood because it is thought that early adverse experiences can be more detrimental than those occurring in later life. Children are less capable of coherently organising their responses to traumatic stimuli and their developing brain, which is characterised by a high turnover of neuronal connections, is more vulnerable to the interference of environmental factors (2).

Anderberg *et al*. (3) found that 51% of their 40 female patients with FM had experienced adverse events in childhood compared with 28% of their age-matched healthy controls, and Goldberg *et al*. (4) found that the percentage of patients with FM and a history of abuse was high as 65%. Imbierowicz and Egle found that FM patients had higher rates of childhood adversity (including sexual and physical maltreatment, parental separation and poor emotional relationships), than a control group of patients with medically explained chronic pain (5). In a study by Walker *et al*., a significantly greater proportion of patients with FM than patients with rheumatoid arthritis reported histories of childhood physical assault, and had

higher mean scores on the emotional abuse, physical abuse, sexual abuse and emotional neglect domains of the Childhood Trauma Questionnaire (CTQ) (6). A meta-analysis of 18 studies has revealed significant associations between FM and self-reported physical and sexual abuse in childhood, but not between FM and childhood emotional abuse (7) and, consistently, a significant association has been observed between rape and a lifetime diagnosis of FM (8). Finally, patients with FM who self-report childhood traumas have more severe physical symptoms (9) and high tender point counts (10), show a greater loss of function (11), and make greater use of healthcare services and pain medications (12).

Retrospective investigations (13, 14) and prospective longitudinal studies (15) have shown that childhood trauma is also a known risk factor for adult major depression disorder (MDD). As in the case of FM, childhood adversity has a negative impact on the clinical presentation of MDD insofar as it is associated with a more severe and/or chronic course, and a reduced response to treatment (16). The lifetime prevalence of MDD is 25.0% among adults who have been maltreated during childhood (15), which is higher than the 16.6% prevalence observed in the general population (17), and the role of childhood adversity is even more crucial when major depression occurs in the context of a bipolar disorder as approximately 30-50% of such patients report traumatic childhood events (18).

A number of studies have demonstrated frequent FM and depression comorbidity. A lifetime MD episode has been diagnosed in more than half of patients with FM, with rates ranging from 20% to 86% (6, 19). The findings of a recent meta-analysis (20) strongly suggest that there is an association between FM and bipolar spectrum disorder; this is particularly true in the case of bipolar II disorder, in which MD is associated with hypomanic syndrome or, on the basis of the broader Zurich diagnostic criteria (21), even only a sub-syndromal hypomanic episode.

The extent to which the high percentage of childhood adversity reported by patients with FM is related to FM itself or to a comorbid depressive or bipolar disorder is a crucial issue that has so only been investigated in two studies with mixed results. The first was a cross-sectional study of 328 German patients with FM receiving different levels of care (22), which found that patients with depressive disorder reported more childhood maltreatment than those without, thus suggesting that comorbid depression is a mediator of the association between childhood maltreatment and FM. The second (32) found that the differences in current depressed mood between FM patients and general population controls were not attributed to self-reported childhood sexual abuse, were partially attributable to emotional abuse, and were totally attributable to physical abuse and emotional neglect.

Both studies only considered current depression assessed using self-rated scales and (in one study) clinical interviews. As it is known that childhood adversities rather than a current MD episode predispose to the development of mood disorders during the course of life, the aim of our study was to evaluate whether the childhood adversities reported by patients with FM is related to FM itself or to a comorbid major depressive or bipolar disorder diagnosed using the DSM-IV Structured Clinical Interview. Only disorders in remission were considered in order to avoid the possible influence of current affective symptoms on the reporting of childhood adversities.

Methods

Subjects

The participants were recruited from a group of 104 consecutive outpatients attending the Rheumatology Department of L. Sacco University Hospital in Milan, Italy, between May 2010 and May 2011. The same sample was used in a previous study with a different aim (23). The inclusion criteria were an age of 18–70 years and a diagnosis of fibromyalgia based on the American College of Rheumatology criteria (24), including widespread pain above and below the waist and on both sides of the body for at least three months, and pain in ≥11 out of 18 tender points detected by applying a pressure of 4 kg/cm^2 for a few seconds. The exclusion criteria were current MD, inflammatory causes of pain, severe and uncontrolled medical illnesses, lifetime neurological disorders, alcohol/drug abuse or dependence, and any clinical condition that might affect the reliability of the assessment.

The study was approved by the Ethics Committee of L. Sacco University Hospital, and all of the participants gave their written informed consent after receiving a complete description of the protocol procedures.

