Prevalence and impact of childhood adversities and post-traumatic stress disorder in women with fibromyalgia and chronic widespread pain

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Abstract

Objective

This study investigates the prevalence of different types of childhood adversities (CA) and posttraumatic stress disorder (PTSD) in female patients with Fibromyalgia or Chronic Widespread Pain (FM/CWP) compared to patients with Functional Dyspepsia (FD) and achalasia. In FM/CWP, we also investigated the association between CA and PTSD on the one hand and pain severity on the other.

Methods

Patient samples consisted of 154 female FM/CWP, 83 female FD and 53 female achalasia patients consecutively recruited from a tertiary care hospital. Well-validated self-report questionnaires were used to investigate CA and PTSD.

Results

Forty-nine percent of FM/CWP patients reported at least 1 type of CA, compared to 39.7% of FD patients and 23.4% of achalasia patients ($p < 0.01$). The prevalence of CA did not differ significantly between FM/CWP and FD, but both groups had a higher prevalence of CA compared to both achalasia and healthy controls ($p < .01$). FM/CWP patients were 6 times more likely to report PTSD than both FD ($p < .001$) and achalasia ($p < .001$) patients.

Conclusion

 In FM/CWP, PTSD co-morbidity, but not CA, was associated with self-reported pain severity and PTSD severity mediated the relationship between CA and pain severity. In summary, the prevalence of CA is higher in FM/CWP compared to achalasia, but similar to FD. However, PTSD is more prevalent in FM/CWP compared to FD and associated with higher pain intensity in FM/CWP.

Significance statement:

As expected and has been shown in other functional disorders, we found elevated levels of childhood adversity in FM/CWP patients. Results of this study however suggest that the impact of childhood adversity (i.e. whether such events have led to the development of PTSD symptoms), rather than the mere presence of such adversity, is of crucial importance in FM/CWP patients. Screening for PTSD symptoms should be an essential part of the assessment process in patients suffering from FM/CWP, and both prevention and intervention efforts should take into account PTSD symptoms and their impact on pain severity and general functioning.

Introduction

Fibromyalgia is described as a syndrome based on American College of Rheumatology (ACR) criteria for fibromyalgia (FM) (Wolfe et al., 1990). Patients with chronic widespread pain with a minimal duration of three months and at least 11 of 18 specified tender points present fulfil the criteria. Patients that do not fulfil the criterion of 11 tender points are typically diagnosed with chronic widespread pain (CWP). The prevalence of CWP in the European population is estimated to be as high as 13% (Branco et al., 2010), while the prevalence of FM is estimated to be around 3% (Branco et al., 2010; Spaeth 2009), with a female/male ratio of 9:1 (Hauser et al., 2011; Yunus 2001). FM/CWP are considered to be part of a larger group of functional somatic syndromes (FSS) (Fink et al., 2005; Wessely et al., 1999) or central sensitivity syndromes (Yunus 2001).

A history of childhood adversities (CA) has been shown to elevate the risk to develop CWP (Jones et al., 2009), with the prevalence of CA in FM typically ranging between 16% and 60% (Bohn et al., 2013; Davis et al., 2005; Häuser et al., 2011; Van Houdenhove et al., 2001; Walker et al., 1997). It has been established that CA prevalence of FM/CWP is higher compared with healthy control groups (Häuser et al., 2011). It is however not clear whether the CA prevalence in FM/CWP is different compared to other FSS, and whether and how CA may play a role in the pathogenesis of these disorders.

Second, given the high prevalence of CA in FM/CWP, it is surprising that most studies in this area have not assessed the prevalence of post-traumatic stress disorder (PTSD) symptoms. The few existing studies found a high prevalence of PTSD in FM, ranging from 45 to 57% (Cohen et al., 2002; Häuser et al., 2013; Sherman et al., 2000), and PTSD has been shown to be associated with symptom severity in FM (Amir et al., 1997; Dell'Osso et al., 2010; Sherman et al., 2000).

