Research Day 2008

Gastrointestinal Biopsychosocial Research at UNC

October 3 -4, 2008
Chapel Hill, North Carolina

UNC Center for Functional GI & Motility Disorders
The University of North Carolina at Chapel Hill

Research Day 2008 booklet was designed by Nicolette DeGroot.

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In October 2004, the UNC Center for Functional GI & Motility Disorders was awarded a grant (R24 DK067674) from the National Institutes of Health (NIH) to foster interdisciplinary research on interactions between the mind and body in health and disease, with a specific focus on the causes and treatment of functional gastrointestinal disorders. As part of this NIH grant, the Center hosted the fourth of what has now become an annual Research Day on October 3-4, 2008, on the campus of the University of North Carolina at Chapel Hill.

The program for this non-CME symposium was focused on five areas of research: (1) Pelvic Floor and Fecal Incontinence, (2) Pathophysiological Mechanisms of FGID Symptoms, (3) Treatments, Symptoms, Health Status and Health Care Impact, (4) Pediatric Functional GI Disorders, and (5) Inflammation and Infection. The format included presentations on the state-of-the-art in each of these areas by visiting senior scientists, followed by overviews of on-going studies involving UNC faculty and investigators. This booklet provides a summary of all presentations.

We greatly appreciate the educational grants from Sucampo Pharmaceuticals, Takeda Pharmaceuticals, Ironwood Pharmaceuticals, Prometheus Pharmaceuticals, Salix Pharmaceuticals, and AstraZeneca Pharmaceuticals that provided additional support for this event.

William E. Whitehead, PhD
Co-Director

Douglas A. Drossman, MD
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Evaluation and therapy of fecal incontinence: Plugging the breach

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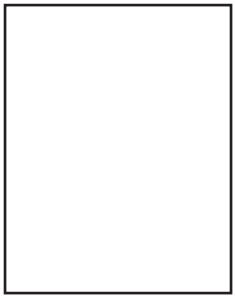

Satish Rao

Epidemiology and impact on quality of life. The prevalence of fecal incontinence (FI) is related to age and sex: Below age 65, the overall prevalence is 0.5-1.3% and it is 6 times more common in women. However, in those aged 65+, the overall prevalence is 3.7% and men outnumber women by 3:2. Prevalence is approximately 25% in nursing homes and psychiatric inpatient units. FI is associated with a significant impairment in most aspects of quality of life and with increased anxiety and depression. The economic impact is poorly documented but is estimated to be $17,166 per patient over the lifespan.

Diagnosis. Clinicians distinguish three subtypes of FI: passive, urge, and seepage without awareness. The physiological mechanisms for FI include anal sphincter weakness, impaired sensation for rectal filling, impaired accommodation of the rectum to filling, pudendal neuropathy, and incomplete evacuation. The clinical presentation (passive, urge, or seepage) is not a reliable guide to the mechanism of FI or to treatment.

Diagnostic evaluation begins with a careful history including the pattern of FI (frequency, precipitating events, passive vs. urge vs. seepage), medical and surgical history, medications, and diet. Physical examination should include inspection of the perineum for dermatitis, rectal prolapse, excessive perineal descent, hemorrhoids, and fistulae; and digital examination to assess anal pressures during squeezing and attempted defecation.

Laboratory tests of anorectal function, in order of clinical utility, are anorectal manometry to quantify resting tone and squeeze pressures, anal endosonography to assess the structural integrity of the anal sphincters, rectal compliance, pudendal nerve terminal motor latency, ability to evacuate a simulated stool, and barium defecography. The greatest yield comes from anorectal manometry which provides new information in an estimated 98% of patients and influences treatment choice in 84%. In some centers, traditional anorectal manometry, which employs 3-4 pressure sensors that are pulled through the anal canal in stages, is being replaced by high resolution manometry which provides more detailed and more accurate information without the necessity of moving the catheter. Similarly, endoanal ultrasound is being replaced at some centers by pelvic MRI, but the published evidence that MRI provides greater clinical utility is mixed.

Pudendal nerve terminal motor latencies are not endorsed by the American Gastroenterological Association because they lack sensitivity and correlate poorly with the outcomes of surgical repair of the sphincters; however, this test continues to be used in some centers. New data suggests that motor evoked potentials recorded in the anal canal that are elicited by non-invasive magnetic stimulation of the lumbar or sacral spine may provide more accurate information on pudendal

S. Rao, continued

neuropathy, but additional research is needed to assess sensitivity and specificity.

Treatment. This may consist of (1) treating the underlying cause of FI (e.g., delirium, diarrhea, constipation); (2) supportive therapy including patient education, diet modification, and fiber supplementation; (3) pharmacological treatment; (4) biofeedback; and (5) surgery. Supportive therapy may include patient education about the best frequency and time of day to attempt a bowel movement in order to minimize FI and dietary advice to increase fiber and decrease caffeine, lactulose, and fructose. There is clinical trial data to support the benefits of increased dietary fiber for diarrhea-related FI. Drugs that have been shown to reduce FI include loperamide, diphenoxylate, and cholestyramine, although FI is not an approved indication for any of these medications (they are indicated for diarrhea).

Biofeedback is a type of neuromuscular re-training which has the following goals: (1) Improved strength of voluntary contractions of the external anal sphincter and puborectalis muscles. (2) Improved rectal sensation and elimination of sensory delays. (3) Improved coordination of pelvic floor muscle contractions with sensations of rectal filling. (4) Correct dyssynergic defecation to allow more complete evacuation of the rectum in patients with seepage secondary to retained stool in the rectum. A large number of uncontrolled trials support the effectiveness of biofeedback for FI, but large randomized controlled trials have been reported only in the last few years. In the first of these Norton and colleagues [Gastroenterol 2003;125:1320-1329] randomized 170 patients with FI to 4 treatment arms: (1) Patient education, dietary advice, and non-prescription medications provided by a specially trained nurse. (2) Procedures from #1 plus pelvic floor exercises taught during digital examination by the nurse. (3) Procedures 1-2 plus biofeedback training taught with electronically amplified information on pelvic floor muscle contractions. (4) Procedures 1-3 plus daily home practice using a battery operated biofeedback device. The investigators found no advantage of instrumented biofeedback over patient education and pelvic floor exercises. Rather different conclusions were drawn by Heymen and colleagues [Dis Colon Rectum 2009; in press] who enrolled 110 patients with FI in a one-month run-in on conservative management (patient education plus use of fiber or medications to normalize stool consistency) and then randomized those who did not achieve adequate relief of FI to either instrumented biofeedback or pelvic floor exercises (taught without digital examination). These investigators found that both pelvic floor exercises and instrumented biofeedback significantly improved continence in patients who had failed to benefit from conservative management. Moreover, biofeedback training was superior to pelvic floor exercises alone. Further support for the efficacy of biofeedback comes from an uncontrolled case series of 105 consecutive patients whose treatment was described by Ozturk and colleagues [Aliment Pharmacol Ther 2004;20:667-674]. These investigators reported substantial reductions in FI following biofeedback that were maintained at one year follow-up. In a novel application of biofeedback to FI, Ozturk and colleagues also reported that biofeedback directed at eliminating dyssynergic defecation (i.e., paradoxical contraction of the pelvic floor during attempts to defecate) was effective at treating the seepage type of FI.

The most commonly employed surgical treatments for FI are sphincteroplasty (suturing the separated ends of the external anal sphincter together), rectal augmentation (injection of collagen or other bulking agents around the external anal sphincter to increase anal canal resting pressure),

S. Rao, continued

creation of a conduit for antegrade colonic lavage, and colostomy. Sphincteroplasty produces good short-term results but most patients experience a recurrence of FI within 5 years. Rectal augmentation yields mixed results and may not be appropriate for urge incontinence. Colostomy produces continence but impairs quality of life and is avoided by most patients and their surgeons. Sacral nerve stimulation is a new treatment approach that is available in Europe but has yet to be approved in the United States. This involves implanting stimulating electrodes in the sacral nerve roots and using an implantable electrical stimulator to trigger contraction of pelvic floor muscles. This technique has produced sustained clinical improvements in published trials to date, although the mechanism of treatment benefits is still disputed. Sacral nerve stimulation is expected to become one of the preferred treatments for severe FI unresponsive to conservative management.

In summary fecal incontinence is a common problem that has significant effects on QOL and psychosocial behavior. Today, it is possible to make an accurate diagnosis and identify the key mechanisms. Treatment paradigms are evolving, but neuromuscular training with biofeedback remains mainstay together with antidiarrheals and behavioral approaches. Surgery should be reserved for highly selected cases only.

Epidemiology of Fecal Incontinence: NHANES 2005-2006 survey

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University of North Carolina at Chapel Hill


William Whitehead

Accurate estimates of the prevalence of fecal incontinence (FI) are needed by policymakers and NIH because current estimates of prevalence vary widely. Reasons for differences include (1) variable definitions of FI (should gas be included?) and (2) unrepresentative samples (only females or only elderly subjects in some studies, use of only clinical or convenience samples, nursing home residents included in some studies but not others).

The aims of our study are (1) to provide nationally representative estimates of the prevalence of FI in non-institutionalized U.S. adults (describe the characteristics of FI, including frequency of occurrence and consistency), (2) determined whether gas should be included in the definition, and (3) identify risk factors.

The database for our study is the National Health and Nutrition Examination Survey (NHANES). This survey includes approximately 5,000 adults surveyed in each 2-year block. The sample is stratified to over-represent minorities and is then adjusted by sample weights to be representative of US population. For 2005-2006, the survey included: Fecal Incontinence Severity Index, Bristol Stool Scale, and a question on frequency of bowel movements.

Our analysis showed that prevalence of FI is strongly associated with age (especially 70+ years) and weakly associated with gender. An estimated 8.3% of non-institutionalized adults in the US – approximately 18 million people -- report FI at least once during the last 30 days. FI is equally prevalent in both genders – 8.9% of women and 7.7% of men. FI increases with advancing age, from 2.6% at age 20-29 years up to 15.3% among persons 70 years and over.

For both men and women, liquid stool incontinence is the most common type of FI. Solid stool incontinence is more often reported by women. Gas is less of a factor for men and women reporting incontinence only 1 to 3 months, however gas increases in importance with greater frequency of incontinence, especially for those reporting FI more than once a day. Both men and women report FI as occurring only 1 to 3 times a month. Increased risk factors for FI include: watery stools, number of comorbid conditions, fair/poor self-reported health status, urinary incontinence, obesity, and inability to do vigorous exercises.

Univariate associations that did not survive multivariate adjustment included hard or lumpy stools, more than 21 stools per week, obesity, vigorous exercise, and poor self-rated health. FI risk factors that were not included in NHANES are rectal urgency (symptom), diagnosis of IBS or IBD, and hemorrhoids or rectal prolapse (soiling).

The prevalence of fecal urgency in women is 14%. For population based studies, this is an OR 5.6-8.3, and remains significant after adjusting for diarrhea. The sensation of urgency is elicited by rectal distention and is common in diarrhea.

W. Whitehead, continued

To summarize, the prevalence of FI in US adults is 9% of women and 8% of men (equates to 18 million people). Liquid is most common type of FI. FI occurs at least 1/week in 2.7% of people. Accidental loss of gas occurs at least monthly in 50% and daily in 11%, but should not be in definition of FI. Age is a strong predictor of FI, but gender, race and SES are not significant predictors.

Diarrhea is strongest risk factor and should be the target of prevention/treatment. Poor health status is a significant risk factor for both women and men. The association of FI with UI is probably related to common innervation and common exposure to trauma. Univariate associations include obesity (increased risk) and vigorous activity (decreased risk). Obstetrical risk factors were not significant in this study of all age groups of women.

Role of incontinence in nursing home referrals

Madhusudan Grover, MD
Michigan State University


Madhusudan Grover

Fecal incontinence (FI) and urinary incontinence (UI) are often said to be a leading cause of nursing home (NH) admission, second only to dementia. However, there is little direct evidence for this statement. A study from an HMO in California found the risk of NH admission was two times higher for women and 3.2 times higher for men with UI. An Australian study found that patients in sub acute care were more than twice as likely to be discharged to a NH if they were incontinent (FI or UI). The prevalence of FI in institutionalized elderly has been reported to be as high as 50-60 percent. According to the 1999 national nursing home survey, 50.6 % of NH residents were found to have FI (1.9% FI alone and 48.7% combined FI and UI). The annual cost of a patient with FI and UI in a long-term facility has been calculated to be $9,711. In the last two decades, the trend towards shorter hospital stays has increased the number of discharges to long-term care institutions.

The aims of our study were (1) to determine the importance of FI, alone and in combination with other patient characteristics, in the decision to refer to a NH or skilled care facility, and (2) to compare the impact of FI to the impact of UI on the decision to refer to a NH.

