Inflammation and Depression: Unraveling the Complex Interplay in Inflammatory Bowel Disease

Aoife O'Donovan

See ''Depression and IBD'' by Salazar on page 543, ''Predictors of Depression in Youth With Crohn Disease'' by Szigethy et al on page 569, and ''Depression Subtypes in Pediatric Inflammatory Bowel Disease'' by Szigethy et al on page 574.

Despite strong evidence implicating inflammation as a causal factor in some forms of depression, there are a number of issues to be resolved before this evidence can be translated into novel interventions. One such issue is the need to understand heterogeneity among individuals with inflammatory disorders and depression. In their report, Szigethy et al (1) described their attempt to tackle this issue using a sample of 226 adolescents with inflammatory bowel disease (IBD) and either minor or major depression. Specifically, the authors used latent profile analysis to identify 3 subgroups within their sample. Adolescents in profile 1 (75%) had mild depressive symptoms and relatively low levels of the systemic inflammatory markers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Adolescents in profile 2 (19%) displayed high levels of anhedonia, fatigue, appetite change, physical complaints, irritability, depressed feelings, and psychomotor retardation as well as elevated CRP, ESR, and IBD activity. In contrast, adolescents in profile 3 (6%) had high levels of morbid ideation, suicidal ideation, weeping, hopelessness, anxiety, fatigue, and depressed feelings, but levels of CRP and ESR that were similar to those seen in profile 1. The most pronounced differences between adolescents in profiles 2 and 3 were in depressed affect and motor hypoactivity (highest in profile 2) and hopelessness and suicidal ideation (highest in profile 3).

There are a number of reasons to welcome this addition to the literature on inflammation and depression. First, the study focused on adolescents with IBD, a group that has received relatively less attention in the field of psychoneuroimmunology to date. Second, the study also focused on subgroups within the population of patients with depression, an important topic because not all individuals with depression have elevated inflammation and not all individuals with elevated inflammation have high levels of depression. Finally, the article yields information that may prove informative for the development of novel treatments for IBD. In general, the use of statistical approaches for subtyping patient groups can yield clues to different etiological pathways that could lead us closer toward precision medicine interventions.

INFLAMMATION AS A CAUSAL FACTOR IN DEPRESSIVE DISORDERS

When confronted with injury or infection, the ability to mount an inflammatory response is critical for survival; however, even in the absence of acute threats, inflammation is critical for the day-to-day functioning of the brain. For example, rodents that are engineered to lack specific inflammatory proteins show impairments in learning and memory (2). Despite the importance of inflammation for brain function, elevated inflammation is also now recognized as a promoter of psychiatric symptoms, including depressive symptoms (3).

Convergent evidence from several compelling lines of work has contributed to the increased recognition of inflammation as a causal factor in some forms of depression. First, experimental work in nonhuman animals has shown that inflammation promotes symptoms analogous to depressive symptoms (4). Second, eliciting an inflammatory response with proinflammatory agents produces transient symptoms of depression, including sadness and anhedonia, in humans (5). Third, proinflammatory treatments for disorders such as multiple sclerosis, hepatitis C, and cancer increase risk for major depressive disorder (6). Fourth, patients with depression tend to have elevated levels of inflammatory markers compared with nondepressed controls (7). Finally, studies using data-driven high-throughput approaches repeatedly find altered inflammatory activity in patients with depression and other psychiatric disorders.

SPECIFICITY IN THE RELATION BETWEEN INFLAMMATION AND PSYCHIATRIC SYMPTOMS?

It is increasingly clear that elevated inflammation is present across psychiatric disorders ranging from depressive to anxiety to psychotic disorders. Thus, inflammation is unlikely to be a specific biomarker for any diagnostic category and instead may explain symptoms common across psychiatric disorders; however, in practice, it is difficult to tease apart any specific effects in patients who present with complex profiles of somatic and cognitive symptoms that frequently co-occur and mutually reinforce one another. Nonetheless, Szigethy et al were able to see some interesting patterns of symptoms in their cohort of adolescents, leading them to describe profile 2 as ''somatic depression'' and profile 3 as ''cognitive despair.'' Systemic inflammation was highest in the group of adolescents who showed high levels of depressed affect and motor hypoactivity, whereas inflammation was relatively low in adolescents who showed high levels of hopelessness and suicidal ideation. This latter finding was somewhat surprising given previous work linking suicidal ideation with elevated inflammation in depressed individuals (7).