Given the above limitations in the literature, the primary aim of this study was to compare the prevalence of CA and PTSD in FM/CWP with (a) patients with Functional Dyspepsia (FD), another highly prevalent FSS characterized by upper gastrointestinal tract symptoms, and (b) patients suffering from a chronic disabling somatic disorder of the upper gastrointestinal tract namely achalasia. Achalasia, like FM/CWP, is a chronic disorder, associated with comparable impairment in quality of life (Ben-Meir et al., 2001; Meshkinpour et al., 1996). It is a rare motility disorder of the esophagus characterized by absence of peristalsis and impaired relaxation of the lower esophageal sphincter (Boeckxstaens et al., 2014).

Based on the literature reviewed above, we hypothesized that levels of CA would be elevated in FM/CWP compared to achalasia patients. Based on other studies comparing CA prevalence in different FSS (Afari et al., 2014), we hypothesized similar levels of CA in FM/CWP compared with FD. The second aim of this study was to investigate the relationship between CA and pain severity in FM/CWP as well as the possible role of PTSD in this relationship. We hypothesized a dose-response relationship between the number of CAs and pain severity in FM/CWP, in line with studies in other FSS (Bradford et al., 2012; Drossman 2011). Moreover, we hypothesized that PTSD would play both a moderating and mediating role in the relationship between CA and pain severity. Similar to other studies, we expected high levels of PTSD in FM/CWP (Cohen et al., 2002; Häuser et al., 2013; Roy-Byrne et al., 2004) compared to both FD and achalasia patients. Finally, we also hypothesized a dose-response relationship between the presence and severity of PTSD and pain severity in FM/CWP (Roy-Byrne et al., 2004).

Methods

Participants and procedures

Participants in the FM/CWP sample were 233 consecutive newly diagnosed female patients with chronic diffuse musculoskeletal pain symptoms who were referred to a tertiary care centre for chronic pain at the University Hospitals Leuven (Belgium) in the period 2011-2014. Exclusion criteria were: not being able to understand and write the Dutch language, and psychiatric comorbidity at the initial consultation. Patients were carefully screened through a clinical examination performed by the physician using the 1990 ACR-criteria for FM, and a clinical examination for CWP (Wolfe et al., 1990). As described in Wolfe et al. (Wolfe et al., 1990), for CWP, pain has to be present axially, in the left and right side of the body as well as above and below the waist. To avoid gender differences as a potentially confounding factor for the analyses within the FM/CWP group, we decided to exclude the few male patients (5) referred to the clinic. As noted above, the vast majority of FM/CWP patients are women, with a 9:1 ratio (Yunus 2001). Patients were on average 42.46 years old (SD = 10.5). Thirty patients did not fully fulfil the ACR-criteria for FM and were diagnosed with CWP. Analyses showed no differences between FM and CWP with regard to different types of CA, PTSD as well as pain severity. Therefore, we report results on both samples combined.

Our control groups were recruited in the period 2009-2012. The FD sample consisted of 108 patients (83 (77%) women; mean age 41.9 ± 14.97 years), consecutively recruited at the neurogastroenterology outpatient clinic of the University Hospitals Leuven.

The achalasia sample consisted of 100 patients (53 (53%) women; mean age 53.79 ± 17.17 years), consecutively recruited at the general gastroenterology and neurogastroenterology outpatient clinic of the University Hospitals Leuven.

Demographic characteristics are presented in Table 1.

Measures

Following informed consent, patients filled out well-validated Dutch versions of the following self-report questionnaires. First, CA was assessed using the short form of the Childhood Trauma Questionnaire [CTQ; (Bernstein D 1998; Bernstein et al., 2003)]. The CTQ measures 5 categories of CA, i.e., emotional, physical, and sexual abuse as well as emotional and physical neglect. Three variables assessing CA were created. First, we used the cut-off scores as defined by Heim (Heim 2006) and described in the CTQ manual (Bernstein D 1998) to identify patients suffering from moderate-to-severe CA in each category. Then, we created a dichotomous CA variable with 0=no CA and 1=at least one type of CA ('with and without CA'). Second, we created an ordinal variable based on the number of CAs reported (0, 1, 2 and 3 or more CAs) ('number of CAs'). Finally, we also calculated a total CA score ('CA severity') based on a sum score of all scores on the CTQ subscales. Given that this variable was highly skewed, we used the log transformed total score of the CTQ in all analyses with this variable.