We invited 2,000 geriatricians and other health care providers from the membership of the American Geriatric Society)AGS) who are frequently involved in the decision to refer an elderly patient to a NH or skilled care facility. The survey presented providers with the clinical scenario of a 70-year-old woman ready for discharge from an acute care hospital, and asked them to rate the likelihood of referral to a NH: (a) in the absence of incontinence, (b) with the addition of UI alone, and (c) with the addition of FI. Subsequent questions modified the clinical scenario to include other conditions (cognitive decline, mobility restrictions, and >2 medical comorbidities) that might affect the decision to refer to a NH. The survey was conducted through e-mail and paper questionnaires, and respondents were paid $10 for completion of the questionnaire. The AGS endorsed the survey as a society project. Significance of differences between scenarios in the relative risk (RR) of referring to a NH was tested by Wilcoxon tests.

716 providers completed the survey (33% response rate). There was broad representation of providers across age groups, sex, years in practice, private vs. academic, and urban vs. rural vs. suburban practice settings. Physicians were the majority of responders (85.6%), followed by nurse practitioners (11.3%) and physician assistants (3.1%). Only 15% were trainees.

In the base clinical scenario, the likelihood of referring to a NH was increased by both UI (RR=1.90, $p<0.001$) and FI (RR=4.71, $p<0.001$); however, the RR was higher in the presence of FI compared to UI (RR=2.48, $p<0.001$). In the absence of UI or FI, the likelihood of referral to NH was increased by the presence of mobility restrictions (RR=18.58, $p<0.001$), cognitive decline (RR=11.16, $p<0.001$),

M. Grover, continued

and multiple medical comorbidities (RR=4.32, $p<0.001$). In all clinical scenarios, both UI and FI significantly increased the likelihood of NH referral ($p<0.001$ for all), and FI increased the NH referral rate more than UI ($p<0.001$ for cognitive decline and additional medical conditions, and $p=0.007$ for mobility restrictions).

Most of the providers (88%) believe that more public education about UI and FI will increase the number of people who raise this concern with their health care provider. Respondents suggested the following groups as targets to increase education about incontinence: caregivers (90.2%), primary care providers (86.2%), geriatricians (51.9%), nurses (61.2%), and others such as patients and the general public (29.9%).

We conclude that: (1) FI, either alone or in combination with other health conditions such as cognitive impairment, mobility limitations, and presence of >2 medical comorbidities, significantly increases the probability that geriatricians will refer to a NH; and (2) fecal incontinence confers a stronger relative risk of NH referral than urinary incontinence.

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Education, Medical Management and Pelvic Floor Exercises for Fecal Incontinence

Steve Heymen, PhD and William E Whitehead, PhD
University of North Carolina at Chapel Hill


Steve Heyman

The prevalence of fecal incontinence (FI) increases with age, increasing from about 2% among adults age 20-29 to close to 16% for adults 70 years and older. FI increases the risk of nursing home referral and causes social isolation and depression. There is a need for improved treatment at the primary care level. Biofeedback is effective but it is costly and not widely available. We have developed an education and medical management treatment that resulted in 60% reductions in FI severity. Enhancements to this treatment led to 80% improvement in FI severity.

In a randomized controlled trial (RCT) of biofeedback for fecal incontinence (N = 168), the run-in protocol included: (1) education about the physiological mechanisms for continence (taught using a cartoon of anatomy) and a review of specific findings from the patient's diagnostic anorectal manometry studies; (2) discussion of triggers (lifting, coughing, attending to urge); (3) behavior techniques for managing FI (toileting schedules and maintaining a diary); (4) use of fiber supplement/Loperamide as needed to normalize stool consistency; and (5) contact with a clinician at least every 4 days to adjust instructions and medications based on a review of the diary. To be included in this investigation, subjects must report at least weekly occurrence of FI (teaspoon). Results from the run-in phase of this study were: (1) 21% (35/168) of patients whose FI had been refractory to previous medical treatment reported adequate relief; (2) 60% average reduction in FI for all 168 patients; and (3) 71% of responders continued to report adequate relief at 12 months follow-up. Prior to participating in this investigation, subjects reported a mean symptom duration more than 7 years and attending an average of more than 3 clinician visits in the previous 6 months, specifically for FI.

Based on these data and the documented need for early effective treatment of FI, the UNC School of Medicine awarded our Center a 3-year Investments for the Future grant with these aims: (1) refine and validate the treatment protocol and (2) prepare an RO1 application to fund statewide dissemination of the FI intervention.

The FIX (Fecal Incontinence Rx) Research Plan involves three phases: (1) test the revised protocol in small groups of patients at UNC Hospitals and modify the FIX protocol based on patient feedback; (2) test the modified protocol in three local continuing care residential communities (CCRCs) and modify the protocol based on patient and nurse feedback; and (3) implement FIX in matched counties across North Carolina and the evaluate impact on (a) MD screening (frequency of FI diagnosis), (b) nursing home admissions, and (c) patient ratings of improvement in FI symptoms.

For our FIX protocol, the original treatment protocol described above is continued: education, behavior strategies, and medical management. The FIX protocol also includes: (1) pelvic floor

S. Heyman, continued

exercise training, (2) additional education and behavior strategies (Defegram; Walk don't run strategy; Preventive squeeze before lifting, coughing; Squeeze/re-clean strategy; Delay strategy); and (3) the development of a DVD as an aid to patient education.

Results from the pilot study to test the enhanced treatment are promising. For Phase 1, we have found: (1) 83% (5/6) reported adequate relief, (2) there was an 80% reduction in FI frequency, (3) 66% were completely continent, and (4) patients offered several suggestions to improve the educational hand-outs and DVD.

Phase 2 to test the modified protocol is ongoing. Screening and treatment entails sending a confidential questionnaire to all residents at the CCRCs, to determine who has FI, whether they have discussed this condition with their doctor, and whether they would like to undergo the treatment. This information is not shared with the CCRCs or the resident's physician, unless requested by the participant. Those who indicate they have a problem with bowel leakage and indicate they would like to participate are contacted by nurses at the CCRC who have been trained in the FIX protocol.

The treatment protocol at the CCRCs entails the following. Interested residents come to one face-to-face meeting with the CCRC nurse for informed consent and training. The nurse telephones each participant weekly to check on progress and answer any questions. Questionnaires on outcomes and feedback on the program are collected 3 months post-treatment. The treatment program lasts 6 weeks.

During the resident's first session with the CCRC nurse, a DVD explaining the techniques will be shown. Instruction is provided on how to perform pelvic floor exercises, and how to collect information in a symptom diary (to monitor success and use in refining the treatment protocol). Benefits to participants are: $15 payment to the patient for returning the questionnaire; $75 per patient to the CCRC nurse for training; free treatment and all medications are provided. We expect most participants will learn the skills needed to prevent bowel leakage long-term.

Phase 3 will be statewide dissemination/implementation of the FIX program, and depends on our Center being awarded an NIH grant. The plan is to disseminate county by county and to compare with control counties. The challenge is to fit the FIX treatment into the existing health care delivery system, and to ensure that providers can be reimbursed for managing FI in this manner. Outcomes will be assessed primarily through claims data files obtained from the state.

[Acknowledgements: Investments for the Future (UNC SOM); R01 DK57048; R24 DK67674]

Genetic Basis of Co-Morbid Conditions: Irritable Bowel Syndrome (IBS) and Vulvar Vestibulitis Syndrome (VVS)

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Denniz Zolnoun

Vulvar Vestibulitis Syndrome (VVS) is clinically defined by the constellation of three symptoms in the vestibule. The vestibule is the small patch of skin bordered by the hymen and skin of the vulva. VVS is defined as: (1) severe pain on touching the vestibule, (2) tenderness to pressure localized within the vestibule, and (3) various degree of erythema confined to the vestibular skin. VVS is the most common cause of painful intercourse. It prohibits or significantly limits sexual activity among women with this condition. It is estimated to affect 12-16% of women of reproductive age. To date, the etiology remains unknown. Collectively, VVS and IBS affect 20% of women, with 7% having both conditions. Upwards of 40% of women in our pain clinic have co-morbid IBS. Estimated health care costs are $30 billion.

Both VVS and IBS are deemed idiopathic with: (1) report of pain greater than objective findings, (2) heightened inflammatory response, (3) psychological distress, and (4) a state of pain amplification. The relative contribution of pain amplification and psychological distress to persistent pain states, such as VVS and IBS, varies among individuals.

Idiopathic pain disorders (IPDs) occurring in isolation are more likely to be governed by a peripheral process versus central process. This variability likely reflects differences in the extent of pathophysiological alteration that occurs at the level of the peripheral versus the central nervous system. An emerging literature suggests that IPDs occurring in isolation result from local increases in peripheral afferent activity and proinflammatory cytokine production, while IPDs occurring in concert result from central dysregulation in pain processing, mood and proinflammatory cytokine production. Thus, current theory frames VVS and IBS as biopsychosocial disorders that share a common central pathophysiology.

We hypothesize that heterogeneity in both conditions may, in part, be explained by differences in the relative contributions of peripheral, CNS-mediated pain amplification and psychological distress. Investigating the clinical and biological overlap may provide additional clues to the nature of heterogeneity in either condition.

In collaboration with a funded study (K23 HD053631), our research team will acquire a clinical dataset that contains assessments of bodily mechanical and thermal pain sensitivity among VVS cases, with and without IBS. Blood samples will be collected for measuring plasma levels of proinflammatory cytokines. Our recruitment goal is a total of 85 study subjects -- 30 VVS concomitant with IBS and 55 VVS alone.

The objective of our study is to investigate differences in pain sensitivity, psychological distress, and circulating cytokine milieu in VVS cases with IBS relative to VVS cases without IBS. We

D. Zolnoun, continued

hypothesize that women with both VVS and IBS will exhibit elevated levels of pelvic muscle pain sensitivity, remote thermal pain sensitivity, psychological distress, and proinflammatory cytokines as compared to women with VVS alone.

Our study has three aims. Aim 1: To compare pelvic muscle pain sensitivity and remote thermal pain sensitivity between VVS cases, with and without IBS. We hypothesize that VVS cases with IBS will exhibit lower pelvic muscle pain threshold and tolerance as well as lower remote (volar surface of the forearm) thermal heat threshold and tolerance when compared to VVS cases without IBS. Aim 2: To compare levels of somatization, depression, anxiety, sexual/physical abuse, and trauma history between VVS cases with IBS and without IBS. We hypothesize that VVS cases with IBS will display increased levels of somatization, depression, and anxiety as well as increased reports of trauma and abuse when compared to VVS cases without IBS. Aim 3: To compare proinflammatory cytokine profiles between VVS cases with IBS and without IBS. We hypothesize that VVS cases with IBS will have increased levels of the circulating proinflammatory cytokines TNFα, IL-1β, and IL-6 when compared to VVS cases without IBS.

Based on our data, we believe that vestibular skin pain may originate from different pathophysiological processes. One process is in the setting of an underlying biologic environment that is already predisposed to dysfunction and thus more difficult to treat. And another process which is not predisposed. In other words, the observed skin pain or tenderness (which is the basis of our current clinical diagnosis) may, in fact, be a symptom – a converging point for a number of distinct pathophysiologic processes.

Our research has significant clinical implications. The challenge now is to phenotype the population in order to gain a better understanding of the underlying pathophysiologic process. Development of rational treatment modalities for this condition is contingent on a thorough understanding of the underlying pathophysiologic process. The diverse psychophysical profiles of women with VVS may reflect different pathophysiologic processes, converging on a shared presentation of localized skin sensitivity. Psychological dysfunction, pain sensitivity, and general muscle dysfunction may, in fact, be a risk factor for the development of VVS in subgroups of women with this disorder. In this setting, skin sensitivity may be a necessary but not sufficient factor for the development of VVS.

State of the Art: Role of the Small Bowel in Irritable Bowel Syndrome

Robin Spiller, MD
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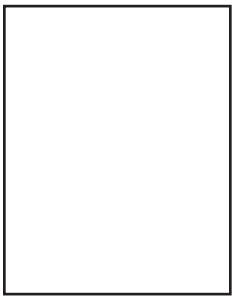

Robin Spiller

The small bowel is a key component of the digestive system through which there are substantial fluxes of secretions and absorption. Minor disturbances in the balance between absorption and secretion can cause IBS like symptoms, the best example being seen with lactose intolerance. The idea that the small bowel might be important in IBS is given credence from the fact that IBS symptoms often come on soon after eating. This was shown in a study of 61 IBS patients who recorded pain, eating and defecation in 30 minute epochs over a 6 week period. Although most of them claimed before the start of the study that their pain was relieved by defecation, from the actual records only 10% of pain episodes were relieved within 30 minutes of defecation while 50% of the episodes worsened within 90 minutes of eating (Ragnarsson & Bodemar, 1998).