Procedures

The patients underwent a detailed medical history and a thorough clinical examination by an experienced rheumatologist, during which they were asked whether they were willing to undergo a psychiatric assessment in the framework of a research study. Socio-demographic and clinical data were collected using interviewer-administered questionnaires, and recorded using a structured interview format; when possible, the data were validated by means of medical records.

Psychiatric diagnoses

Lifetime major depression (including current or remitted episodes) was diagnosed by a senior psychiatrist using the Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version, Mood module (SCID-CV) (25) in a cross-sectional, single assessment. The SCID-CV was modified in a semi-structured manner because the possibility of changing the wording makes it possible to check the level of understanding of each patient. As FM patients frequently have bipolar II disorder (BIP-II), which is characterised by major depression and hypomanic syndrome (20), the SCID-CV was also modified in order to improve the detection of this population as suggested by Benazzi and Akiskal (36), increased goal-directed activity was considered a stem criterion on a par with euphoria and irritability, and the DSM-IV-TR 4-day minimum duration of hypomania required for a diagnosis of BIP-II was not adhered to. The patients with hypo-

mania lasting for at least one day were included on the basis of the findings of studies showing close similarities in diagnostic validators between BIP-II disorder with short periods of hypomania (1–3 days) and DSM-IV-TR BIP-II (21). Using this broader definition of bipolar spectrum disorders (the Zurich criteria) (21), MD episodes were therefore diagnosed as follows:

1. single or recurrent major depressive episodes (major depressive disorder, MDD);
2. major depressive episodes associated with a manic syndrome (bipolar I disorder, BIP-I);
3. major depressive episodes associated with a hypomanic syndrome as defined below (bipolar II disorder, BIP-II);
4. major depressive episodes associated with a sub-syndromal hypomanic syndrome as defined below (bipolar disorder not otherwise specified, BIP-NOS).

Hypomanic syndrome was defined using the Zurich criteria (21): 1) euphoria, irritability, or overactivity; 2) the patients have themselves experienced problems or received comments from others that something must be wrong with them (consequences); and 3) the patients present at least three of the seven signs and symptoms of DSM-IV hypomania.

Sub-syndromal hypomanic episodes were defined as episodes of at least two hypomanic symptoms that did not meet the DSM-IV criteria for hypomania (a number of symptoms below the DSM-IV cut-off value, no mood changes, or a duration of ≥1 day) and did not have any consequences.

Current depressive symptoms

Depressive symptoms were measured at baseline and during follow-up using the validated Italian version of the Zung Self-rating Depression Scale (SDS) (26). The 20 items of the scale are each scored from 1 (little or none of the time) to 4 (most of the time), thus leading to total SDS scores ranging from 20 to 80. A total score of <50 was considered as indicating the absence of depression, and scores of 50–59, 60–69 and ≥70 were respectively considered as indicating mild, moderate, and severe depression.

Childhood maltreatment

Childhood trauma was measured using the short form of the Childhood Trauma Questionnaire (CTQ), a 28-item, self-report instrument that assesses five types of trauma: physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse. The reliability and validity of the CTQ have been previously documented (27).

Each of the five categories of maltreatment was assessed using five items, and the responses to each item were recorded using a 5-point Likert-type scale in which 1 = "never true" and 5 = "very often true". In addition to total scores ranging from 25 to 125, the questionnaire yields five sub-scale scores ranging from 5 (no abuse or neglect) to 25 (maximum abuse or neglect). Cut-off scores for none-to-low, low-to-moderate, moderate-to-severe, and severe-to-extreme exposure are provided for each subscale. In this study, the cut-off scores for moderate-to-severe exposure (28) was used to classify the study participants as positive for a history of each type of childhood trauma: these score were ≥13 for emotional abuse, ≥10 for physical abuse, ≥8 for sexual abuse, ≥15 for emotional neglect, and ≥10 for physical neglect.

The CTQ also includes a 3-item Minimisation/Denial Scale, which is used to identify problematic cases because of potential underreporting of maltreatment, probable minimisation, unrealistic statements, or severe psychological defences. Only extreme scores (5) are counted for this scale, and the participants were categorised as minimising if they responded 'very often true' to all three items but had none/minimal trauma scores for the other sub-scales.

Parental loss

Parental loss was investigated by a senior psychiatrist and defined as being present if the subject reported that at least one parent (or surrogate parent) had left home because of death or separation (for at least one month) before he/she was 18 years old. The following data were also obtained: time, type (mother / father / surrogate parent), and causes of the parental loss.