PTSD was measured by the Self-Rating Inventory for PTSD (PTSD-ZIL) (Hovens et al., 2000). The cut-off score used to diagnose PTSD is 52 (Hovens et al., 2000); the log transformed total score of the PTSD-ZIL was used as a continuous measure of PTSD severity.

Pain severity in FM/CWP patients was assessed using the McGill Pain Questionnaire (MPQ-Dutch Language Version) (van der Kloot and Vertommen 1989).

For further details, see *Supplementary Material.*

Statistical analysis

First, we investigated the prevalence of different types of CA in the three samples using χ^2-square tests on a 2 (with versus without CA) x 3 (group) contingency table. This test was followed by 2 planned contrasts consisting of pairwise comparisons (with Bonferroni correction) between the FM/CWP sample on the one hand and the FD and achalasia samples on the other, controlling for age differences between groups when appropriate (i.e. in case of the FM-achalasia comparison, see below). Further, we investigated the association between CA and pain severity in FM/CWP using a t-test comparing pain severity between FM/CWP with and without CA. We also used 'CA severity' as independent variable in linear regression analysis with pain severity as the dependent variable. Finally, we investigated a possible dose-response relationship between the number of CAs and pain severity. The number of CAs was entered into an ANOVA followed by post-hoc t-tests with Bonferroni correction to investigate potential group differences with pain severity as the dependent variable. Effect sizes of group differences are reported as Cohen's d (for effect size interpretation see *Supplementary Material*).

Second, for PTSD, we used the same strategy as described above to compare overall PTSD prevalence in FM/CWP with FD and achalasia using χ^2-tests to test for differences across the 3 samples followed by 2 pairwise comparisons with Bonferroni correction as planned contrasts. Further, we compared PTSD severity in FM/CWP with the two other samples. For this purpose, we used ANCOVA, followed by 2 planned contrasts using t-tests with Bonferroni correction. The prevalence of PTSD and PTSD severity in FM/CWP with and without CA was investigated using χ^2-square and t-tests, respectively. The relationship between the number of CAs and PTSD severity was investigated using ANOVA and the relationship between CA- and PTSD severity was investigated using linear regression analysis with PTSD severity as dependent variable. Finally, we investigated the association between

PTSD and pain severity in FM/CWP using a t-test comparing pain severity between FM/CWP with and without PTSD. We also used 'PTSD severity' as independent variable in linear regression analysis with pain severity as the dependent variable. To investigate whether PTSD moderated or mediated the relationship between CA and pain severity in FM/CWP, we used the PROCESS macro developed by Hayes (Hayes 2012).

Results

In total, 197 patients initially agreed to participate in the study (85%). Of these 197 patients, 38 patients (19%) did not return complete data (more than 5% missing data), and were therefore excluded from further analysis.

Demographics

We controlled for age when comparing the FM with the achalasia sample because there was a significant age difference between the different groups ($F_{(2)}=24.84$, $p<.001$), driven by significant differences between participants in the achalasia sample on the one hand (mean age 53.8±1672) and in both the FM (42.5±10.5, $p<.001$) and FD (41.9±15.0, $p<.001$) samples. There were no significant differences in age for FM and FD patients ($p=0.98$) (see table 1).