The mechanism of this postprandial pain is unclear but could be either excessive motility, hypersensitivity to distension of the small bowel by intestinal contents, or postprandial release of algesic mediators such as mast cell tryptase or pancreatic enzymes. The manometric evidence of abnormalities of motility in IBS is somewhat inconclusive and although early studies in 16 IBS patients (Kellow & Phillips, 1987) linked "discrete clustered contractions" (DCC) to symptoms, larger studies found no difference in the incidence of DCC's (Schmidt et al., 1996; Small, Loudon, Hau, Noor, & Campbell, 1997). These larger studies did demonstrate slightly increased amplitude of contractions and frequency, although the significance of this is unclear. Distending the small bowel does induce pain at lower volumes in IBS patients (Accarino, Azpiroz, & Malagelada, 1995) and infusion of duodenal nutrients enhance visceral hypersensitivity (Barbera, Feinle, & Read, 1995; Simren, Simms, D'Souza, Abrahamsson, & Bjornsson, 2003). However motility and barostat sttudies are very arduous to the patients and those who take part may well not be representative. A non-invasive technique is obviously much preferable to allow study of a more representative sample of IBS patients.

The physiology of lactose malabsorption has been studied in the past in which it was demonstrated that 180 mls of water with 50 grams of lactose was diluted substantially during its passage down the gut and by the time it reached the terminal ileum it had expanded to 1800 mls in lactase deficient subjects (Christopher & Bayless, 1971). However, lactose exclusion has a disappointing effect in IBS patients, probably because most patients who are lactose intolerant recognise this and avoid milk and hence never consult an MD. Furthermore, IBS patients that are found to be lactose intolerant rarely take in enough lactose to induce symptoms because small amounts, less than 12 g a day, can be absorbed even in the absence of lactase.

However there may be other substances which are poorly absorbed which have recently been grouped under the term FODMAPs -- Fermentable Oligosaccardies (e.g. fructans inulin) Disaccharides (lactose) and Monosaccharides (fructose) and polyhydric alcohols (e.g. sorbitol, mannitol). The average daily intake of fructose in the USA ranges from 15 to 54 grams, and the average intake of fructans (polymers of fructose) is 1-20 grams. Much of this comes from high fructose corn starches whose consumption in

R. Spiller, continued

soft drinks has increased markedly in the last few decades. A recent double blind randomised control trial of fructose and fructans versus glucose showed that IBS patients who had responded to a low FODMAP diet were able to recognise the presence of these, which induced increasing amounts of pain, bloating and flatulence (Shepherd, Parker, Miur, & Gibson, 2008).

Wheat is another substance that patients commonly report aggravates symptoms, particularly bloating. We have recently developed a novel MR technique looking at small bowel water using an MRCP sequence (Hoad et al., 2007). Using this technique, we find that after a mixed liquid/solid rice pudding meal taken with 150 mls of orange juice we observe an initial fall in small bowel water followed by a rise which is significantly increased by the presence of 15 gm of bran. If we give meals with osmotically active non-absorbable material like mannitol, we get a dramatic rise in small bowel water associated with symptoms of bloating and subsequent diarrhoea. We have applied this technique to IBS patients with diarrhoea and find that IBS patients have significantly lower small bowel water content both fasting and post prandially and that this is associated with an accelerated small bowel transit and increased flow index. We also find a reduced fasting terminal ileal maximal diameter in IBS-D (Marciani et al., 2007). This increased tone could be mediated by a stress response or possibly mast cell activation, which has been shown in IBS-D duodenal biopsies (Foley, Coleman, Holmes, Bennett, & Spiller, 2008; Guilarte et al., 2007).

In summary, the small bowel is a neglected but important region in the IBS, and food related symptoms are likely to originate at least in part from the small bowel. Excessive fructose and excessive fructans in the diet are worth considering. Our MR studies show that IBS patients with diarrhoea have accelerated transit and reduced small bowel volumes, possibly reflecting increased tone which could be mediated by stress or an inflammatory response.

Genes which distinguish IBS from healthy controls: Preliminary findings

William Whitehead, PhD
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Previous studies have failed to identify reliable genetic markers for irritable bowel syndrome (IBS) because they have not adequately addressed the heterogeneity of this disorder. In a previous NIH grant, we identified four phenotypes of IBS based on principal components analysis and cluster analysis of multiple physiological and psychosocial variables. We were recently awarded a 5-year renewal of this grant with the aims of (1) identifying genetic single neucleotide polymorphisms (SNPs) that differentiate these four IBS subtypes, (2) identifying environmental exposures that separate the subtypes, and (3) developing and testing models of gene-environment and gene-gene interactions for each subtype. The purpose of this presentation is to describe a pilot study carried out to assess the feasibility of the new grant.

Background. Biological pathways believed to be involved in the etiology of IBS are: (1) serotonin, (2) inflammation, (3) pain sensitivity; (4) motility (transit), and (5) affective disorders and somatization. Most of the previous research on the genetics of IBS have focused on serotonin because (a) 95% of the serotonin in the body is found in the gut, (b) serotonin is known to play a role in gastrointestinal motility and sensation, and (c) drugs that were either 5-HT4 agonists or 5-HT3 antagonists were found to be at least moderately effective for the treatment of IBS. However, a meta-analysis of 8 studies (1034 IBS patients and 1377 controls) addressing the association between polymorphisms in the serotonin transporter gene, SCL6A4, and IBS found no significant association with IBS diagnosis overall or with IBS-D or IBS-C subtypes [Aliment Pharmacol Ther 2007;26:979-986] . A systematic review of studies of other candidate genes likewise finds no consistent associations of candidate genetic polymorphisms with IBS in general or with subtypes of IBS (IBS-Diarrhea and IBS-Constipation).

Methods. The aims of this pilot study were (1) to demonstrate the feasibility of using a Pain Panel of selected genes/SNPs (described below), and (2) to identify candidate SNPs for the larger, planned study by comparing (a) all IBS vs. healthy controls, (b) IBS-D vs. healthy controls, and (c) IBS-C vs. healthy controls. IBS-D and IBS-C are approximately equivalent to two of the four IBS phenotypes identified in our previous research. Identification of patients with IBS was based on questions in the PILL somatization questionnaire [Pennebaker JW. The psychology of physical symptoms. New York: Springer-Verlag, 1982]: IBS-D was defined as having abdominal pain at least monthly plus diarrhea at least monthly (n=31), and IBS-C was defined as having abdominal pain at least monthly plus constipation at least monthly (n=18). To be classified as healthy controls, subjects had to report neither constipation nor diarrhea as often as monthly and to have no chronic pain conditions. The 209 subjects in this pilot study were all Caucasian females.

The genotyping protocol utilized a gene chip referred to as the Pain Panel which covers genotypic diversity within gene loci related to pain sensitivity, inflammation, and mood and emotion. This chip includes 3,300 SNPs in 320 genes. This chip is a compromise between a candidate gene approach and a genome wide survey. For the data analysis, the PLINK computer program [Am J Hum Genet 2007;81:559-575] was used to assess association between diagnosis and SNP. Alpha=0.01 identified

W. Whitehead, continued

probable associations. SNPs significant for either IBS-D or IBS-C were grouped into 5 biological pathways. However, some genes affect multiple pathways.

Results. (1) Inflammatory mediators – 20 SNPs in 11 genes were identified that distinguish IBS-D and/or IBS-C from healthy controls. The genes with the highest odds ratios (ORs) were MAP2K1, NFKBIA, and CCL3. (2) Adrenoreceptors – Six SNPs in 3 genes distinguished IBS-D and/or IBS-C from healthy controls. These genes were ADRA1A, ADRA2C, and ADRB2. (3) Pain sensitivity – Eleven SNPs in 9 genes distinguished IBS-D and/or IBS-C from controls. The genes with the highest ORs included SCN11A, GABRG2, and COMT. (4) Motility and secretion – Ten SNPs in 7 genes distinguished IBS-D and/or IBS-C from healthy controls. The highest ORs were associated with 5-HT1B, CACNA2D1, and NOS3. (5) Affective disorders – Four SNPs in 3 genes distinguished IBS-D and/or IBS-C from healthy controls. These genes were CNSK1E, GRIA4, and ERBB4.

Summary. This pilot study identified several novel candidate genes, and these candidate genes cluster in plausible biological pathways. Multiple SNPs in some genes lend credibility to the findings, and some of the genes identified replicate previous studies by other investigators. However, these findings require replication in a larger study because the sample size was small and because IBS diagnosis was based on surrogate criteria rather than the Rome III diagnostic criteria and clinical evaluation.

The Role of intestinal bacteria in the pathophysiology of functional bowel disorders

Yehuda Ringel, MD
Assistant Professor of Medicine, Division of Gastroenterology & Hepatology, UNC at Chapel Hill

Yehuda Ringel

Development of "Hypervigilance for Visceral Pain" Questionnaire

William E. Whitehead, PhD and Olafur Palsson, PsyD
University of North Carolina at Chapel Hill

It is important to have a non-invasive measure of visceral pain sensitivity. Pain threshold is significantly correlated with clinical pain (r~0.3 to 0.4). Pain sensitivity defines a subgroup of IBS which may require a different treatment. However, invasive barostat testing is poorly tolerated and too expensive for large group studies.

When pain sensitivity is separated into neurosensory sensitivity and response bias by sensory decision analysis, only response bias separates IBS from controls. Response bias is correlated with pain threshold about r=0.68. Perceptual response bias is most likely related to the psychological concept of hypervigilance.

Olafur Palsson

The aims of our study are (1) to develop a new, non-invasive questionnaire for pain sensitivity, and (2) to validate our questionnaire against pain thresholds measured by barostat. We expect to recruit and test 84 Rome III positive IBS patients. They will receive a barostat test for pain sensitivity by ascending method of limits (AML) and sensory decision theory (SDT). We will administer 5 questionnaires and pool responses. We will then select items that are significantly related to response criterion B (an inverse indicator of psychological response bias), and use principal components analysis to reduce the number of items in the questionnaire. The source questionnaires are: (1) Pain Vigilance & Awareness Questionnaire (PVAQ), (2) Somatosensory Amplification Scale (SAS), (3) Visceral Sensitivity Index (VSI), (4) Recent Physical Symptoms Questionnaire (RPSQ), (5) Pennebaker Inventory of Limbic Languidness (PILL), (6) Tellegen Absorption Scale (TAS), and (7) Trauma Symptom Checklist Dissociation Subscale (Dissoc).

So far, our preliminary analysis of the data suggests that the source questionnaires show only modest correlations ($r<0.32$) with pain response criterion B, AML pain thresholds, and IBS symptom severity. In a preliminary factor analysis of pooled questions, seven factors were identified with a pooled variance of 49 percent. These factors were: (1) attention to body sensations (8.6% of variance), (2) fear or anticipation of symptoms (7.9%), (3) muscle and joint soreness (7.8%), (4) dissociative experiences (7.0%), (5) cardiovascular symptoms (6.7%), (6) attention to pain (6.3%), and (7) facial tics, rash or diarrhea (4.7%). The factor analysis is underpowered at this point.

Our scales seem able to measure hypervigilance to a limited degree and to separate it into at least two dimensions: (1) attention to bodily sensations and (2) anticipation and fear of symptom occurrence. At approximately the half-way point in data collection, however, the scales and items show only modest predictive power. We may have to consider a different non-invasive approach, such as measuring somatic sensory thresholds.

Impedance-pH Monitoring for Patients with Refractory GERD Symptoms

Ryan D. Madanick, MD
UNC School of Medicine, Center for Esophageal Diseases and Swallowing

Ryan Madanick

"PPI failure" is a common problem in GI practice today. The definition is unclear and the epidemiology undefined. The question is whether it is "Refractory GERD" (gastroesophageal reflux disease) or is it "NERD" (neuroerosive reflux disease)? An estimated 30 to 50% of patients remain symptomatic despite proton-pump inhibitor (PPI) therapy.

There are several possible reasons for "PPI failure": (1) persistent esophageal acid exposure (hypersecretory state, large hiatal hernia, nocturnal acid breakthrough, patient non-compliance with medications, medication pharmacokinetics/pharmacodynamics), (2) acid-sensitive esophagus, (3) non-acid reflux, and (4) not GERD (wrong diagnosis -- Eosinophilic esophagitis, functional heartburn).

Impedance is the inverse of the electrical conductivity of an organ and its contents. A small AC voltage (V) is applied to two electrodes on an impedance probe. This generates a small current (I) that is proportional to the conductivity of the organ and its contents. The ratio of voltage to current is the impedance (Z): Z=V/I.

Looking at impedance of the gastrointestinal (GI) tract, we find that impedance of air is very high -- impedance of the organ wall is 10 to 30 times higher than impedance of the transported contents. Low impedance of the bolus makes it easily distinguishable from its surroundings. High conductance suggests low impedance. When the organ is empty and relaxed, the impedance is high. When the organ contains a bolus and expands, the impedance is low.

When multiple impedance channels are placed onto a pH-testing catheter that is inserted into a patient's esophagus, both the chemical nature (acid, weak acid, or non-acid) and directional flow (antegrade or retrograde) of the intraesophageal boluses can be determined by performing a 24-hour pH-impedance study.

