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Predictors of Depression in Youth With Crohn Disease

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Abstract

Objective—The aim of the study was to determine whether infliximab use and other potential predictors are associated with decreased prevalence and severity of depression in pediatric patients with Crohn disease (CD).

Methods—A total of 550 (n = 550) youth ages 9 to 17 years with biopsy-confirmed CD were consecutively recruited as part of a multicenter randomized controlled trial. Out of the 550, 499 patients met study criteria and were included in the analysis. At recruitment, each subject and a parent completed the Children's Depression Inventory (CDI). A child or parent CDI score ≥ 12 was used to denote clinically significant depressive symptoms (CSDS). Child and parent CDI scores were summed to form total CDI (CDIT). Infliximab use, demographic information, steroid use, laboratory values, and Pediatric Crohn's Disease Activity Index (PCDAI) were collected as the potential predictors of depression. Univariate regression models were constructed to determine the relations among predictors, CSDS, and CDIT. Stepwise multivariate regression models were constructed to predict the relation between infliximab use and depression while controlling for other predictors of depression.

Results—Infliximab use was not associated with a decreased proportion of CSDS and CDIT after adjusting for multiple comparisons. CSDS and CDIT were positively associated with PCDAI, erythrocyte sedimentation rate, and steroid dose (P<0.01) and negatively associated with

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socioeconomic status (SES) ($P<0.001$). In multivariate models, PCDAI and SES were the strongest predictors of depression.

Conclusions—Disease activity and SES are significant predictors of depression in youth with Crohn disease.

Keywords

depression; infliximab; pediatric Crohn disease

Pediatric Crohn disease (CD) is a chronic, lifelong inflammatory bowel disease (IBD) that often involves an unpredictable cycle of flares and remissions. Symptoms can include abdominal pain, bloody diarrhea, weight loss, and rectal bleeding (1). The patients with pediatric CD are at additional risk for the developmental problems, including growth retardation and pubertal delay (2). In addition, this population also has a high rate of depression compared to community controls and the children with other chronic illnesses (3).

Several factors may contribute to an increased risk of depression in IBD. It has been shown that depression and disease activity are interrelated (3,4). The IBD-related morbidity may contribute to depression through negative cognitive processing of the experience, which may manifest as low self-esteem, feeling lack of control over the disease, or a negative processing style, such as rumination (5). Other related psychosocial factors may include the stress associated with coping with a physical illness and decreased opportunities for socialization (6). It has also been suggested that depression may be related to the direct effect of inflammation on the brain (7,8). According to this hypothesis, some cases of depression may be caused by systemic proinflammatory cytokines. One of these cytokines, tumor necrosis factor-α (TNF-α), has been implicated in both depression and IBD (9,10).

Basic and clinical research already indicates that TNF-α antagonism with biological medications (eg, etanercept, adalimumab, infliximab) can reduce depressive symptoms in certain populations. For example, O'Connor et al (11) demonstrated that mice pretreated with etanercept are resistant to depressive behavior following a challenge with the immune-stimulator bacille Calmette-Guérin. Clinical randomized controlled trials have shown that etanercept and adalimumab yield significant improvements in depressive severity compared with placebo (12,13). Notably, patients treated with adalimumab, who experienced a 75% or greater reduction in psoriasis area and severity index score, experienced an even greater decrease in depressive severity (13). Another trial found that the patients with psoriatic arthritis showed clinically relevant improvement in the mental component summary of the 36-Item Short-Form Health Survey following treatment with infliximab (14). Each of these trials showed a significant decrease in depressive symptoms in the patients with inflammatory illness; however, it is unclear whether these improvements in depressive symptoms were caused by a reduction in chronic disease severity or the more direct effects of infliximab on a brain-based inflammation.

This study is a cross-sectional examination of the relation between infliximab use and depression in pediatric patients with CD. We hypothesized that the infliximab use is

associated with a lower prevalence and severity of depressive symptoms, and that this effect would be statistically significant even when controlling for other potential mediators of depression severity, including CD severity, sex, age, systemic inflammation, steroid dose, and socioeconomic status (SES). The relation between depression and these other potential predictors was also assessed, and models were constructed to predict the prevalence and severity of depression in this population.