In interpreting the findings, it is important to note several important ways that the present study differs from prior work. First, the authors excluded patients with IBD who did not meet criteria for minor or major depression, and the study lacks a control group of adolescents without IBD and depression. Thus, levels of inflammation are compared only within groups with both IBD and depression, which may lead to different patterns of findings than those that would be seen when comparing with healthy individuals or individuals with IBD and no depressive symptoms. Second, the present study focused on adolescents with a chronic inflammatory disorder that may have independent effects on both inflammation and depressive symptoms, whereas most previous work is based on samples without physical disease. Finally, in contrast with most

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From the Department of Psychiatry, University of California, San Francisco.

Address correspondence and reprint requests to Aoife O'Donovan, PhD, San Francisco VA Medical Center, Mental Health Service, 4150 Clement Street (Building 16), San Francisco, CA 94121 (e-mail: aoife.odonovan@ucsf.edu).

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depression-inflammation studies, inflammation in the present cohort may be the result of the inflammatory disorder and may therefore differ in type or degree compared with inflammation driven by other factors such as psychosocial stress. Future studies including healthy controls and patients with IBD without depression will further our understanding of the relation between inflammation and depression in IBD.

A ROLE FOR PSYCHOLOGICAL STRESS?

The literature reports increases in inflammation in individuals exposed to early adversity (8), and a growing literature links early life adversity with shorter telomere length, an indicator of cellular age and a risk factor for elevated inflammation and autoimmune disorders (9). Therefore, one possibility is that life stress contributes to both elevated inflammation and depressive symptoms in some adolescents in this sample. In fact, adolescents in profile 2 who showed high levels of inflammation and depressive symptoms tended to have lower socioeconomic status, which is a frequently used but imperfect indicator of chronic life stress. This finding raises the possibility that a background of chronic stress or exposure to the psychologically distressing aspects of IBD could increase inflammation and symptoms of depression. Future studies should directly assess chronic and traumatic life stress to examine effects on the physical and mental health of individuals with IBS. If psychological stress exacerbates disease activity and inflammation and contributes to symptoms of depression, stress-management interventions may prove beneficial for youth with IBD and high levels of psychological stress.

CLINICAL IMPLICATIONS

If inflammation indeed promotes specific depressive symptoms in patients with IBD, anti-inflammatory interventions may also reduce such symptoms and improve quality of life; however, merely reducing inflammation will likely be insufficient, as evidenced by the fact that a sizeable number of adolescents in profile 2 were on high-dose anti-inflammatory glucocorticoid treatments and nonetheless demonstrated high levels of depressive symptoms. Clearly, there is a great need to both identify the precise molecular mechanisms of inflammation-associated depression and develop highly targeted and personalized treatments.

One of the first studies to attempt such an approach was completed by investigators who administered infliximab, an antagonist for the proinflammatory cytokine tumor necrosis factor-α (TNF-α), in a group of patients with treatment-resistant depression (10). Although the authors found no overall differences in depressive symptoms following treatment with infliximab versus placebo, individuals with elevated inflammation—as indexed by CRP levels >5 mg/L—had a positive response to the medication. In contrast, individuals with lower levels of inflammation showed worse symptoms on infliximab versus placebo. This clinical trial of infliximab is of high relevance to the present work in underscoring that there are subgroups of depressed individuals who may benefit from targeted anti-inflammatory treatments, and subgroups for which such treatments may be deleterious. Notably, elsewhere in this issue, Clark et al (11) reports decreased depression in adolescents with Crohn disease treated with infliximab, but this effect was no longer significant when adjusting for confounds. Randomized controlled trials will be needed to clarify the effects of infliximab on depressive symptoms in IBD.