The current algorithm used for patients with symptoms suggestive of GERD starts with a trial of PPI. When symptoms persist despite PPI, many experts suggest testing the patient with a 24-hour ambulatory pH-impedance study while still taking PPI. This testing helps to determine whether patients have persistent acid reflux, persistent non-acid reflux, or no significant persistent reflux. In one multicenter study of 168 patients with refractory symptoms who underwent pH-impedance testing on acid suppressive therapy, symptoms were associated with persistent acid reflux in 16 patients (11%) and with persistent non-acid reflux in 53 patients (37%). Symptoms were not associated with significant persistent reflux in 75 patients (52%), and 24 patients (14%) had no symptoms during testing.

UNC has a tertiary care esophageal center (CEDAS) with statewide catchment area. Since 2006, approximately 300 studies have been conducted with pediatric and adult patients, on and off treatment. The majority of referrals are internal, although there are also some open access studies. All tracings are archived in the motility lab.

R. Madanick, continued

The purpose of our study is to (1) describe the pH-MII findings of patients who have undergone pH-impedance testing at UNC, (2) compare the clinical features and reflux parameters between subgroups of patients with refractory GERD symptoms, and (3) describe the clinical utility of pH-impedance testing for GERD.

Sources of data for our study include: (1) clinical data (demographics, symptoms, prior therapies, co-morbidities including psychiatric and other "somatic" disorders, medications, endoscopic findings); (2) pH-impedance data (esophageal, gastric acid exposure; reflux events detected by impedance -- upright, supine, total); proximal extent of reflux; symptom association by SI; medications used during test); and (3) post-testing clinical data (treatment -- alteration of antireflux therapy, central/peripheral-modulating agents, or surgery; response to therapy).

Our study has three aims. Aim 1: Determine the percent of patients with persistent acid reflux, non-acid reflux, non-GERD (hypersensitive, functional.) Aim 2: Compare reflux parameters between subgroups (esophageal acid exposure, gastric acid suppression in patients on medical treatment, number of reflux events, proximal extent of reflux, and symptom association) and compare clinical features between subgroups (presenting symptoms, co-morbidities, medications, prior treatment and evaluation, endoscopic features). Aim 3: Describe treatment decision following test and compare between subgroups (alteration of antireflux therapy, central/peripheral-modulating agents, surgery) and describe response to treatment within and between subgroups.

In summary, PPIs often do not control GERD symptoms. PH-impedance testing is a novel technology that can stratify patients into subgroups based on all types of reflux, and our center has had extensive experience with pH-impedance testing. This study will further define the reflux parameters and clinical features in pts with refractory GERD symptoms. We will also be able to further delineate how pH-impedance testing alters management in a tertiary care esophageal center.

Development of a More Sensitive Method to Measure Visceral Pain Sensitivity in IBS Patients

Chloé Hill, B.Sc.
Third Year Medical Student; Doris Duke Fellow

Chloé Hill

Visceral hypersensitivity in irritable bowel syndrome (IBS) patients is a leading hypothesis regarding the pathophysiology of this disorder, and is supported by bowel distention studies which demonstrate a lower threshold to pain among IBS patients (Drossman 2006; Mertz 1997). Two measures of pain perception in bowel distention studies are Ascending Method of Limits (AML) and Sensory Decision Theory (SDT).

The AML pain threshold is unreliable, since it is vulnerable to psychological influences. By contrast, SDT measures experimental pain by dividing pain threshold into two components – neurological and psychological. The neurological component, named the Discrimination Index, is the ability to differentiate between stimuli. It is affected by analgesia and is unaffected by bias. The psychological component, named the Report Criterion, is the tendency to report stimuli. It is affected by bias and is unaffected by analgesia.

A prior study (Dorn 2007) assessed pain threshold using the discrimination index and report criterion, and concluded that the increased sensitivity of IBS patients is more likely psychological than physiological. However, many subjects in the study were performing discrimination at chance levels. Therefore, the methods may not have been sensitive enough to detect a small difference. In our study, we will measure neurosensory sensitivity with a novel adjusting schedule protocol, in which the subject will be presented with a pair of stimuli at two different pressures. If the subject is able to successfully distinguish the higher pressure stimulus, then the stimuli will be converged and the subject re-tested with this new pair of pressures. The subject's performance will determine how the protocol advances.

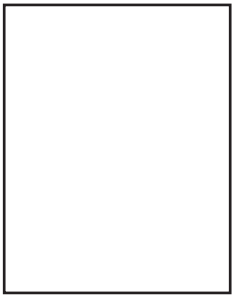
The rationale for our study is two-fold: (1) distinguishing the basis of hypersensitivity will advance both our conceptual understanding of the disease as well as our ability to treat; and (2) research has been inconclusive, probably because a more sensitive method of determining sensory discrimination is required. Our hypothesis: Using an adjusting schedule protocol, we will find a measurable difference in neurosensitivity between IBS patients and healthy controls.

Our study design includes both a distention experiment (measuring pain threshold by Ascending Method of Limits, and discrimination threshold by Sensory Decision Theory with Adjusting Schedule) and questionnaires (Brief Symptom Inventory-18 to measure psychological distress, and Visceral Sensitivity Index to measure stress over gastrointestinal symptoms). Part I entails developing the functional protocol and establishing reliability across trials in one session (5 healthy controls). Part II entails establishing reliability across trials in two sessions, spaced one week apart (10 healthy controls). Part III will investigate reliability across pressure ranges (10 healthy controls). Part IV will compare visceral pain sensitivities between 30 IBS patients and 30 healthy controls.

Data analysis for Parts I through III will test the protocol for reliability of pain threshold and discrimination threshold using Pearson coefficient and Bland-Altman plot. Data analysis for Part IV will (1) compare pain threshold and discrimination threshold using Mann-Whitney U-test, and (2) assess correlation between variables using Spearman correlations.

Endogenous Appetite Hormones and Gastric Emptying in Postprandial Distress Syndrome: Project Update

Kimberly A. Brownley, PhD
UNC Department of Psychiatry



Kimberly Brownley

According to the Rome III Diagnostic Questionnaire for Adult FGIDS, Postprandial Distress Syndrome (PDS) is defined as: (1) bothersome postprandial fullness, occurring after ordinary sized meals, at least several times per week, and (2) early satiation that prevents finishing a regular meal, at least several times per week. These criteria must have been met for last 3 months, with symptom onset at least 6 months prior. The Rome questionnaire includes "alarm questions" regarding recent bowel changes, family history, anemia, and weight loss.

Ghrelin is an appetite stimulant, active at meal initiation. PYY is an appetite suppressant, active at meal cessation. Ghrelin infusion/ administration: (1) reduces gastric emptying time and postprandial pain/discomfort (Tack et al , 2005); (2) induces premature gastric phase III of the migrating motor complex in healthy volunteers (Tack et al., 2005); and (3) increases gastric fundus contractility (Levin et al., 2005). Endogenous ghrelin augments spontaneous phase III-like contractions (Ariga et al., 2007) and mediates chronic stress-induced acceleration of gastric emptying (Ochi et al., 2008).

Research questions: (1) Are fasting ghrelin and PYY associated with gastric emptying and early satiety in PDS? (2) Do individuals with PDS differ from healthy individuals in their endogenous postprandial ghrelin and PYY responses? (3) Do postprandial ghrelin and PYY responses relate to symptom severity, early satiety, and gastric emptying in PDS?

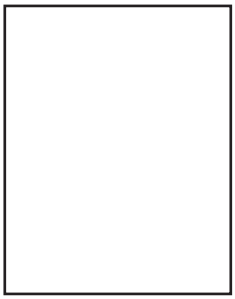
Eight non-obese PDS (3 male, 5 female; 4 White, 4 Black; 20-47 years old; BMI 19-26.5) and 6 matched controls (3 male, 3 female; 4 White, 2 Black; 20-45 years old; BMI 21.9-26.6) have enrolled and completed the study thus far. The two test conditions were: a low fat (25%) 500 kcal test meal, and a high fat (55%) 500 kcal test meal. During and 4 hours after a test meal, the following tests were conducted: (1) 13C-Spirulina plantensis breath test to assess percent 13CO2 dose (PCD) excreted, a marker of gastric emptying time; (2) plasma ghrelin and PYY levels at 15-minute intervals; and (3) dyspepsia and appetite-related symptoms.

For the primary goal -- obtain effect size and variance estimates for group (patient vs. control) differences – planned data analyses include: (1) mixed model RMANOVAs -- gastric emptying (i.e., kPCD), intensity of dyspepsia symptoms and appetite, and fasting and postprandial ghrelin and PYY, and (2) correlation coefficients with 95% CI -- ghrelin and PYY with kPCD, and ghrelin and PYY with symptoms.

[Acknowledgements: UNC GCRC/CTRC; ABDiagnostics; UNC Center for Functional GI & Motility Disorders. Collaborators: W.E. Whitehead, D. Chitkara, Y. Ringel]

State of the Art: The Mystery of Cyclic Vomiting Syndrome

Kevin Olden, MD
University of Arkansas for Medical Sciences



Kevin Olden

Cyclic Vomiting Syndrome (CVS) was first described by the English physician Samuel Gee in 1882. Although it was initially thought to be a pediatric disorder, CVS has increasingly been seen in adults over the last few years. The Rome III criteria for Adult CVS are (must include all of the following): (1) stereotypical episodes of vomiting regarding onset (acute) and duration (less than one week); (2) three or more discrete episodes in the prior year; and (3) absence of nausea and vomiting between episodes. Supportive criterion: history or family history of migraine headaches.

One problem associated with this disorder is that, because it is relatively rare, it is somewhat difficult to study. Indeed, the Rome III criteria for CVS are very generic and, more importantly, have not been validated in a variety of settings. What is clear is that CVS is divided into four distinct phases. These are characterized by a "well phase" where the person is completely and totally asymptomatic. This is followed, usually in a fairly predictable way, by a "pre-emetic phase" characterized by pallor, diaphoresis and intense nausea. This, in turn, is followed an "emetic phase" of intense (up to 20-30 vomiting episodes per day) vomiting which can last anywhere from 1-4 days. Finally, there is "recovery phase" where the patient's vomiting begins to cease, nausea abates, and they are able to take in liquids orally. The recovery phase is characterized by intense hunger and increased alertness, in contrast to the somewhat stuporous state seen during the acute vomiting phase.

The exact mechanism of CVS is unknown. A number of interesting findings have been identified and have been associated with the disorder. These include the possibility of abdominal epilepsy, the possibility that the disorder may be a manifestation or meta-phenomenon of abdominal migraine, and the possibility that it may be associated with mitochondrial dysfunction. In addition, symptoms consistent with panic attacks, the frequent use of hot showers or baths to abate symptoms, and frequent marijuana use have been associated with this condition.

Because of its stereotypic nature, the possibility of abdominal epilepsy, and especially childhood epilepsy, has been a question for sometime. One study (Fleisher 2005) studied 900 epilepsy patients, 24 of which had vomiting during seizure activity. In this study, the investigators noted that all vomiters with epilepsy had normal brain imaging, none had migraines, and both the vomiting and seizures resolved in all patients. The study did note that childhood vomiting in the presence of epilepsy was associated with occipital spikes ($p<0.001$) and not associated with any other electroencephalographic abnormalities. Investigators in this study concluded that CVS did not represent an epileptiform disorder.

The association of migraine headaches, particularly with CVS in childhood, raises the possibility of CVS being a migraine equivalent. This is particularly interesting given that the diagnostic criteria for abdominal migraine, as outlined by the International Headache Society, are quite similar to those for CVS: (1) pain is severe enough to interfere with normal daily activity; (2) pain is dull or colicky

in nature; (3) pain is periumbilical or poorly localized; (4) pain is associated with any two of the following – (a) anorexia, (b) nausea, (c) vomiting, and/or (d) pallor; (5) each attack lasts for at least one hour: and (6) complete resolution of symptoms between attacks.

The fact that drugs commonly used for migraine prophylaxes, such as third generation anticonvulsants and tricyclic antidepressants, also have efficacy in CVS provides further indirect evidence that CVS might represent a migraine equivalent. However, the fact that the CVS/migraine association is mainly true in childhood and less so in adults, and the fact that most CVS patients have no headache symptoms, makes arriving at this conclusion somewhat challenging.

Cannabis (marijuana) use is frequently seen in adults with CVS. They describe relief of symptoms consistent with cannibis' known antiemetic properties. However, what is frequently seen with CVS is patients who are using relatively large amounts of cannabis, in an attempt to treat their severe vomiting symptoms. Unknown to most patients and most clinicians is the fact that, although cannabis is antiemetic at low doses, higher doses actually have an emetic property. This suggests that the cannaboid receptors are involved in some way in CVS, however, their precise role remains to be determined. This is further supported by the fact that low-dose THC decreases GABA activity and is consistent with the finding that intervenous benzodiazepine treatment is one of the most efficacious ways to induce remission during an acute CVS episode. The fact that cannabis receptors are preferentially found in the hippocampus, amygdala, the prefrontal cortex, and the anterior cingulate cortex in the brain offers an interesting opportunity to investigate those anatomic areas of the brain and their relationship to a possible etiology for CVS.