METHODS

All of the study participants were recruited between 2008 and 2012 as part of a 2-site randomized controlled trial comparing 2 psychotherapies for the treatment of depression in youth with IBD (15). Written informed assent and consent were obtained from the youth and parent/guardian, respectively. Research personnel administered a screening questionnaire and clinical interview to gather data concerning demographics, psychological characteristics, and medical history. Medical data were gathered from the electronic medical record. If a patient was screened more than once, only data from the final screening was used. The protocol for this study was approved by the institutional review boards at the Children's Hospital of Pittsburgh and Boston Children's Hospital.

A total of 765 participants were consecutively screened for this study. Each subject and a parent/guardian completed the Children's Depression Inventory (CDI). Youth were eligible for inclusion in this study, if they met the following criteria: age 9 to 17 years, English-speaking, capacity to complete the CDI, diagnosis of CD, absence of mental retardation by history, and presence of at least 1 biological parent. The diagnosis of CD was determined by pediatric gastroenterologists based on the Porto criteria (16). Patients whose evaluation suggested ulcerative colitis or indeterminate colitis were not included in this study. The exclusion criteria included history of bipolar disorder, eating disorder requiring past or present hospitalization, or psychotic disorder; suicide attempt within 1 month of study entry; pharmacological treatment for mood disorders; substance abuse within 1 month of study entry; and the use of any biological medication other than infliximab within the 8 weeks preceding the study.

Study Measurements

CDI—The CDI is a 27-item self-report of depressive symptoms that is completed by the child (CDIC) and a parent (CDIP) (17). Scores range from 0 to 54, with higher scores indicating greater depressive severity. The CDI was used to estimate 2 outcome measures: the proportion of patients with clinically significant depressive symptoms (CSDS) and average depressive severity. A cutoff score of CDIC or CDIP ≥ 12 was used to indicate CSDS because this has been demonstrated to be a reliable cutoff in populations with a relatively high incidence of depression (18). For depressive severity, the total CDI score (CDIT), which was defined as the sum of CDI scores from the parent/guardian and child, was used as an outcome measure. This combined score has shown adequate sensitivity in the previous studies of depression in pediatric IBD (19,20).

Paris Classification—The Paris classification is a system used to define phenotypes of pediatric IBD (21). The classification consists of descriptions of disease location, behavior,

and growth restriction. This information was collected from the medical record by a pediatric gastroenterologist and a medical student. Patient data with indeterminate results or missing records were left blank.

Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Edition—The Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Edition (KSADS-PL) is a semistructured interview designed to identify present and past psychiatric disorders according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria (22). This interview was simultaneously administered to the child and parent. This interview was only offered to patients who screened into the larger randomized controlled trial with CDIC or CDIP scores ≥10.

Pediatric Crohn's Disease Activity Index—The Pediatric Crohn's Disease Activity Index (PCDAI) is a clinician-rated instrument that comprises subjective (abdominal pain, stooling, overall well-being), biochemical (inflammatory markers, hematocrit), and physical examination (weight, linear growth, abdominal examination, perianal examination, extra-intestinal manifestations). Scores range from 0 to 100, with higher scores representing greater disease activity (23). The participant's disease was categorized by PCDAI score as inactive (0–10), mild (11–30), and moderate/severe (31–100) (24).

Erythrocyte Sedimentation Rate—The erythrocyte sedimentation rate (ESR) is a blood test used to determine overall inflammatory load (25). This laboratory measurement was collected from the electronic medical record within 1 month of assessment date.

Infliximab Use—For the purposes of this study, infliximab use was defined as receiving 1 dose of infliximab within the last 8 weeks. This period was deemed appropriate because the half-life of infliximab is 8 to 10 days and doses are given at most 8 weeks apart (26).