Groups differed also on work status ($\chi2=37.52$, $p<0.001$). There was a greater proportion of FM patients that had a job and received an allowance (health insurance or work compensation) compared with the other groups. More FD patients were pensioned (z-test, see table 1). We investigated in an ANOVA the relationship between work status and CA severity but found no significant differences ($F_{(2)}=2,25$, $p=.11$). We also investigated a possible relationship between work status and the different types of CA using χ^2-square tests on a 2 (with versus without CA)x 3 (group) contingency table but again, found no differences. Hence, further analyses were only controlled for age.

Prevalence and impact of CA

Prevalence of CA

Forty-nine percent of FM/CWP patients reported at least one type of CA compared to 39.7% of FD, and 23.4% of achalasia patients (χ^2=10.22, p=0.006) *(Table 2)*. As hypothesized, the prevalence of CA was not significantly higher in FM/CWP compared with FD (OR=1.48, [0.85-2.57], p=0.33), but the prevalence of CA in FM/CWP was significantly higher than in achalasia (OR= 4.35, [1.87-10.12], p=0.0014 Bonferroni corrected) *(Table 2)*.

With regard to specific types of CA, the prevalence of sexual abuse, emotional abuse, and emotional neglect was significantly higher in FM/CWP compared to achalasia (ORs ranging from 3.38 to 8.37), but no significant differences were found for physical abuse or physical neglect *(Table 2)*.

Association between CA and pain severity in FM

There was no relationship between CA severity and both quantitative (β=.06, p=.45) and qualitative pain severity (β=.03, p=.73) in FM/CWP. Neither was there a dose-response relationship between CA severity and both quantitative (F(3)=.75, p=.53) and qualitative pain severity in FM/CWP (F(3)=.87, p=.46).

Prevalence and impact of PTSD

Prevalence

The prevalence of PTSD was 26.0% in FM/CWP, 4.9% in FD and 12.2% in achalasia (χ^2=17.61, p<0.001). FM/CWP patients were about 5 to 7 times more likely to meet PTSD-criteria compared to FD (OR= 6.98, [2.38-20.52], p<0.001) and achalasia (OR= 4.60, [1.55-13.66], p<0.001), respectively. An ANOVA for group differences in PTSD severity was also

significant ($F(2)=35.84$, $p<.001$, $\eta^2=.20$). Planned contrasts with Bonferroni correction for multiple testing revealed that FM/CWP reported higher PTSD severity (3.75±0.27) compared to both FD (3.47±0.26), d=1.05) and achalasia (3.50±0.32), d=.88) (both $p<.001$) (*Figure 1*).

Further, FM/CWP with CA compared to FM/CWP without CA reported higher rates of PTSD (34% versus 17.9%, $\chi^2=5.29$, $p=.021$) and higher PTSD severity (3.82 ($\pm$ .27) vs. 3.68 ($\pm$ .25), $t(150)=-3.37$, $p=.001$).[1]

Finally, there was a dose-response relationship between the number of CAs and PTSD severity in FM/CWP ($F(3)=3.88$, $p=.01$, $\eta^2=.07$) *(Figure 2)*. Post-hoc tests revealed a significant difference between patients without any CA and those reporting three or more CA categories ($p=.04$, mean score 3.68 ($\pm$ .25) vs. 3.84 ($\pm$ .26), $d=-.65$). There also was a dose-response relationship between CA severity and PTSD severity ($\beta=.22$, $p=.006$).

Association between PTSD and pain severity in FM/CWP

Regression analyses showed a significant relationship between PTSD severity in FM/CWP and both quantitative ($\beta=.21$, $p=.027$) and qualitative ($\beta=.37$, $p<.001$) pain ratings. This was confirmed by the finding that FM/CWP patients with PTSD reported higher pain levels compared to FM/CWP patients without PTSD, representing medium effect sizes, both for quantitative pain (70.0 ($\pm$14.0) vs. 62.4 ($\pm$14.4), $t(152)=-2.91$, $p=.004$, $d=.54$, CI=1.71-2.79) and for qualitative pain (36.5 ($\pm$9.6) vs. 30.4 ($\pm$9.4), $t(152)=-3.51$), $p=.001$, $d=.65$, CI=0.84-2.14).