Panic-like symptoms are commonly seen in CVS patients. In our experience, approximately 60% of CVS patients have panic-like symptoms. More importantly, treating the panic with antidepressant and benzodiazepine therapy can relieve CVS symptoms (Olden 2008). Interestingly both CVS and panic disorder have been noted to activate areas of the brain mentioned immediately above (Fillenz 1990). It is also known that abnormalities of the cholecystokinin (CCKB) are panicogenic in humans. The fact that another form of CCKA can decrease gastric emptying and increase gastric sensitivity makes the panic-CVS connection more intriguing. Clearly, there is still work that needs to be done in this area.

Mitochondrial dysfunction has been noted in pediatric CVS patients by Boles and others (Abell 2008). The fact that L-Carnitine, which transports long chain fatty acids (LCFA) into mitochondria for oxidation, and that low levels of L-Carnitine have been found in patients with both migraine and childhood CVS raises the possibility of a connection between mitochondrial dysfunction and CVS (Chepyala 2007). In mitochondrials dysfunction, an inability to transport LCFAs leads to elevated urinary organic acids and migraine headaches as well as autonomic instability. The fact that CVS responds both to IV dextrose and to L-Carnitine provides indirect evidence that this mechanism may be operative in CVS patients.

In summary, a number of intriguing mechanistic possibilities exist to help explain the perplexing and highly disabling disorder known as Cyclic Vomiting Syndrome. Further mechanistic work is desperately needed to help improve treatment and to provide an underpinning to validate the treatments which we are currently using. CVS patients suffer greatly from this disorder.

Suicide Ideation and Attempt in Adolescents with Chronic Pain

Miranda van Tilburg, PhD

Miranda van Tilburg

Chronic abdominal pain can lead to such profound personal suffering that some patients may contemplate suicide. Previous studies have shown that non-malignant chronic pain is associated with 2-3 fold increases in suicide among adults, and that suicide rates may be the highest for chronic abdominal pain compared to pain in other locations. Even though suicide is the third leading cause of death in adolescents and chronic abdominal pain is common in this group, chronic pain is usually not considered a risk factor for adolescent suicide. The current study investigated the link between pain and suicidality 1 and 5 years later in a population study of adolescents in the US and whether this association is explained by depression and maltreatment, which are major co-morbidities in pain and important risk factors for suicide.

Secondary data analyses were conducted of the AddHealth database, a representative sample of US adolescents. Data is collected in three waves: Wave I (1994-95), Wave II (1996), and Wave III (2001-02). Pain and depression data is used from Wave I and II, suicide ideation/attempt from Wave II and III, and maltreatment from Wave III. For more detailed study information, see http://www.cpc.unc.edu/projects/addhealth/design.

Subjects were 10,695 adolescents in Wave I (53% girls, 53% Caucasian, 19% African American, 16% Hispanic). Age ranged from 11 to 21 in Wave I, 11 to 23 in Wave II, and 18 to 27 in Wave III. Prevalence of pain and suicide did not differ between waves. Weekly chronic abdominal pain was reported by 17% of the study subjects, headache by 29%, muscle/joint ache by 27%, suicidal ideation by 11%, and suicide attempt by 4% of the sample in Wave II. Maltreatment during any time in their lives was reported by more than half of the sample at Wave III.

Logistic regression analyses were performed predicting suicide ideation or suicide attempt by pain, depression, and maltreatment. All chronic pain (independent of location) significantly predicted suicide ideation and attempt 1 year later (odds ratios range from 1.4 to 1.9). After controlling for depression and maltreatment, these associations remained significant. Only abdominal pain significantly predicted suicide ideation (OR=1.5) and attempt (OR=1.8) 5 years later. Entering maltreatment into the regression did not change this relationship, but entering depression made the association between chronic abdominal pain and suicide insignificant. The gender-by-pain interaction was significant only for Wave III suicide attempt data (OR=0.27 for girls vs. boys, 95% CI 0.1-0.6). Significant associations between suicide attempt and chronic abdominal pain were observed in boys (OR=3.1; 95% CI 1.4-7.1) after controlling for depression, but not in girls (OR=.97; 95% CI .6-1.7).

We find: (1) chronic pain is associated with increased suicidality in adolescents, (2) abdominal pain in adolescence predicts suicidality in young adulthood, (3) adolescent boys who report chronic stomach aches are at increased risk for suicide attempt in early adulthood, (4) child maltreatment and depression are independent risk factors for suicidality within 1 year, and (5) depression mediates long-term risk for suicidality. These data show the need for increased screening and treatment for suicidality and mood disorders among adolescent pain patients.

CONQUEST Study: Impact of Constipation on Quality of Life and Healthcare Costs

Olafur S. Palsson, PsyD
UNC-Chapel Hill Department of Medicine

Chronic constipation (CC) is defined in the Rome II and III diagnostic criteria by the presence of at least 2 of the following 6 symptoms with a certain frequency in the past 3 months: infrequent bowel movements, straining, obstructed defecation, hard stools, a sensation of incomplete evacuation, and manual facilitation of defecation. CC is a common health problem, affecting an estimated 15-17% of adults (Pare et al 2001; Talley et al 1991) when measured using Rome criteria. The majority of individuals meeting CC criteria in the community do not seek medical care; only 23.4% of people with CC in Pare et al's community study in Canada had seen doctors for their CC symptoms. Little information is available on many aspects of constipation: e.g., how common it is in general clinical populations, how much it affects costs of care or quality of life, how it is generally treated and how effectively, or how it is associated with other disorders. We addressed these and other issues in a large-scale prospective survey study of HMO patients in Seattle (Group Health Cooperative).

The research questions were: (1) prevalence of CC consulters and non-consulters, (2) factors associated with seeking medical care, (3) impact of CC on quality of life and health care costs, (4) what treatments are used for CC, and their associated satisfaction, effectiveness and side effects, (5) overlap and interchange between CC and constipation-predominant irritable bowel syndrome (IBS-C), (6) comorbid conditions associated with CC, and (7) risk factors associated with CC and influencing CC course.

The questionnaires used in our study included a Constipation History Questionnaire, Demographics, Rome III modular questionnaire for CC and IBS, Constipation-Related Quality of Life Impairment Scale (PAC-QOL); SF-12 Quality of Life Scale, Work Productivity and Impairment Scale (WPAI), Brief Symptom Inventory 18 (BSI-18), Recent Physical Symptoms Inventory (RPSQ); Visceral Sensitivity Index (VSI); fluid and fiber intake questionnaire; and treatment satisfaction questions. Subjects were sent a questionnaire set three times: at baseline and at 6-month and 12-month follow-up (FU).

Study participants were individuals age 18 years or older who were identified through the electronic medical records of the HMO and invited to participate: 1100 HMO subscribers who had at least one clinic visit associated with a constipation diagnosis between September and December 2005 (ICD-9CM codes 564.0X), and 1700 control subjects matched on age and gender to the constipation group with at least one clinic visit during the same period but no constipation visit in the past five years. We achieved a 66.2% response rate for our baseline questionnaires (n=1701), of which 86.8% completed the 6-month FU questionnaires (n=851) and 83% completed the 12-month FU questionnaires (n=813). The study groups consisted of 520 CC consulters and 416 CC non-consulters (individuals who met CC criteria but had no constipation diagnosis on record); we also had 524 non-GI controls. The non-GI controls had a significantly lower proportion of female subjects. The CC non-consulters had a significantly lower proportion of college graduates and annual incomes were more likely to be below $40,000. There were no significant differences among the three groups with regard to age, race or marital status.

Only 1.3% of patient visits with HMO physicians resulted in a medical diagnosis of constipation (ICD9 code 564.0X). Most of these patients (77.5%) met Rome III criteria for chronic constipation.

O. Palsson, continued

However, nearly half of the control sample (individuals with no constipation diagnosis) met Rome III criteria for a constipation diagnosis – either CC or IBS-C. Among the 1031 subjects with no constipation diagnosis from an HMO physician in the last 5 years, 40.5% met Rome III criteria for CC and 8.4% met the criteria for IBS-C (51.1% did not meet criteria for constipation).

Using BSI-18 scale scores, CC consulters and CC non-consulters in our sample scored significantly higher than non-GI control for depression, anxiety, somatization, and general psychological distress. On the Constipation Severity Scale (CSS -- a composite scale using the Rome III ordinal scale ratings for constipation symptoms), CC consulters scored significantly higher than constipation non-consulters, and both groups scored significantly higher than non-GI controls. CC consulters had significantly higher frequency of constipation, abdominal pain, and bloating symptoms in the past 3 months than CC non-consulters. CC non-consulters scored significantly higher than CC consulters on both the SF-12 physical and mental quality of life scores, and the non-GI controls scored significantly higher than both CC groups. On the PAC-QOL overall score, reflecting constipation-related impairment in quality of life, CC non-consulters scored significantly lower than CC consulters. CC consulters scored significantly higher than CC non-consulters in the Visceral Sensitivity Index, and both groups scored significantly higher than non-GI controls.

Significantly more CC consulters than CC non-consulters met Rome III criteria for IBS and for IBS-C. In a binary logistic regression analysis of predictors of consulting, only the PAC-QOL scores (psychosocial, worries, dissatisfaction) were significant predictors (Nagelkerke R2=0.20). Visceral Sensitivity Index scores and constipation severity score each accounted for nearly half of the total explained variance in QOL impairment (PAC-QOL), with a small additional contribution from female gender; the total QOL variance explained was 63.7%.

Looking at total annual health care costs over the past 5 years at the HMO, statistically significant differences were found between all three groups. Total annual healthcare costs averaged $7,510 for CC consulters, $5,241 for CC non-consulters, and $4,644 for non-GI controls. GI-related costs were $506 for CC consulters, $229 for CC non-consulters, and $182 for non-GI controls. Non-GI costs averaged $5,479 for CC consulters, $3,445 for CC on-consulters, and $2,873 for non-GI controls. CC consulters averaged 10.3 healthcare visits a year, 8.2 visits for CC non-consulters, and 7.1 for non-GI controls. We found no significant correlation between constipation severity and healthcare costs or utilization.

Annual out-of-pocket expenses for constipation-related remedies were $165 for the CC group and $225 for the IBS-C group. At baseline, the most commonly used treatments for CC were oral laxatives (42.1%), fiber supplements (38.9%), exercise (24.5%), enemas/suppositories (15.1%), and diet (14.6%). At 6-months follow-up, continued use was highest for fiber supplements (74.4%), oral laxatives (71.4%), exercise (58.1%), herbal medicines (51.9%), diet (49%), and enemas/suppositories (48%). Both treatment effectiveness and side effects were highest in this order (descending): oral laxatives, enemas, suppositories, fiber supplements, and alternative therapies. Satisfaction with the treatment was in the following order (descending): oral laxatives, enemas, alternative therapies, fiber supplements, and suppositories.

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Conclusions from this project so far include the following: (1) Four out of every 10 adult HMO patients have diagnosable chronic constipation that does not get medical attention; (2) Patients are more likely to consult physicians about constipation if it is severe and associated with gut-focused anxiety, but especially if impairment of their quality of life from CC is considerable. General psychological symptoms do not appear to influence their consulting decision; (3) Laxatives and fiber are the most commonly and persistently used treatments for chronic constipation in this HMO, and laxatives are deemed the most effective treatment by users. (4) CC affects both activities of daily living and psychosocial aspects of quality of life adversely, and is associated with elevated symptoms of anxiety and depression; (5) CC increases health care costs, especially for consulters, but almost all of the extra cost is associated with non-GI costs. CC consulters have $2600 extra health care costs per year; (6) Visceral anxiety and constipation severity are equal contributors to the QOL impairment of CC patients, and together explain 2/3 of the variance in the QOL impact.

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What is an "Episode" of IBS? The Ecological Momentary Assessment Perspective

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Stephan Weinland

Several fundamental aspects of Irritable Bowel Syndrome (IBS) still remain to be characterized. What is it that makes up an 'episode' of IBS? Does pain change across an episode? What about bowel habit and stool form, and how do they change? Visceral hypersensitivity is a hypothesized contributor to episodes, but how can we measure it? The Rome Foundation criteria have gone a long way towards helping clinicians understand the diagnosis of IBS; however, patient-centered evaluation of qualitative and quantitative experiences are necessary in order to get a true picture to answer the question "What is IBS?"

Ecological Momentary Assessment (EMA) is a research procedure that utilizes brief but frequent assessments of a few variables at a time to put together a more complete picture of how symptoms change over a very brief period of time. It utilizes pocket PC (personal computer) technology to assess symptoms at randomly alarmed times as well as event driven times (i.e., pre-post bowel movement, bedtime, wake up). By utilizing this rapid, brief assessment methodology, models of symptom experience can be created and analyzed to quantify symptom experience.