Statistical analyses

Linear regression analysis was used to investigate the association between lifetime MD episodes (as the independent dichotomous variable) and the levels of childhood trauma (the dependent variables) on the basis of the total score of the CTQ and the scores of its five subscales. Further linear regression models were used to investigate the associations between the Zung SDS scores and the levels of childhood trauma.

Logistic regression analysis was used to investigate the association between lifetime MD episodes and both the history of each type of childhood trauma, and the presence/absence of early parental loss. It was also used to investigate the associations between the Zung SDS scores and the same categorical dependent variables.

Age, gender, years of education and length of illness were inserted in all of the models as covariates in order to control for confounding effects.

As the preliminary data analyses indicated violations of the linear regression assumptions (i.e. the normality of residuals and homoschedasticy), we used a bootstrap approach (29) to replace the original sample with 10,000 generated samples in each of which the statistics of interest were calculated, and the distribution of the results was used to calculate confidence intervals and the significance of the estimated parameters. Bootstrap resampling was also applied to the logistic regression models.

In the case of the linear regression model, we used "wild" bootstrapping, which consists of resampling the residuals and multiplying them by a random variable with a mean value of 0 and a variance of 1. This approach is advised when homoschedasticy is violated (30). Given the multiple comparisons made in the study, the significance level (α) was lowered to 0.01. All of the analyses were made in R (31).

Results

Ten of the 104 originally screened FM patients were excluded: seven because they were categorised as minimisers

of childhood maltreatment with CTQ, and three because they were experiencing an episode of MD. The analysis was therefore based on data relating to 94 patients: 10 males and 84 females, with a mean age of 45.63 years. The patients were all Caucasian and their mean duration of education was 11.8 years. Table I shows their descriptive statistics.

Mood disorder diagnoses

Sixty of the 94 patients (63.8%) had experienced a lifetime MD episode on the basis of the DSM-IV-TR criteria; 35 (37.2%) met the broader Zurich criteria for BIP-II disorder; 24 (25.5%) met the DSM-IV-TR criteria for a diagnosis of BIP NOS; one met the DSM-IV-TR criteria for a diagnosis of MDD (a single episode); and none had a diagnosis of BIP-I disorder.

Childhood adversities

The data concerning childhood maltreatment are shown in Table I. Thirty-three patients (35%) reported a childhood parental loss and 10 (10%) the death of a parent before the age of 18 years (the father in nine cases, and a surrogate parent in one). Their mean age at the time of the loss was 9.7 years (range 4–17).

An additional 23 subjects (24%) reported at least one separation from one or both parents lasting for more than one month at a mean age of 9.4 years (range 3–15). The reasons for the separations were the child attended boarding school (9 cases), the hospitalisation of a parent or child (7 cases), and divorce or marital separation (7 cases).

Associations between childhood adversities, lifetime major depression and SDS scores

There were no significant associations between childhood trauma levels and the occurrence of a lifetime major depression episode (Table II) or the Zung SDS scores (Table III), no significant associations between parental loss and the occurrence of lifetime major depression episode (Table IV) or the Zung SDS scores (Table V), and no significant associations between the presence/absence of specific childhood maltreatment levels (based on CTQ moderate-to-severe exposure cut-off scores) and the occurrence of a lifetime major depression episode or the Zung SDS scores (data available on demand).

Table I. Characteristics of the study population.

		No lifetime major depressive episode n=34		Lifetime major depressive episode n=60	
		Mean	SD	Mean	SD
Age		45.00	13.02	45.98	11.32
Years of education		11.72	4.19	11.85	2.62
Length of illness, months		120.24	118.17	130.97	107.40
Zung SDS Score		45.10	5.07	48.07	7.38
CTQ - Physical abuse score		6.56	3.19	6.58	2.40
CTQ - Physical abuse score		10.91	5.24	10.88	4.60
CTQ - Sexual abuse score		6.03	2.46	6.52	2.78
CTQ - Physical neglect score		7.50	3.08	8.00	2.68
CTQ - Emotional neglect score		12.47	5.52	12.60	4.53
CTQ - Total score		43.44	14.21	44.33	12.54
		n	%	n	%
Gender	Male	4	11.80%	6	10.00%
	Female	30	88.20%	54	90.00%
Early parental loss	No	25	73.50%	36	60.00%
	Yes	9	26.50%	24	40.00%
Early parental death	No	31	91.20%	53	88.30%
	Yes	3	8.80%	7	11.70%
CTQ - Physical abuse*	No	25	73.50%	41	68.30%
	Yes	9	26.50%	19	31.70%
CTQ - Emotional abuse*	No	28	82.40%	44	73.30%
	Yes	6	17.60%	16	26.70%
CTQ - Sexual abuse*	No	29	85.30%	43	71.70%
	Yes	5	14.70%	17	28.30%
CTQ - Physical neglect*	No	29	85.30%	43	71.70%
	Yes	5	14.70%	17	28.30%
CTQ - Emotional neglect*	No	22	64.70%	40	66.70%
	Yes	12	35.30%	20	33.30%