Steroid Dose—Systemic steroid use was recorded from the medical record. Daily steroid dose was defined as the number of milligrams of prednisone prescribed on the day of the assessment divided by the weight of the child in kilograms. Yearly steroid dose was estimated by adding together the total number of milligrams of prednisone prescribed during the previous year divided by the weight of the child on the day of the assessment.

SES—SES was defined by taking the income category and dividing it by the number of people in the household living on the income. Income category ranged from 1 to 7, with each number representing a $15,000 range. Scores of 1 and 7 were categorized as "< $15,000" and ">$90,000."

Statistical Methods

Univariate regression was used to examine the relation between infliximab use and CSDS or CDIT. We hypothesized that several other variables, including age, sex, PCDAI, ESR, yearly steroid dose, daily steroid dose, and SES, could influence the relation between depression and infliximab. Because our dataset did not contain complete data on all of the variables, and to ensure that multivariate regression models represented the largest number of possible patients, we performed preliminary univariate regression on all potential

predictors of depression. Predictors significant at $P<0.10$ in these models were then included as potential covariates of infliximab use and CSDS or CDIT in stepwise multivariate regression models. Models for CSDS were fit using logistic regression, whereas models for CDIT were fit using linear regression. Multivariate regression models adjusting for other covariates were constructed using stepwise regression by including all of the variables significant at $P<0.10$ and forcing infliximab use into the model.

Using an initial α of 0.05 and the Bonferroni correction for multiple comparisons, we set the overall level of statistical significance at $P<0.00625$ (0.05/8). An assessment of collinearity was performed for all multiple regression models. Goodness of fit was estimated using the Cox and Snell R^2 statistic in logistic regression, and as the square of the correlation coefficient (R^2) in linear regression. Statistical analysis was completed using SPSS version 21 (IBM, Armonk, NY).

RESULTS

A total of 550 patients with CD were consecutively recruited. Nine patients were excluded because CDI data were incomplete from either the child or parent. Eleven additional patients were excluded because they were taking antidepressants when screened. Twenty-nine patients were excluded because they were taking a biological medication other than infliximab. Two patients were excluded because they were >17 years, leaving 499 patients available for analysis.

Fifty-two percent (52.0%) of the subjects were male. Most participants were white, and had average IBD disease activity scores in the inactive to mild categories (PCDAI scores 0–30). Clinically significant depressive symptoms were identified in 38.1% of patients, and the correlation coefficient between CDIC ≥ 12 and CDIP ≥ 12 was $R = 0.338$ ($P<0.001$). Average CDIT scores were 27.4 in patients with CSDS, and 7.1 in patients without CSDS. Approximately 30% of the subjects were receiving infliximab at that time (Table 1). Included and excluded subjects had similar baseline characteristics (data not shown).

Of the 190 patients with CSDS, 153 completed the KSADS-PL assessment. A total of 89 (58.2%) of these patients were diagnosed as having major depressive disorder, 50 (32.7%) were diagnosed as having minor depression, and 14 (9.2%) did not qualify for a diagnosis of depression. Extrapolating this figure to all 190 patients with CSDS indicates that approximately 22.1% of subjects qualified for a diagnosis of major depressive disorder.

Univariate logistic regression found that infliximab use was associated with a decreased proportion of CSDS (31.3% vs 41.0%, OR 0.66, $P = 0.046$). Univariate logistic models also showed that SES was negatively associated with CSDS, whereas PCDAI, ESR, and daily steroid dose were positively associated with CSDS (Table 2). Infliximab use was no longer statistically significant in the stepwise regression model after controlling for other potential predictors (Table 3). PCDAI and SES were the strongest predictors of CSDS in these models. Multivariate models that did not force the inclusion of infliximab showed similar results (data not shown).

Univariate linear regression showed that infliximab use was associated with decreased CDIT (mean CDIT 13.2 vs 15.5, $P = 0.035$). Additional univariate regression also showed that SES was negatively associated with CDIT, and that PCDAI, ESR, and daily steroid dose were positively associated with CDIT (Table 4). Infliximab use was no longer a statistically significant predictor of CDIT in stepwise regression models after controlling for other predictors (Table 5). PCDAI and SES were the strongest predictors of CSDS in these models. Multivariate models that did not force the inclusion of infliximab showed similar results (data not shown).