Using this methodology, we have recently completed data collection on 60 subjects with physician diagnosed IBS and 20 healthy controls. Twenty participants with IBS-Diarrhea (IBS-D), IBS-Constipation (IBS-C) or IBS-Mixed (IBS-M) engaged in electronic diary data collection at three random and four event driven times over the course of a two week assessment period.

Preliminary results are scheduled to be presented at DDW in 2009 and include some remarkable findings relating to the nature and clinical characteristics of IBS. Of note, 93% of subjects who participated in the study reported experiencing discrete episodes of symptom exacerbation during the 2-week rating period. 36.5% of the 4311 ratings colleted were listed by participants as being indicative of their symptom experience during an 'episode' of IBS. Episodes of IBS-D reported the shortest 'episodes', with mean episode length of approximately 9 hours, while patients with IBS-C had episodes lasting approximately 16 hours, and IBS-M nearly 18 hours. Episodes of IBS occur in patients approximately 6 to 10 times in a 2-week period. Additionally, pain and bloating symptoms were much improved with the resolution of 'episodes' of IBS.

A more detailed analysis of these preliminary results using our complete database is underway. Going forward, we intend to use this information to give patients and the pharmaceuticals industry a better idea of how to measure change in symptom experience. Ideally, pharmaceutical and other treatment strategies should result in lower levels of pain, shorter and more infrequent 'episodes' of IBS, and improvement in quality of life for those living with this condition.

International Survey of Patients with IBS: Symptom Features and their Severity, Health Status, Treatments and Risk Taking to Achieve Clinical Benefit

Douglas A. Drossman, MD

Douglas Drossman

Clinicians make treatment decisions for functional gastrointestinal disorders (FGIDs) based on the nature and severity of the symptoms, health-related quality of life (HRQOL), and the risks versus benefits of a treatment. Understanding symptom severity and the degree of risk-taking with new drugs from the patient's perspective is needed. The Food and Drug Administration (FDA) has focused on two issues related to IBS and FGIDs. First, what is an acceptable end point for a new drug (i.e., symptom related or global measure of change)? Second, drugs for IBS should have low risk-benefit ratios; the FDA has removed drugs from the market with uncertain risk. One question is -- are these views shared by patients? Furthermore, we know that more and more patients are using the Internet to understand their symptoms and treatment options, yet we know relatively little about the interests and needs of this population.

To address these issues, UNC collaborated with the International Foundation on Functional Gastrointestinal Disorders (IFFGD) to conduct an Internet-based survey to investigate: (1) what are the demographic, clinical and health status profiles of patients with IBS who are accessing the internet; (2) how severe is their IBS and what factors contribute to severity; (3) what types of medications are being taken; (4) how much risk would patients take to achieve clinical improvement with a new medication (5) what are patient views when the FDA withdraws a medication because of possible risk; and (6) how satisfied are patients with their care.

To be eligible to participate in this study, patients had to be over 18 years of age and have accessed two popular IBS informational websites: International Foundation for Functional GI Disorders (www.iffgd.org) or UNC Center for Functional GI and Motility Disorders (www.med.unc.edu/ibs). They must also have had a diagnosis of irritable bowel syndrome (IBS) by a physician, and this diagnosis was later confirmed by Rome III criteria.

Study participants were asked to complete several questionnaires: (1) 2002 "IBS in Real World" Survey; (2) standard research questionnaires developed at UNC Center (Functional Bowel Disorder Severity Index/FBDSI, Quality of Life/IBS-QOL, and standard demographic and health status instruments); (3) other standardized measures (Hospital Anxiety and Depression/HADS, BEST (Spiegel), IBS Symptom Severity Score/IBS-SSS (Whorwell); (4) question sets developed specifically for this survey (self-perception of IBS severity; checklist of factors influencing severity; modified time-trade off to reduce years of life for clinical benefit; risk taken to achieve perfect health with possible death, serious or mild AEs); and (5) other questions relating to medication use, satisfaction with care, etc.

We had 1,966 respondents (78% of those who started the on-line survey). Their average age is 40.4 (+14.4), and they have an average of 15.2 years of education (+2.7). Most are females (82.8%), Caucasian (91.1%), and married/co-habiting (59.3%). Respondents are from the USA (71.7%), Canada (6.7%), and other countries (21.6%). Rome criteria for IBS were fulfilled by 90.9%. The IBS subtypes are: IBS-

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D (diarrhea-predominant) 29.3%, IBS-C (constipation-predominant) 9.7%, and IBS-M/U (mixed or undetermined) 61%. The average number of years with a gastrointestinal disorder before physician diagnosis is 6.6 (+9.7 years).

Moderate-severe symptoms were self-reported by 43.3% (FBDSI). The average abdominal pain today (0-100 VAS) was 35.7 (+27.5). Their symptoms caused them to restrict usual activities an average of 73 days (20% of the year) and to be out of work due to health 12.8% of the year. Subjects had seen an MD 2.7 times (+4.5) in the past 6 months. The total number of health care providers seen for IBS in their lifetime was 4.6 (+6.3). The number of times hospitalized in the past 2 years was 3.0 (+1.9). The variety of health care providers seen in the past 12 months included primary care physicians 89.3%, gastroenterologists 54.9%, gynecologists 34.2%, or PA or FNP 27.4%.

When asked how bad their bowel symptoms were (BEST questionnaire), 13.6% responded very severe (i.e., markedly affecting lifestyle), 41.4% severe (affecting lifestyle), 39% moderate (cannot be ignored), and 6% symptoms mild (can be ignored) or none. Self-reported symptom severity was described as mild/none by 22.8%, moderate by 41.8%, and severe by 35.5% of the respondents. Pain behavior (using the FBDSI) was 31.4% mild/none, 48.3% moderate, and 20.4% severe. IBS symptom severity (IBS-SSS) was mild/none for 11.1%, moderate for 33.6%, and severe for 55.4%.

The IBS-QOL total score showed considerable impairment at 51.1 (+21.9). The domains most affected included: food/dietary restrictions/avoidance 32 (+27.4), emotional dysphoria 45.6 (+28.4), and interference with activities 48.8 (+26). On the HADS scale (>11 clinically significant), 47% were found to be clinically anxious (anxiety 10.1+4.4) and 13.7% were clinically depressed (depression: 6.2+4.0). Using the BEST Anxiety scale, respondents were tense or wound up most of time 17.4%, a lot of time 34.3%, occasionally 41.9%, not at all 6.5%. Using the BEST Depression scale, respondents reported "still enjoying things" hardly at all 5.7%, only a little 8.6%, not quite as much 59.5%, or definitely as much 25.7%.

We though it important to understand what factors patients indicated as contributing to their perception of severity. These included (in decreasing order of important): pain, bowel difficulties, bloating, and limitations imposed on eating/diet reported at least 2/3 of the time, limitations on social activity, cannot leave home, limits on school/work, limits on thinking at least ½ the time, and trouble sleeping, nausea, limits on home activities, poor quality of life, and incontinence over ¼ of the time. Also, there was clustering in the responses; 35.1% of the respondents reported problems with the top four factors, and 68.2% endorsed 3 out of 4 of the top four problems.

Respondents used a variety of medications to treat their symptoms. Five of the top 6 took medications primarily for relief of pain including non-narcotic pain killers and antidepressants (both 31%), acid blockers (28%), antispasmodics (19%) and even narcotics (18%). Antidiarrheals were used in 24% and anti-anxiety medication in 13%. Complementary and alternative medications (CAM) are used by 36.9% of the respondents and include (in this order): dietary supplements, probiotics, meditation, massage therapy, relaxation therapy, homeopathy, acupuncture, Chinese herbal therapy, biofeedback, and/or colonic irrigation. Their most reliable resources for information were: physician 72.7%, pharmacist

D. Drossman, continued

49.3%, Internet 37.5%, professional organization 34.9%, other patient 31.8%, the Food and Drug Administration (FDA) 30.7%, news media 18.8%, and DTC ads 10.4%.

We also looked at risk-taking issues. Respondents would give up an average of 15.1 years (25% of remaining life) to be in perfect health. If subjects were able to obtain a medication that would put them in perfect health 14% would accept a 1/1000 chance of death, 10% would accept a 1/1000 chance of severe or permanently disabling side effects and 56% would accept a 1/1000 chance of milder side effects

Questions were also asked with regard to risk taking as related to FDA decisions relating to withdrawal of a medication because of potential side effects: "Let's assume you are taking a medication for over a year because it is helpful for your symptoms. The FDA then decides that the medication may be harmful, for example to cause heart disease. There is some controversy as to whether this is truly the case. The FDA removes the drug from the market until the question of harm is resolved". In response to this, over 80% felt they would be affected at least a moderate amount, 68% would be at least moderately worried about taking that medication, and 57% believe moderately that harm might already have been done. In that regard, 45% would prefer that the medication remain of the market until safety was established but 21% would continue to take the medication. Finally, over 85% preferred that restrictions on medication use involve more than a "black box" warning; the physician needs to be involved in the safety process either by signing a form or by prescribing monthly.

Satisfaction with all types of treatments is very low; less than 10% described themselves as very satisfied or extremely satisfied. Satisfaction with medications is a little higher, but no more than 25% described themselves as very satisfied or extremely satisfied. A similar proportion expressed high levels of satisfaction with their medical care from a physician over the past year.

From these findings, we conclude: (1) there appears to be greater health care impairment (within the internet population) than anticipated; (2) these patients are willing to take considerable risks to achieve relief; and (3) there is an unmet need to find effective treatments for IBS (no specific treatments for IBS readily available). The FDA might consider: (1) using patient-rated endpoints that incorporate the main multiple components of IBS as perceived by patients; (2) raising risk-benefit ratios when evaluating new products; and (3) keeping a drug on market with restrictions when potential risk is identified until risk is established. In addition, we may not be fully meeting the needs of our patients in terms of their satisfaction with their care.

Association of Psychosocial Factors and Disease Markers with Health Status in Celiac Disease

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Spencer Dorn

Celiac disease, a chronic inflammatory disease of the small intestines caused by gluten sensitivity, affects approximately 1% of the U.S. population. In these individuals, health status (i.e., health related quality of life and health care utilization) is highly variable. This variability is typically assumed to relate directly to underlying disease activity (i.e., histopathologic severity) and clinical presentation (i.e., classical or silent disease). An estimated 38% of all diseases are "silent" and present as atypical symptoms (dermatological 5%, neurological 7%) or are asymptomatic (discovered through workup for anemia or osteopenia 15%, detection at endoscopy 8%, screening given family history 10%).

The relationship between underlying disease activity and clinical presentation has not been proven for celiac disease, and evidence from other digestive diseases suggests that it might be weaker than anticipated. For example, in inflammatory bowel disease (IBD), histopathologic severity and health care utilization are only weakly associated. In irritable bowel syndrome (IBS), physiologic abnormalities are poorly related to symptoms and quality of life. Instead, in both IBD and IBS, health status is strongly predicted by psychosocial factors, such as depression and abuse. As such, these patients benefit from a biopsychosocial treatment approach. However, whether patients with celiac disease will benefit from a similar approach first requires that the key determinants of health status be identified.

Therefore, the aim of our study was to determine a relationship between psychosocial factors and disease measures in predicting HRQOL and health care utilization. All adults who presented with newly diagnosed, biopsy proven celiac disease were recruited for the study. Those who had a history of other structural gastrointestinal (GI) GI disease as well as asymptomatic patients with a family history referred for screening were excluded. The assessment included: (1) EGD with biopsy, (2) standardized health care provider assessment, (3) laboratory testing, (4) psychosocial questionnaires, and (5) Daily Diary Cards for 2 weeks.

To date, 84 subjects have participated in our study (63% female, 93% Caucasian, 54% married, mean number of years of education 16.8). Three-quarters of all subjects reported GI symptoms, with a mean duration of 126 months. Mean weight loss was 6 pounds, and 76% had a classical presentation of celiac disease. Over half (55%) also had concurrent IBS. Twenty percent reported sexual or physical abuse, and 8% had minor or major depression (PHQ). The mean score for psychological distress (BSI GSI) was 52.1, and for catastrophizing (CSQ) it was 5.3. Mean pain level (VAS) was 17.9, the mean quality of life score (IBS-QOL) was 81.4, and the mean daily function score (SIP) was 4.2. Forty-one percent have diarrhea, and 20% rated their health as fair or poor.

Multivariate analyses revealed the following: (1) greater psychological distress predicts increased pain; (2) increased psychological distress and decreased control over symptoms predict diarrhea; (3) milder

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Marsh, more negative life events, increased psychological distress, and less control over symptoms predict poorer daily functioning; (4) atypical symptoms, lower depression, and lower catastrophizing predict high health-related quality of life; (5) higher education, shorter symptoms, lower psychological stress, and increased ability to decrease symptoms predict higher perceived health; and (6) more negative life events, normal TTG, and atypical presentation predict more GI doctor visits.