SD: standard deviation; n: number of subjects; CTQ: Childhood Trauma Questionnaire.
*Positive for childhood maltreatment on the basis of moderate-to-severe cut-off score.

Discussion

The results of this study suggest that patients with FM are not characterised by an association between childhood adversities and comorbid lifetime depressive disorder, but our findings are partially different from those of two other studies. Kosseva (22) suggested that comorbid current depression is a mediator of the association between different form of childhood maltreatment, and Hauser (32) that the differences between FM patients and controls were partially attributable to a current depressed mood due to emotional abuse, totally attributable a current depressed mood due to physical abuse and emotional neglect, and not attributable to a current depressed mood due to sexual abuse.

Our findings cannot be fully compared with those of these studies, which assessed current depression, whereas we excluded patients with a current MD episode and included those with only limited depressive symptoms as assessed by the Zung SDS in order avoid the possibility that depression may have interfered with the self-reporting of childhood adversities. Although there is little evidence supporting a relationship between depression and the distortion of early memories (especially in the case of events such as childhood maltreatment), questions have been raised about the accuracy of the retrospective reports of childhood

Table II. Associations between a lifetime major depressive episode and CTQ.

	B	Bootstrap 95% CI (BCa)		*p*-value
Lifetime major depressive episode		CTQ - Physical abuse		
	0.144	-0.95	1.204	0.82
		CTQ - Emotional abuse		
	0.234	-1.562	1.975	0.821
		CTQ - Sexual abuse		
	0.453	-0.487	1.377	0.41
		CTQ - Physical neglect		
	0.487	-0.63	1.597	0.439
		CTQ - Emotional neglect		
	0.302	-1.787	2.371	0.793
		CTQ - Total score		
	1.368	-3.854	6.145	0.638

B: Coefficient of the effect of a lifetime major depressive episode in the linear regression models, with age, gender, years of education, and length of illness as covariates; it indicates the mean difference between the male and female subjects. CI (BCa): bias-corrected and accelerated confidence interval calculated using wild bootstrap resampling. CTQ: Childhood Trauma Questionnaire. Significance level: $p<0.01$, calculated using wild bootstrap resampling.

Table III. Associations between Zung SDS score and CTQ.

	B	Bootstrap 95% CI (BCa)		*p*-value
Zung SDS score		CTQ - Physical abuse		
	0.064	-0.01	0.136	0.115
		CTQ - Emotional abuse		
	0.056	-0.073	0.187	0.433
		CTQ - Sexual abuse		
	0.039	-0.039	0.115	0.351
		CTQ - Physical neglect		
	0.073	-0.012	0.158	0.119
		CTQ - Emotional neglect		
	0.114	-0.012	0.246	0.101
		CTQ - Total score		
	0.333	-0.021	0.679	0.08

B: Coefficient of the effect of the Zung SDS score in the linear regression models, with age, gender, years of education, and length of illness as covariates; it indicates the mean difference between the male and female subjects. CI (BCa): bias-corrected and accelerated confidence interval calculated using wild bootstrap resampling. CTQ: Childhood Trauma Questionnaire. Significance level: $p<0.01$, calculated using wild bootstrap resampling.

Table IV. Associations between major depressive episode and early parental loss.

	B	Bootstrap 95% CI (BCa)		*p*-value
Lifetime major depressive episode		Early parental loss		
	0.557	-0.655	1.873	0.321
		Early parental death		
	0.348	-2.213	21.861	0.638

B: Coefficient of the effect of a lifetime major depressive episode in the logistic regression models, with age, gender, years of education, and length of illness as covariates; it indicates the mean difference between the male and female subjects. CI (BCa): bias-corrected and accelerated confidence interval calculated using wild bootstrap resampling. CTQ: Childhood Trauma Questionnaire. Significance level: $p<0.01$, calculated using bootstrap resampling.

experiences made by people with depression at the time of recall (33).