Finally, we found an indirect effect of CA severity on qualitative pain reports through PTSD severity ($\beta=2.15$, CI [.65-4.48], $K^2=.09$, CI=.03-.17). We also found a similar indirect effect of CA severity on quantitative pain through PTSD severity ($\beta=1.60$, CI [.25-4.65], $K^2=.04$,

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[1] See Supplementary Materials for the prevalence of PTSD in relation to different types of CA.

CI=[.01-.11]). We did not find any significant moderation effects of PTSD on the relationship of CA and pain severity.

Discussion

The primary aim of this study was to compare the prevalence of different types of CA in female FM/CWP and female patients with another FSS (FD), and with a chronic organic condition (achalasia). Results showed that the prevalence of CA did not differ between FM/CWP and FD. Further, FM/CWP patients had higher levels of all types of CA compared to achalasia. The odds of reporting at least one type of CA was four times higher compared to achalasia patients. In the present study, about half of all FM/CWP patients reported at least one type of CA. This finding is consistent with figures reported in other studies and meta-analyses (Borsini et al., 2013; Davis et al., 2005; Häuser et al., 2011), although most other studies did not investigate emotional CA (Häuser et al., 2011). A recent European study investigating the prevalence of CA in FM in tertiary care (Bohn et al., 2013) with the CTQ (Bernstein D 1998) reported similar prevalence rates of all types of CA as in the current study.

The second aim of this study was to investigate the relationship of CA with pain severity in FM/CWP. No relationship was found between the presence or severity of CA and pain severity in FM/CWP. This was somewhat unexpected because it contrasts with findings reported by Loevinger et al. (Loevinger 2012). These authors identified different clusters of FM, with a cluster of patients reporting most pain and disability having the highest scores on CA. Yet, other studies have also typically failed to find a relationship between CA and pain severity in FM (Aaron et al., 1997; Waller et al., 2015). It is possible that other measures, e.g. disability, are more appropriate than pain intensity to demonstrate an impact of CAs on the

clinical outcome of FMS-patients. However, we also did not find a relationship between CA and FM disability (measured by FIQ) in our data (data not shown).

Further, the prevalence of PTSD in this study was lower than in other studies using other self-report questionnaires (Cohen et al., 2002; Häuser et al., 2013; Sherman et al., 2000), but similar rates were found in a study by Raphael et al. (Raphael et al., 2006) who did not find any current PTSD in FM using a psychiatric interview to assess PTSD. However, in the current study, FM/CWP patients were about 6 times more likely to meet PTSD criteria compared with FD and achalasia. In addition, in FM/CWP, severity of CA and PTSD were strongly associated, as expected. Yet, only PTSD, and not CA, was associated with pain severity in FM/CWP. In experimental studies, PTSD has been related to hyposensitivity to acute pain (Defrin et al., 2008; Geuze et al., 2007) but in chronic pain, including FM, PTSD has been associated with higher pain levels (Amir et al., 1997; Beckham et al., 1997; Häuser et al., 2012; Sherman et al., 2000). In this study, PTSD severity mediated the relationship between CA and pain severity, despite the lack of a direct relationship between both. This may indicate that the impact, rather than the mere presence, of CA is of crucial importance when it comes to the influence of CA on pain severity. These findings contrast somewhat with a prospective study by Raphael et al. (Raphael and Widom 2011) in which abused and/or neglected children were matched with non-abused and non-neglected children of similar age, race/ethnicity, gender, and parental social class and followed prospectively into adulthood. This study did not find that PTSD mediated the relationship of CA and pain severity in adulthood. Yet, in this study more strict criteria for mediation were used requiring a significant relationship between the independent and the outcome variable (Baron and Kenny 1986), while we used more recent state-of-the-art recommendations for testing mediation (Preacher and Hayes 2004; Zhao et al., 2010). The mediating role of PTSD in the relationship between CA/trauma and pain symptoms has on the other hand been demonstrated in veterans

(Campbell et al., 2008; Häuser et al., 2012; Lang et al., 2006). Moreover, there is evidence from animal studies that CA may lead to persistent alterations in amygdala development, circuitry and function ,with dysfunctional fear regulation as a consequence. More specifically, heightened amygdala activity might increase the risk for developing psychopathology such as anxiety disorders (Cohen et al., 2013).