Importantly, gastrointestinal symptoms did not correlate with a single biological disease marker. This suggests that in the era of screening, patients with celiac disease who continue to have diarrhea and/or pain are more likely suffering from an overlapping functional gastrointestinal disorder, such as "celiac-IBS." Additionally, disease based measures were not predictive of health status (lower Marsh score = higher SIP, normal TTG = more physician visits). Conversely, psychosocial factors strongly predicted health status. Coping appeared to be particularly important; lower control over symptoms and higher catastrophizing predicted greater QOL impairment and lower self-reported health. These findings suggest that patients with celiac disease would be best served using a biopsychosocial approach.

For the current project, recruitment is ongoing (goal ~ 120 patients). Concurrent projects are (1) the development of a celiac QOL scale, (2) analysis of correlation with cytokines, and (3) identification of predictors of response to a gluten free diet. Future projects may examine psychological therapy and/or centrally acting agents for the treatment of patients with celiac disease and persistent gastrointestinal symptoms.

Partner Burden in Irritable Bowel Syndrome

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Reuben Wong

There is the saying that disease afflicts one person but affects many. Strong anecdotal evidence suggests that the psychological, social, and physical effects of illness in a patient can have profound effects on the family. There is also increasing evidence from studies on burden of illness for family members (spouses, next of kin) and caregivers.

Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder (FGID) that impacts physical and social functioning. Clinical experience suggests that IBS definitely has an effect on the partner, but no studies to date have evaluated this "effect" in the partners of IBS patients.

Our hypotheses are: (1) IBS poses a burden in the partners of patients; (2) the burden is proportional to the severity of illness and its impact; and (3) the burden affects multiple aspects of the relationship. The aims of the study are to: (1) define the degree of burden (quantify burden; compare with other studied diseases); (2) identify factors affecting the burden (disease severity; relationship characteristics; disease perception; individual factors); and (3) identify areas of relationship that are affected (daily life; sexual functioning).

As our recruitment strategy for this study, we aim to identify patients with IBS who have a "significant live-in other" partner. Patients and their partners will be surveyed using either a paper and pencil questionnaire, or via an internet survey questionnaire.

Demographic data and a relationship assessment scale will be collected from both patients and partners. Patients will also complete an IBS symptom severity questionnaire (FBDSI). The questionnaire set for the partners consists of: (1) the Zarit Burden Interview, (2) a questionnaire on sexual relations, and (3) a panel of questions assessing their perception of the diagnosis of IBS.

Outcomes of interest include: (1) degree of burden (comparison of ZBI score against scores for other illnesses), (2) severity of IBS relative to burden, (3) relationship characteristics relative to burden, (4) patient/partner characteristics relative to burden, (5) effects on sexual relationship, and (6) perception/attitudes towards IBS relative to burden

Through this study, we hope to validate the suffering and burden that the spouses and partners of IBS patients have always felt, and what are the characteristics of both parties that affect the degree of burden.

Mindfulness Treatment for IBS: Correlations of Dispositional Mindfulness with Physical and Psychological Factors at Baseline

Susan Gaylord, PhD
UNC Department of Physical Medicine & Rehabilitation


Susan Gaylord

The overall goal of our study is to test the feasibility of conducting a study to compare outcomes of a Mindfulness Program (intervention) and a Support Group (control) on IBS outcomes, psychological and health-related quality of life outcomes, and process outcomes in preparation for a large clinical trial. Our initial pilot study was funded through a seed grant from the UNC Center for Functional GI & Motility Disorders. The current project is funded by NIH National Center for Complementary and Alternative Medicine (NCCAM) grant R2-AT003619.

The primary specific aim is to determine the feasibility of developing a clinical trial comparing effectiveness of a Mindfulness-based Stress & Pain Management Program (treatment group) vs. IBS Support Group (control group) in reducing the severity of symptoms in women with irritable bowel syndrome (IBS). To date, we have completed four cohorts (2 groups each) and a fifth started in October 2008. For this study, 237 potential study subjects have been screened and 73 have completed the intervention.

The primary outcome of interest is measured with the IBS Symptom Severity scale. We are also interested in measuring effects on: (1) symptom relief (adequate relief), (2) symptom frequency (Daily Symptom Diary), (3) IBS-related anxiety (Visceral Sensitivity Analysis), (4) economic impact of IBS (Work Productivity and Activity Impairment for IBS), (5) co-morbid symptoms (Recent Physical Symptoms Questionnaire), (6) general psychological distress (Brief Symptom Inventory), (7) anger and its expression (State-Trait Anger Expression Inventory), (8) quality of life specific to IBS (IBS-QOL), and (9) maladaptive coping methods (Coping Strategies Questionnaire). In addition, we are interested in effect modification measures: (1) expectancy of success of intervention (Borkovec and Nau Credibility scales), (2) catalogue of distressing prior events (Family Inventory of Life Events), and (3) demographics (age, race, education, marital status, income). For process measures, we are using a Five Factor Mindfulness Questionnaire (described below) for the trait construct and the Toronto Mindfulness Scale for the state construct. For an exploratory analysis of the data, correlations between dispositional mindfulness factors (Five Facet Mindfulness questionnaire) and both physical (IBSS, IBS-QOL, RPSQ) and psychological symptoms (BSI-18, VSI) in an IBS population will be considered.

We have developed a Five Facet Mindfulness Questionnaire based on exploratory and confirmatory factor analyses of five existing questionnaires designed to explore constructs of mindfulness (Baer 2006). The questionnaire includes 39 items measuring five identified facets of mindfulness: (1) non-reactivity to inner experience, (2) non-judging of inner experience, (3) acting with awareness, (4) describing, and (5) observing. Likert scale response categories range from never or rarely true = 1 to very often or always true = 5. A recent study has shown that an 8-week mindfulness course produced significant increases in all five facets, with effect sizes (Cohen's d) ranging from 0.47-0.91 (Carmody 2007).

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Examples of "Describe Items" are: (1) My natural tendency is to put my experiences into words; (2) I'm good at finding words to describe my feelings; (3) I can easily put my beliefs, opinions and expectations into words; and (4) When I have a sensation in my body, it's difficult for me to describe it because I can't find the right words. Examples of "Act with Awareness" items are: (1) When I do things, my mind wanders off and I'm easily distracted; (2) I don't pay attention to what I'm doing because I'm daydreaming, worrying, or otherwise distracted; (3) I find it difficult to stay focused on what's happening in the present; and (4) It seems I am "running on automatic" without much awareness of what I'm doing. Examples of "Non-Judgment" items are: (1) I criticize myself for having irrational or inappropriate emotions; (2) I tell myself that I shouldn't be thinking the way I'm thinking; (3) I think some of my emotions are bad or inappropriate and I shouldn't feel them; and (4) I disapprove of myself when I have irrational ideas.

Pearson correlation analysis was conducted with the physical symptom variables and were found to be significant at the $p<.05$ level for Observe with RPSQ, and for Non-judgment with IBS-QoL and Severity. Correlation analysis was also conducted with psychological symptom variables and were significant for: (1) Observe with VSI, (2) Describe with BSI, (3) Aware with all three BSI, (4) Non-judgment with VSI and all three BSI, and (5) Non-react with all three BSI.

Among women with IBS, specific facets of dispositional mindfulness are associated with psychological symptoms, but are relatively unrelated to IBS morbidity: (1) increased levels of awareness, non-judging and non-reactivity are correlated with decreased psychological distress (depression, anxiety); (2) increased levels of non-judging are correlated with increased quality of life; and (3) increased levels of observing are correlated with decreased levels of gut focused anxiety (decreased catastrophizing, more sensory-based perception of gut signals). Regarding the connection between mindfulness and IBS symptoms: (1) increased levels of non-judging were associated with higher levels of gut-focused anxiety (evidence of willingness to accept rather than repress negative affect?); (2) increased levels of non-judging were associated with higher levels of abdominal pain (evidence of coping?); and (3) increased levels of observing were associated with increased report of somatic symptoms.

Dispositional mindfulness correlates with IBS symptomatology, particularly psychological symptoms. Training designed to enhance these mindfulness traits could be salutary for individuals suffering from psychological symptoms related to IBS.

Quetiapine and the treatment of IBS

Stephan R. Weinland, PhD

Severe, refractory functional gastrointestinal disorders (FGIDs) comprise up to 20% of patients in primary care and up to 70% of patients in referral centers. Patients with this condition report higher levels of: (1) pain; (2) psychiatric disorders (anxiety or depression up to 40-50%; PTSD -- history of sexual or physical abuse; sleep disturbances 50-70%; somatization -- overlap with somatic pain disorders); (3) health care utilization; and (4) treatment dissatisfaction. Centrally acting agents are the current treatment of choice (TCA, SSRI, or SNRI).

Quetiapine is an atypical antipsychotic. It has anxiolytic properties (Anti 5HT2, 5HT3) and has been used to treat social anxiety (independent of sedation) and PTSD (by reducing re-experiencing, hyper arousal, and nightmares). It has also been shown to have sleep benefits (Anti H1, Anti adrenergic), increasing total sleep time, efficiency, and subjective quality. Quetiapine is a potential analgesic (anti-dopaminergic) and has been used with patients suffering from fibromyalgia, migraines, low back pain, and cancer pain. It has a favorable safety profile (anti 5HT > anti dopamine) and fewer extrapyramidal side effects.

Reasons for adding Quetiapine to treatment for patients with severe refractory FGIDs are: (1) population with a difficult disorder that has failed single and combinations of traditional antidepressants; (2) associated anxiety (PTSD/anxiety disorders); (3) associated sleep disturbances; and (4) potential augmentation of analgesia.

The present study is an open label study of Seroquel XR (Quetiapine) for the treatment of refractory and treatment resistant functional bowel disorders. The primary objective is to show treatment response of IBS symptoms, as reported through a binary measure of adequate relief and an ordinal symptom relief measure. Secondary objectives are to assess: (1) improvement in IBS-Quality of Life, (2) reduction in visual analog scale rated pain, (3) improvement in global distress measures, (4) improvement in somatization and catastrophizing measures, and (5) improvement in sleep as reported by sleep diary cards.

For this study, 50 subjects will be recruited, with 40 estimated to be evaluable assuming a 20% dropout rate. Patients must: (1) maintain a diagnosis of a moderate to severe painful functional bowel disorder for at least six months (Rome III Criteria), (2) have a physician diagnosis of IBS, constipation with pain, or functional abdominal pain, (3) scores >37 on the FBD-SI (Functional Bowel Disorder Severity Index), (4) be in the process of attempting one trial of antidepressant medication (lasting at least one month) prior to study participation without sufficient benefit (as measured by TEQ), and (5) not have achieved adequate relief from all prior interventions.

The study will be conducted in three phases: (1) Baseline (one week beginning at the screening visit), (2) Active Treatment (eight weeks on present antidepressant plus Quetiapine), and (3) Follow-Up (four week follow-up on antidepressant without Quetiapine). We are currently actively recruiting for this study -- working on referrals from local outside clinicians -- and 110 patients have been screened through WEBCIS records for possible entry into study. So far, five patients have been recruited. One subject dropped out due to intolerance to the study medication, and another subject dropped out after being diagnosed with pancreatic carcinoma. We continue to look for study participants and look forward to reporting results from our investigation in the upcoming year.

Characterization of IBS Symptom Episodes

Olafur S. Palsson, PsyD

Our UNC team is conducting a single-group prospective IBS diary study, in which a large sample of well-characterized IBS patients record every bowel movement (BM) over a 90-day time frame and assess day-to-day (and BM-to-BM) variation in symptoms. This study is being conducted entirely online and involves no visits to the study site.

The general aim of this descriptive study is to characterize the natural history and episodic pattern of IBS with respect to day-to-day variations in stool consistency, frequency and urgency, and daily symptoms of pain and bloating. Additional aims are (a) to provide data that will enable the study sponsor to design a Phase III study of the efficacy of an anti-diarrheal drug for the treatment of diarrhea episodes in patients with IBS, and (b) to examine the causal role of life stress in IBS symptom episodes.

The study subjects are 200 patients with physician-diagnosed IBS, 18 years and older, who meet Rome III diagnostic criteria for IBS. At least half of these patients will have had 3 or more episodes of loose or watery stools in the prior month. Patients enrolled in this study must not have been diagnosed with inflammatory bowel disease (IBD), be lactose intolerant, or have celiac disease. Enrolled patients must not be on daily prescription medication for IBD or narcotic pain medications. They must have daily access to the internet at their home.

Potential participants are recruited through invitations to patients in our Center's research participant registry and through advertisements on IBS websites. Potential subjects are screened online. Qualified participants are enrolled via mail. They receive a package with diary books, consent form, and release of information form to allow us to contact their physicians. Subjects access a secure website, www.uncdiary.com, use their unique ID to set their own password, and complete an initial questionnaire set online. They then use diary pocket books with daily rating forms to rate every BM during the day for 90 days, and electronically transfer the diary ratings of the BM each evening during the 90-day study period, where they also report their global symptoms for the day.