A lifetime MD episode was diagnosed in 60 of our 94 FM patients (63.8%), a proportion that is consistent with the published rates of 20–86%, with a median of 58% (34). Unlike earlier studies (19, 36, 35), we found that MD rarely occurred in the context of MDD, but almost always in the context of BIP-II disorder. The reason for this may be methodological because we used broader diagnostic criteria (21), and the clinical interview was modified in order to improve the identification and diagnosis of bipolar spectrum disorders (36). This means that we probably detected a higher prevalence of hypomanic features than that found in other studies, thus leading to a lower prevalence of "pure" MDD. In line with our data, a recent meta-analysis strongly supports an association between FM and bipolar spectrum disorders, particularly BIP-II disorder (20).

Only three (2.9%) of the 104 originally screened patients had a current episode, which is lower than the 14–36% reported in the literature (6, 37) probably because more than 90% of the patients were being treated with antidepressants.

The prevalence of at least moderate-to-severe childhood maltreatment in our population is similar to that reported in the two previous studies that had a similar aim (22, 32).

Childhood parental loss due to death or separation has hardly been investigated in patients with FM, although animal studies suggest that maternal separation in infancy lead increases affective pain processing (38) and visceral hyperalgesia (39) in adult rats. In a preliminary study, FM patients had higher childhood adversity rates (including parental separation) than a control group with medically explained chronic pain; in addition, the loss of parents during childhood as a result of parental divorce or death, or separation from parents was associated with higher tender point counts regardless of the presence of chronic pain (10).

Our findings suggest that childhood adversities are related to FM itself and not to comorbid lifetime bipolar spectrum disorders, which contrasts with the sizeable literature describing a relationship between childhood adversities and mood disorders. One possible explanation for this is that the comorbid presence of bipolar spectrum disorders

and FM characterises a particular condition whose clinical expression is not associated with predisposing childhood adversities, unlike FM itself.

It is well known that mood disorders are clinically and biologically/genetically heterogeneous: for example, MD is highly heterogeneous, and two patients with a DSM-IV diagnosis may not share a single symptom. Recent studies have also shown that specific MD symptoms may be different from each other in terms of their impact on functioning, responses to specific life events, and their relationship to biological markers and risk factors (40).

It is known that biological changes caused by early life stress can lead to multimorbidities in adulthood in genetically predisposed subjects, including chronic pain, depression, and cardiovascular and metabolic conditions. There is also substantial evidence supporting the view that genetics can influence chronic widespread musculoskeletal pain (CWP, a key feature of FM) (41), with rates of inheritance reaching 58%. Furthermore, data from the UK adult twins register show that the association between CWP and depression is due to shared genetic factors (42). It can therefore be hypothesised that childhood adversities may directly make a genetic vulnerability to FM manifest, and indirectly lead to a predisposition to bipolar spectrum disorders. Given the high cost of FM, and the inadequate efficacy of current pharmacological and non-pharmacological treatments, recent research has concentrated on disease prevention, and led to the development of predictive models in order to identify high-risk patients. In addition to the risk factors suggested by previous research, such as the higher rates of illness and use of healthcare resources (43), childhood adversities can be considered in future investigations aimed to identifying people at high risk of developing FM (44, 45).

In order to put our findings into perspective, it is necessary to take into account some of the limitations of this study. First of all, the inferences made on the basis of the study results are limited by the small sample size and the study's retrospective, cross-sectional design.

Table V. Associations between Zung SDS score and early parental loss.

	B	Bootstrap 95% CI (BCa)		*p*-value
Zung SDS score		Early parental loss		
	0.047	-0.031	0.14	0.209
		Early parental death		
	0.047	-0.574	43.816	0.355

B: Coefficient of the effect of a lifetime major depressive episode in the logistic regression models, with age, gender, years of education, and length of illness as covariates; it indicates the mean difference between the male and female subjects. CI (BCa): bias-corrected and accelerated confidence interval calculated using wild bootstrap resampling. CTQ: Childhood Trauma Questionnaire. Significance level: $p<0.01$, calculated using bootstrap resampling.

Future longitudinal studies of larger populations are needed to confirm our findings and clarify the causal relationships between the considered variables. Secondly, the analysed data only relate to patients attending a tertiary care facility specialised in the treatment of FM, who may tend to be more complex and more refractory to treatment, and so caution is necessary when generalising the findings to FM patients as a whole. Finally, childhood maltreatment was retrospectively assessed using self-report questionnaires, and are there subject to recall and response biases.

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