AN AGENDA FOR FUTURE RESEARCH

Szigethy et al describe their study as ''hypothesis generating,'' and it does indeed raise important questions for future research. Below are some critical next steps for interdisciplinary research in IBD and other autoimmune conditions. First, the developmental trajectory of interrelated symptoms in IBD may offer critical clues to causal pathways. Prospective longitudinal studies that track changes in IBD disease activity and inflammation with changes in depressive symptoms over time are therefore warranted. Second, are the subtypes of patients observed in this study specific to IBD or present across other autoimmune disorders as well? Previous work has suggested increased proinflammatory cytokine production in colonic biopsies of patients with IBD and this may be 1 source of elevated inflammation in this group but not others (12). Third, what are the implications of depression for health behaviors in adolescents with IBD? To what extent does depression reduce health-enhancing behaviors such as physical activity and the avoidance of tobacco, alcohol, and other substances that would influence levels of inflammation? Would enhanced health behaviors reduce depressive symptoms in some but not all patients? Finally, what drives group differences observed in this study? Are there genetic or environmental factors that predict subgroup membership in this sample of adolescents with IBD? Can these markers be used clinically to personalize treatments? Such personalized treatments may present an opportunity to enhance quality of life for adolescents with IBD.

In sum, Szigethy et al have presented provocative data that merit more dialogue and further study. Given the prevalence of comorbid depressive symptoms in IBD, it is imperative for the field to further the research agenda to enhance understanding and treatment of the complex interplay of inflammation and depression in IBD.

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Depression and IBD

Guadalupe Salazar

See ''Inflammation and Depression: Unraveling the Complex Interplay in Inflammatory Bowel Disease'' by O'Donovan on page 541, ''Predictors of Depression in Youth With Crohn Disease'' by Szigethy et al on page 569, and ''Depression Subtypes in Pediatric Inflammatory Bowel Disease'' by Szigethy et al on page 574.

Predictably, mental health conditions such as depression and anxiety are common among pediatric patients diagnosed as having IBD (1,2). Studies document that 60% of children and adolescents with IBD experience depression compared with 15% of healthy controls and children with other chronic illnesses (eg, 20% with diabetes) and reduced psychosocial functioning (3). Contributors to depression in patients with IBD include biological and psychosocial domains such as disease activity, therapies, and adverse effects; the effects of inflammation on the brain, body image, and lifestyle; and difficulties adjusting to life with a chronic condition (1). The task of identifying and measuring contributing factors to mental health is complex, especially when dealing with children and adolescents living with a stigmatizing chronic condition.

PREDICTORS OF DEPRESSION IN YOUTH WITH CROHN DISEASE

In this issue of the *Journal of Pediatric Gastroenterology and Nutrition*, Clark et al (4) present a cross-sectional examination of the relation between infliximab use and other contributors to depression among pediatric patients with CD. They hypothesized that infliximab use is associated with lower prevalence and severity of depressive symptoms, an effect they expected to be statistically significant when controlling for contributors to depression. Baseline characteristics of the study participants (N = 499) included assessment of clinically significant depressive symptoms (CSDS) using the Children's Depressive Inventory (CDI) scores for children and parents and depression severity as denoted by the sum of child and parent CDI scores to produce a total CDI (CDIT). Data regarding predictors of depression were also collected, specifically, use of infliximab, Pediatric Crohn's Disease Activity Index (PCDAI) scores, erythrocyte sedimentation rate, steroid use, and socioeconomic status (SES). Clark et al applied univariate regression models to determine relations between predictors of depression, CSDS, and CDIT. Multivariate regression models predicted the relation between infliximab use and depression while controlling for other predictors of depression.

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From the San Jose State University, San Jose, CA.

Address correspondence and reprint requests to Guadalupe Salazar, PhD, MPH, San Jose State University, 1 Washington Square, San Jose, CA 95192-0113 (e-mail: guadalupe.salazar@sjsu.edu).

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The study documented CSDS in 38.1% of the participants (190/499). The Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Edition (KSADS-PL) was offered to these participants and their parents; 153 completed the schedule, resulting in 89 (58.2%) diagnosed as having major depressive disorder and 50 (32.7%) as having minor depression. Univariate logistic regression revealed an association between infliximab use and a reduced proportion of CSDS. After controlling for predictors in stepwise regression models, infliximab use had no statistically significant impact. PCDAI and SES had the strongest association with CSDS. Univariate linear regression models showed an association between infliximab use and lower CDIT; however, after controlling for predictors in stepwise regression models, infliximab was no longer significantly predictive of CDIT. Instead, PCDAI and SES were the strongest predictors of CSDS.