DISCUSSION

These results failed to confirm our hypothesis that the infliximab use is significantly associated with decreased depressive symptoms in pediatric patients with CD. Although there appears to be a small association between depression and infliximab use, this effect was not present when the data were adjusted for multiple comparisons. In addition, multivariate models that controlled for other predictors of disease activity did not show infliximab use to be a significant predictor of the rate or severity of depression.

Even with adjustments for multiple comparisons, CD activity, ESR, and daily steroid dose were found to be strong predictors of depression in the youth with CD. Our interpretation is that the elevated disease activity is associated with depression, and that ESR and daily steroid dose are appropriate proxies for disease activity; however, other studies have suggested that steroid use may also have an independent effect on depression (27). Low SES is another risk factor for depression, possibly because it serves as a marker for psychosocial adversity or lower treatment adherence. Clinically, this suggests that the control of disease activity is an important goal for preventing symptoms of depression. Appropriate pharmacological treatment of CD is a critical component of this effort.

This cohort also has a relatively high rate of depression. The studies have shown cross-sectional CSDS rates of 25% in pediatric patients with IBD (28). In that study, 81% of patients with CSDS were shown to have major depressive disorder by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria. This is comparable with the 22.1% rate of major depressive disorder estimated in this study. Our study may have also had a higher rate of depression for at least 2 reasons. First, we did not include patients with ulcerative colitis, who had a relatively lower rate of CSDS in our larger sample (33.5% compared with 38.1% in this cohort). Second, our study included patients who were screened for depression multiple times. This methodology was chosen to detect incident cases of depression for a larger randomized depression treatment trial. Although we were systematic in this study and only included the last screening event for each patient (whether they were included in the larger randomized trial or not), this methodology increased the proportion of patients identified in a depressive episode. This design makes it difficult to interpret the point prevalence of depression in our cohort, but it does highlight the importance of continued screening for depression in the patients with IBD.

Notably, only a small proportion of patients were receiving antidepressants at the time of screening, suggesting the potential for significant under treatment of depression in this

population. Several factors may contribute to this finding. Time pressures may cause gastroenterologists and their staff to focus on the physical aspects of disease, and in the absence of behavioral health providers, mental health needs may be neglected. Children and adolescents may also underreport depression symptoms, making it important to use both child and parent reports when assessing depression.

The limitations of this study include a cross-sectional design and recruitment from tertiary care centers. In addition, subjects were recruited at different stages in their infliximab treatment (ie, induction vs maintenance). We also did not account for infliximab antibodies or resistance, nor did we control for other potential confounders. For example, surgical history, presence of an ostomy, disease location, and family history of depression may be important predictors of depression that were not examined.

The findings of this study support the presence of a significant relation between systemic inflammation and brain-based symptoms of depression. It further supports the implementation of targeted depression screening and the development of an integrated healthcare approach to pediatric CD, in which both physical and behavioral treatments are considered together. Further work is needed to enhance treatments for patients with pediatric CD with persistent depression despite well-managed disease activity.

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TABLE 1

Baseline characteristics

Male sex, n, %	259	52.0
White race, n, %	455	91.2
Infliximab use, n, %	152	30.5
Clinically significant depressive symptoms, n, %	190	38.1
Disease location		
Terminal ileum ± limited cecal, n, %	72	15.9
Colonic, n, %	69	15.2
Ileocolonic, n, %	306	67.4
Upper GI proximal to ligament of Treitz, n, %	304	69.4
Distal to ligament of Treitz to prozimal ileum, n, %	44	11.5
History of ostomy, n, %	8	1.6
History of IBD-related surgery, n, %	44	8.8
Age (mean years, SD)	14.4	2.6
SES, mean, SD	1.35	0.61
CDIT, mean, SD	14.8	12.3
PCDAI, mean, SD	13.4	14.2
Yearly steroid load, mean mg · kg^{-1} · y^{-1}, SD	17.0	25.0
Daily steroid dose, mean mg · kg^{-1} · y^{-1}, SD	0.1	0.3
ESR, mean mm/h, SD	19.1	15.2
Duration of disease, mean years, SD	2.3	2.5

CDIT = total Children's Depression Inventory; ESR = erythrocyte sedimentation rate; GI = gastrointestinal; IBD = inflammatory bowel disease; PCDAI = Pediatric Crohn Disease Activity Index; SD = standard deviation; SES = socioeconomic status.