Findings of this study need to be interpreted within the context of some limitations. First, due to the retrospective design, we had limited comparable demographic characteristics in all three samples. Further, FMS/CWP patients were not assessed for FD and vice versa, nor were patients with achalasia tested for FMS/CWP. Second, as all patients were sampled from a tertiary care centre, and thus selection or referral bias might have influenced results. This may limit the generalizability of findings to FM/CWP patients in primary care or in the general population. Third, we used a self-report questionnaire, and not an interview, to assess CA. However, the CTQ has been shown to be a reliable and valid instrument to assess CA as is shown by its convergence with CA assessed by means of a structured interview (Bernstein et al., 2003). Fourth, as the prevalence of CA in this study was lower compared to other studies (Bohn et al., 2013), under-reporting (Raphael et al., 2001), rather than over-reporting (Hardt and Rutter 2004), might be the case. Fifth, we used achalasia as a chronic organic disease control group. Although achalasia is associated with comparable quality of life impairment as FM/CWP, is not characterized by chronic pain symptoms. Therefore, the prevalence of CA in FM/CWP should be compared with chronic pain symptoms due to organic causes, such as rheumatoid arthritis (Walker et al., 1997), in future studies. Sixth, 19% of the participants provided more than 5% missing data. This might be a group with higher psychiatric comorbidity and/or CA, suffering from cognitive problems e.g. concentration problems. Therefore, selection bias can be an issue. Finally, since most studies in this domain, including

the present study, are cross-sectional, no firm conclusions can be drawn on the directionality of the reported associations. There remains a need for prospective research in this area.

Despite these limitations, this study showed a similar prevalence of CA in FM/CWP and FD, another FSS, but both groups showed significantly higher levels of CA compared to both healthy controls and patients with an organic disease. Further, compared with FD and achalasia, FM/CWP patients were about 6 times more likely to report PTSD. In FM/CWP, there was no direct relationship between CA and pain severity. However, PTSD mediated the relationship between CA and pain severity. Together, these results suggest that screening for PTSD symptoms should be an essential part of the assessment process in patients suffering from FM/CWP, so that patients can be referred for evidence-based treatment to mental health care specialists when appropriate (Bisson et al., 2007; Stein et al., 2009). Semi-structured interviews such as the MINI (Lecrubier et al., 1997) or well-validated self-report questionnaires such as PTSD-ZIL (Hovens et al., 2000) may be used for this purpose. In the context of multidisciplinary treatment of FM/CWP, psychotherapeutic strategies need to focus on treatment of PTSD symptoms and on the possible impact of these symptoms on pain severity.

Legends

Figure 1. Posttraumatic stress disorder severity measured by PTSD-ZIL. Boxplot: whiskers showing the minimum and maximum, the thick line showing the medium and the other lines showing the 1th and3th percentile. On the X-axis the three groups (FM= Fibromyalgia/CWP=Chronic widespread pain) and on the Y-axis the PTSD severity scores, $p < .025$ ($p < .05$ Bonferroni adjusted)* $p < .005$ ($p < .01$ Bonferroni adjusted) ** $p < .001$ (Bonferroni adjusted) ***

Figure 2. **Dose-response relationship PTSD/CA in FM/CWP patients.** Boxplot: whiskers showing the minimum and maximum, the thick line showing the medium and the other lines showing the 1th and3th percentile. On the x-axis the number of CA measured by CTQ and on the Y-axis the PTSD severity scores, $p < .025$ (.05 Bonferroni adjusted)* $p < .005$ (.01 Bonferroni adjusted)** $p < .001$ (Bonferroni adjusted)***

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