IMPLICATIONS

Infliximab is routinely used to treat severe cases because it often leads to the control of active disease and is effective in maintenance therapy (5). Although infliximab may treat disease activity, IBD exacts a heavy toll in psychosocial arenas of patients' lives. The findings of Clark et al do not support their hypothesis that the use of infliximab decreases the incidence and severity of depression among this population; however, it is important to consider whether patients treated with it are experiencing more severe disease and its associated physical, psychological, and social sequelae. Patients with more severe disease activity may experience more stigma and lead to depressive symptoms (6), substantiated by this study's finding of an association between elevated disease activity and depression.

Perhaps most valuable was the discovery of undertreatment of depression among this population, especially given the risk involved. This observation highlights that one of the most important goals of medical treatment for IBD is to maximize the efficacy of drug therapies in inducing and maintaining remission (7). Unfortunately, psychosocial needs are secondary to biological ones in this setting; however, children and adolescents, still developing physically, cognitively, and psychosocially, experience a diminished quality of life and may not have adequate coping mechanisms to help them manage and improve their quality of life (8). Mental health needs and concerns may be slipping through cracks in the health care system.

THREE WAYS PHYSICIANS CAN HELP PEDIATRIC IBD PATIENTS COPE BETTER

A diagnosis of IBD and its successful management requires learning to adjust to and live with a challenging chronic condition that affects physical, psychological, and social domains. How can physicians help their patients cope better with IBD? Listening is key, because the stories patients tell are important indicators of psychosocial struggles and adjustment. Patient narratives provide context, which is critical to better understanding patients' perspectives. Physicians need to learn how to ask ''What matters to you?'' and ''What is the matter?'' to minimize discrepancies between physician and patient health concerns (9). Encouraging patients to participate in social interactive forums, including support groups (online or in person) or IBD-specific summer camps, is another way to help patients cope. Camps, in particular, provide traditional camping experiences along with opportunities to network with true peers, allowing underlying IBD to recede to the background and letting the patients be kids and have fun.

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Calretinin and Pathologic Diagnosis of Hirschsprung Disease: Has the Time Come to Abandon the Acetylcholinesterase Stain?

*Susan S. Baker and †Rafal Kozielski

See ''Does Calretinin Immunohistochemistry Reduce Inconclusive Diagnosis in Rectal Biopsies for Hirschsprung Disease?'' by de Arruda Lourenção et al on page 603.

Hirschsprung disease (HD) results from a failure of the enteric-derived neural crest cells to migrate to and colonize the distal bowel. HD occurs in 1 in 5000 live births; in the most common form of HD, boys predominate, and the disorder involves only the distal sigmoid colon and rectum. In the absence of ganglion cells, which secrete mediators that regulate normal gastrointestinal motility, the bowel functions as if an obstruction were present. HD is usually sporadic, but approximately 20% is familial and 30% has other associated abnormalities that are recognized as clinical syndromes (1).

Overall mortality is estimated to be 3%, and children born with associated anomalies are at maximum risk. If the aganglionic segment is long, intestinal failure secondary to short bowel syndrome can result from surgical treatment (2). The presentation in infants varies from delayed meconium passage to life-threatening bowel dysfunction in total intestinal aganglionosis.

The diagnosis is based on the demonstration of absent ganglion cells in rectal biopsies (RBs), the test of choice (3). Multiple hematoxylin and eosin–stained serial sections must be examined before a definitive diagnosis is rendered. Many centers use an ancillary acetylcholinesterase (AChE) histochemistry stain. AChE identifies nerve fibers throughout the lamina propria and muscularis mucosae and is considered diagnostic of HD. Herein lays the difficulty in making a diagnosis quickly with reproducible accuracy. AChE requires a second biopsy and processing of frozen tissue. The interpretation of the stain is associated with high rates of interobserver disagreement and false-positives (4). Additionally, approximately 17% of RBs (5) are inadequate for interpretation because they are too superficial or too distal. In neonates, the ganglion cells may be undifferentiated and difficult to identify. Some general surgical pathologists may not be sufficiently experienced in diagnosing HD, and the interpretation of findings can be perplexing and onerous. There is a lot at stake in accurate interpretation of RB findings; the diagnosis commits the patient to a major surgery. These factors can cause confusion for the clinician, require patients to undergo repeat biopsy procedures, and lead to delay in diagnosis and treatment.

Immunohistochemistry is considered a sensitive, specific, simple, and efficient technique used daily by pathologists. It is a valuable tool in the diagnosis of HD. Calretinin, a vitamin D–dependent calcium-binding protein involved in calcium signaling, is found in ganglion cells and small intrinsic nerve fibers throughout the colon. An immunohistochemical stain (Cal) using an anti-calretinin antibody can be performed on the formalin-fixed tissue and is reported to be superior to AChE in the diagnosis of HD (6,7).