TABLE 2

Association between CSDS and potential predictors

Independent variables	n	OR	95% CI	*P*
Infliximab exposure	498	0.663	(0.443–0.993)	0.046
Age	499	0.975	(0.908–1.045)	0.472
Sex	498	1.351	(0.940–1.941)	0.104
PCDAI	438	1.066	(1.048–1.084)	<0.001*
ESR	438	1.023	(1.010–1.036)	<0.001*
Yearly steroid load	209	1.002	(0.991–1.013)	0.726
Daily steroid load	495	2.308	(1.271–4.189)	0.006*
SES	443	0.464	(0.319–0.676)	<0.001*

CI = confidence interval; CSDS = clinically significant depressive symptom; ESR = erythrocyte sedimentation rate; OR = odds ratio; PCDAI = Pediatric Crohn's Disease Activity Index; SES = socioeconomic status.

*Significant at $P < 0.0063$.

TABLE 3

Multivariable models predicting CSDS

n = 360	Independent variables	OR	95% CI	*P*
Model 1	Infliximab exposure	0.828	(0.497–1.381)	0.470
R^2 = 0.151	PCDAI	1.066	(1.046–1.086)	<0.001
	Constant	0.288		<0.001
Model 2	Infliximab exposure	0.808	(0.481–1.355)	0.419
R^2 = 0.164	PCDAI	1.063	(1.043–1.083)	<0.001
	SES	0.607	(0.394–0.935)	0.024
	Constant	0.580		0.125

CI = confidence interval; CSDS = clinically significant depressive symptom; OR = odds ratio; PCDAI = Pediatric Crohn's Disease Activity Index; SES = socioeconomic status.

TABLE 4

Association between CDIT and potential predictors

Independent variables	n	R^2	β	95% CI	*P*
Infliximab exposure	498	0.008	−2.359	(−4.712 to −0.005)	0.049
Age	499	0.000	0.000	(−0.424 to 0.424)	0.999
Sex	498	0.006	0.079	(−0.213 to 4.130)	0.077
PCDAI	438	0.152	0.338	(0.263–0.414)	<0.001*
ESR	438	0.020	0.115	(0.040–0.190)	0.003*
Yearly steroid load	209	0.002	0.022	(−0.050 to 0.094)	0.542
Daily steroid load	495	0.033	7.446	(3.894–10.998)	<0.001*
SES	443	0.046	−4.405	(−6.282 to −2.529)	<0.001*

CDIT = total Children's Depression Inventory; CI = confidence interval; ESR = erythrocyte sedimentation rate; PCDAI = Pediatric Crohn's Disease Activity Index; SES = socioeconomic status.

*Significant at $P < 0.0063$.

TABLE 5

Multivariable models predicting CDIT

n = 360	Independent variables	β	95% CI	*P*
Model 1	Infliximab exposure	−1.638	(−4.241 to 0.965)	0.217
R^2 = 0.149	PCDAI	0.326	(0.241–0.410)	<0.001
	Constant	11.014	(9.137–12.891)	<0.001
Model 2	Infliximab exposure	−1.696	(−4.350 to 0.795)	0.175
R^2 = 0.172	PCDAI	0.306	(0.222–0.390)	<0.001
	SES	−3.068	(−4.350 to 0.795)	0.002
	Constant	15.447	(12.112–18.781)	<0.001

CDIT = total Children's Depression Inventory; CI = confidence interval; OR = odds ratio; PCDAI = Pediatric Crohn's Disease Activity Index.