In this issue of the journal, de Arruda Lourenção et al (8) present the results of the addition of Cal to their panel of stains. They used historical controls, an acknowledged weakness. Nevertheless, they show that the addition of Cal decreased the rate of inconclusive results and increased the likelihood of a confirmed diagnosis. In the Cal group 11.9% of biopsies were inconclusive compared with 37.8% in the non-Cal group. These results are in agreement with previous studies and argue for the addition of Cal to the routine repertoire of stains used to diagnosis HD.

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From the *Department of Pediatrics, Digestive Diseases and Nutrition Center, Women and Children's Hospital of Buffalo, and the †Department Pathology, SUNY at Buffalo, Buffalo, NY.

Address correspondence and reprint requests to Susan S. Baker, MD, PhD, Digestive Diseases and Nutrition Center, SUNY at Buffalo, Women and Children's Hospital, 219 Bryant St, Buffalo, NY 14222 (e-mail: sbaker@upa.chob.edu).

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Infantile Hypertrophic Pyloric Stenosis: Closing In On the Cause

*Melvin Dassinger and †George J. Fuchs

See ''Question of an Infectious Etiology or Contribution to the Pathogenesis of Infantile Hypertrophic Pyloric Stenosis'' by Modarressi on page 546.

Infantile hypertrophic pyloric stenosis (IHPS) is a common condition that causes gastric outlet obstruction in affected infants; however, determining a precise etiology has proven vexing. The etiology is complex, but includes a genetic predisposition likely modulated by environmental factors such as erythromycin exposure, feeding practices, among others (1,2). It is within this conceptual framework that Modarressi in the present issue of the *Journal of Pediatric Gastroenterology and Nutrition* presents the hypothesis for infection or an infectious component to the etiology of IHPS (3).

Modarressi provides a comprehensive summary of causes, including infectious organisms and changes in the neuronal nitric oxide synthase (nNOS) gene, *NOS1*. He details the literature relating to possible bacterial, fungal, and viral etiologies; unfortunately, most of these studies experience low sample size, competing results among studies, or inability of results to be reproduced in the pediatric population. Although an infectious component to etiology cannot be excluded, many of the epidemiologic characteristics of IHPS that Modarressi proposes to be circumstantial evidence in support of an infectious etiology have alternate, more convincing explanations. For example, data on seasonality of IHPS incidence are contradictory, as he points out (4). Although both IHPS and urinary tract infections are independently increased in boys, an increase in urinary tract infection rates is more likely related to male urethral anatomy than increased susceptibility to infection. The contention that intrafamilial aggregation of IHPS is consistent with an infectious etiology because inheritance patterns in IHPS are unclear is not supported by the evidence. A genetic predisposition to IHPS is well established with not only strong familial aggregation and male-to-female predominance (4–5:1) but also an up to 6-fold increase in risk among monozygotic compared with dizygotic twins (5).

Dr Modarressi refers to the literature implicating the *nNOS* gene in the pathogenesis of IHPS and interprets NOS1's role as an immune modulator to reflect a causal relation with infection. We do not believe, as he does, this necessarily supports an infectious etiology but instead more likely highlights the importance of genetic polymorphisms. Interestingly, a recent report demonstrates a genomewide locus for IHPS on chromosome 1;12, with the polymorphism most strongly associated with IHPS located immediately downstream of *APOA1* (6). Perhaps of relevance, *APOA1* codes for cholesterol metabolism, and an observation of a possible inverse relation has been observed between neonatal circulating cholesterol concentration and IHPS risk. Future investigation in this area may further an understanding of the pathogenesis of IHPS. Modarressi presents an intriguing case for an infectious etiology for this common, heritable condition, but in the context of established risk factors as well as the absence of direct evidence or strong epidemiologic evidence, the case for infection remains theoretical.

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From the *Department of Pediatric Surgery, and the †Section of Gastroenterology, Hepatology, and Nutrition/Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock.
Address correspondence and reprint requests to George J. Fuchs, MD, University of Arkansas for Medical Sciences, 4301 W Markham St, Little Rock, AR 72205 (e-mail: fuchsgeorgej@uams.edu).
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