Baseline questionnaires include: (1) Rome III modular questionnaire for IBS, (2) IBS Symptom Severity Scale, (3) IBS-QOL, (4) BSI-18, (5) demographic questions, (6) detailed medication questions, and (7) symptom history. Data analyses will be descriptive and will determine: (1) proportion of patients likely to meet the study criteria for the planned Phase III study; (2) best ways to describe/define onset and end of diarrhea episodes; (3) estimate of the duration and variability of IBS symptoms, and the episodic nature of symptoms for different IBS subtypes; and (4) the temporal relationship between stress and IBS symptoms.

The first subject for this study was screened in July 2008. Since then, 89 patients have completed the baseline assessment on-line, and 10 more have qualified for participation and are awaiting their mailed enrollment packages. 81 patients have started the 90-day diaries, and 40 have completed the first 30-day period. Among subjects who have completed the first month, there is a 99% diary completion rate. Compliance has been very good in this study. We have had 100% diary data completion to date by 79% of the participants.

[Sponsored by McNeil Pharmaceuticals]

State of the Art: An Overview of Where We Have Been and Thoughts for Next Directions for Research on Pediatric FGIDs

Rona Levy, PhD, MPH, AGAF, FACG

Rona Levy

There are a number of reasons why research with children lags behind adult research. One important explanation has to do with the greater potential for harm and the related practicalities of obtaining consent with children. Nevertheless, it is important to conduct research with children because, while significant medical problems exist, adult research cannot be generalized to children: their physiology is different and changing; there are differences in their psychology that must be considered, such as developmental aspects, reading and understanding levels, and exposure to some risk factors "in process"; and finally, their life circumstances are different: adults control much of the environment of children, as reinforcers of behaviors, enablers of medical care visits, and the like.

There is a good deal of exciting new information becoming available about children. In a 2006 article, Carlo DiLorenzo, MD, noted that animal models of early life stress are elucidating potential long-term developmental explanations for the functional gastrointestinal disorders (FGIDs). We are also gaining new insights into the pathophysiology of pediatric FGIDs based on studies in children using new diagnostic techniques, such as barostat, transit and other nuclear medicine imaging studies, and water load tests. For example, Dr. Denesh Chitkara and others showed that adolescents with functional dyspepsia display increased postprandial symptoms, delayed gastric emptying, and reduced gastric volume response to feeding. Psychiatric disorders and psychological traits are also being identified in children with FGIDs. Aiding this trend, legislation enacted in 1999 allows the Food and Drug Administration (FDA) to request pediatric tests of any drug being developed for adults that may be given to children.

Diagnosis: The Rome III committees have also acknowledged the increasing importance of the pediatric FGIDs with now two chapters and major diagnostic categories for children: (1) Childhood functional gastrointestinal disorders: Neonate/Toddler (for example, infant regurgitation, infant rumination), and (2) Childhood functional gastrointestinal disorders: Child/Adolescent (for example, abdominal migraine and childhood functional abdominal pain).

Pathophysiology: Recent studies into the pathophysiology of the FGIDs include a finding of fructose intolerance in children presenting with abdominal pain (Gomara et al 2008), and our own study (Levy et al, 2009) of childhood GI symptoms and diet, which found a significant correlation between lack of vegetables and missing days of school due to due to abdominal pain.

Measurement. Advances in measurement also are facilitating GI research with children, including the new Functional Disability Inventory for Pain (FDIP; Claar & Walker 2006), and the parent version of the Pain Catastrophizing Scale (Goubert et al 2006).

In a study assessing parents' ability to 'read pain' in their children's faces (Zeltzer and Tsao 2006), parents were asked to identify their child's true pain, faked pain. They were able to identify all pain conditions, with better ability to identify faked pain than the other conditions.

Van Tilburg et al (2006) investigated parents' worries about recurrent abdominal pain (RAP) in children

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and found that parental cognitions about RAP revolved around the fear of a disease and a desire for diagnosis and effective treatment. Many parents stated they felt helpless and did not know how to deal with their child's suffering. These fears and worries may explain why parents reinforce illness behavior by showing empathy for their child. The findings also identified areas of possible miscommunications between clinicians and parents.

Co-morbidities. Petersen et al (2006) reported that half of the children with recurrent pain symptoms indicated pain symptoms from several body locations, and, in children with weekly pain symptoms, two out of three reported multiple pain. Their data also indicate that multiple, not single, pain symptoms became more prevalent with age

Coping strategies. Many recent investigations have focused on effective strategies for coping with pain. A study by Lu et al (2007) reported on a study of healthy children and adolescents who were exposed to pressure, thermal, and cold pain stimuli. Using a Pain Coping Questionnaire, the authors found that internalizing/catastrophizing and seeking emotional support were pain-prone coping strategies, while positive self-statements and distraction were pain-resistant coping strategies.

Studies by Walker et al have found that the relationship between stress and symptoms in pediatric patients may be explained in part by the children's appraisal and coping with stressors (2007), and she provided a typology of pain coping strategies in pediatric patients with chronic abdominal pain (2008) that included: infrequent, inconsistent, avoidant, dependent, self-reliant, and engaged.

Risk factors and mechanisms for pain and coping. Guite et al's (2007) work determined that perceptions of self-worth appear to play an important role in understanding the relation between pain and functional disability among adolescents with chronic musculoskeletal pain and functional disability. In a study by Claar et al (2008), children whose parents were overly protective or critical of their child's pain experienced more impairment or somatic symptoms, particularly those children who were already at risk for difficulties due to higher levels of emotional distress. Among adolescents who report infrequent use of passive and active coping responses, Simons et al (2008) state that parental protective responses to pain may inadvertently promote greater disability and symptom complaints. Dufton et al (2008) found that children with RAP were higher than healthy children but not significantly different from children with anxiety on total internalizing and anxiety symptoms, and that RAP and anxiety are closely related.

In a study (McMurtry 2007) about parental reassurance and pediatric procedural pain, it was found that certain parental behaviors are associated with child coping and others with child distress when children undergo painful medical procedures. The finding that parental reassurance is linked with increases in child distress is perplexing and counterintuitive. This detailed linguistic approach offers new insights into the qualities of parental reassurance during painful medical procedures. Zohsel et al's (2008) research showed that at the abdominal site, pain sensitivity in children with RAP did not differ significantly when compared to controls. There was no evidence for somatic hyperalgesia in RAP, arguing against generalized hyperalgesia in these children.

Our own work (Levy et al, 2004) work, which has clear clinical implications, found associations between maternal reinforcement and seriousness of children's stomachache. And more recently, our group also found that multiple independent factors additionally contribute to learning: (1) mothers with IBS and

their children are alike in the tendency to report most types of somatic symptoms, not only GI symptoms; (2) children are also similar to their mothers in the severity and types of psychological symptoms they have; (3) psychological symptom severity in the child is associated with increased symptom reports; and (4) passive coping with stomach aches by the child also contributes to both GI symptoms and non-GI symptoms in children. Our model showed that a child's GI symptoms were a function of (Adjusted R-squared 9%) the mother's IBS status, the child's psychological status, and the child's passive coping skills. These variables, coupled with the child's self-worth and age, accounted for 14% of the variance in the child's non-GI symptoms.

Treatments for functional constipation. Although biofeedback is an effective therapy for adults, van der Plas et al (1996) found no significant differences between conventional therapy for childhood constipation and conventional therapy coupled with biofeedback. Commenting on this finding, Chiarioni and Whitehead conclude: "Biofeedback requires complex cognitive processing and sustained attention that could be beyond the capability of very young children."

A randomized, controlled trial of behavioral therapy for childhood constipation recently completed (van Dijk 2008), aimed to evaluate the clinical effectiveness of behavioral therapy with laxatives compared to conventional treatment in treating functional constipation in childhood. The behavioral intervention included (van Dijk 2007): (1) psychoeducation, (2) anxiety reduction, (3) laxatives and skill learning, (4) reinforcement of appropriate behavior, and (5) establishing a toileting routine. They found that defecation frequency was significantly higher for conventional treatment at post-treatment, but after 22 weeks, success rates (defecation frequency of >3 times per week) did not differ between conventional treatment and behavioral therapy, nor did it differ at 6 months of follow-up.

Treatments for pain. Youssef (2004 and 2008) has reviewed treatments for pain in the pediatric FGIDs. Hypnotherapy has been used successfully in children with functional abdominal pain or irritable bowel syndrome (Vlieger at el 2007), but Hyams (2008) has commented that "the dearth of skilled hypnotherapists, particularly for children, as well as associated cost, could further limit the implementation." Robins et al's 2005 study of a cognitive-behavioral family intervention for pediatric recurrent abdominal pain found (1) less reported pain and school absences in the CBT/Standard Medical Care (SMC) condition than SMC alone, and (2) no change in functional disability and somatization. However, this study had a relatively small sample, and there was no comparison condition.

Based on some of the mechanism studies, Walker et al (2006) addressed the question of whether symptom talk can be affected by manipulating parental distraction levels in a laboratory setting. She found that when parents are trained to distract children from symptoms, symptom talk is lower.

In an effort to determine if similar results went beyond the laboratory, we conducted an RCT to see if we could alter children's illness behavior by teaching parents and children to respond differently. Study participants were children referred for functional abdominal pain. Those assigned to the treatment arm received a combination therapy of cognitive behavior therapy and social learning (SLCBT). There was also a comparison condition that controlled for time and attention. While data are still being analyzed, preliminary analysis indicates change in the expected direction, with the SLCBT group showing greater improvement.

This research is also currently being extended to children with IBD, and we are asking whether we can

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decrease the disease impact of children with inflammatory bowel disease (IBD) by teaching parents and children to respond differently. A prospective, longitudinal pilot study is now underway, again using the SLCBT combination therapy.

In summary, there is considerable recent activity in pediatric functional GI on many fronts: diagnosis, pathophysiology, measurement, co-morbidities, coping strategies, risk factors and mechanisms for pain and coping, and treatment.

A Cochrane review of the treatment literature (2008) determined that the number of RCTs is still small, many have methodological weaknesses, and many had inappropriate detail regarding numbers. Nevertheless, they conclude: "In spite of these methodological weaknesses and the clinical heterogeneity, the consistency and magnitude of the effects reported provides some evidence that cognitive behavioural therapy may be a useful intervention for children with recurrent abdominal pain although most children, particularly in primary care, will improve with reassurance and time."

Finally and in conclusion, as research moves to address these methodological weakness, the field would be well advised to expand in directions that address all aspects of Turner and Turk's (2008) wise suggestion (primarily addressed to the pain research community) that further studies are needed "that answer questions regarding what treatments are effective, for what outcomes, for what patients, with what adverse effects, compared to what alternatives, and at what costs."

Long-Term Follow-Up on Guided Imagery for Functional Abdominal Pain

Miranda Van Tilburg, PhD

Functional Abdominal Pain (FAP) is a common childhood disorder defined by the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition as "long lasting intermittent or constant abdominal pain without evidence of an organic cause". It afflicts 8-20% of children and is associated with disability and decreased quality of life. Since there is no readily identifiable cause for FAP, treatment is focused on reductions of symptoms and disability rather than a cure. Standard medical care consists of reassurance that nothing major is wrong with the child, education, setting realistic treatment goals, and medications to relieve symptoms. This approach is helpful, but in many cases children continue to have debilitating symptoms and are in need of additional therapies.

Two recent placebo controlled trials have found evidence for the use of guided imagery and self-hypnosis, which are two related techniques, to treat pediatric FAP (Weydert et al., 2006; Vlieger, Menko-Frankenhuis, Wolfkamp, Tromp, & Benninga, 2007). In Guided Imagery, the therapist uses verbal guidance to help the patient experience detailed vivid imagery that has beneficial effects on their behavior, cognitions, emotions or physiology. However, these treatments are currently not available to the majority of children with FAP. There is a shortage of trained therapists who specialize in pediatric pain, and the treatment is costly and time consuming. To overcome these challenges, we developed a guided imagery on DVDs and CDs that can be used by children independently in the comfort of their home. This home-based program can be easily prescribed by any clinician without specialized training in behavioral treatments.

In a randomized trial, we compared standard medical care with or without home-based guided imagery in a group of 29 children. Those who received standard medical care only were crossed over to guided imagery after 2 months. Six-month follow-up data were available for 11 children from each original group. All treatment materials were reported to be self-explanatory, enjoyable, and easy to understand and use. The compliance rate was 98.5%, and almost no side-effects were reported. In the standard medical care combined with guided imagery group, 60% of children were treatment responders (> 50% reduction in pain) compared to 14.3% in the standard medical care group alone. Once the children in the standard medical care group also received guided imagery, 58.3% became treatment responders. At 6 month follow-up, paired t-tests revealed no significant differences in pain and disability from post-treatment but did yield significant differences from pre-treatment to 6 month follow-up for abdominal pain ($p=.000$) and disability ($p=.005$).

In conclusion, this study found that home based guided imagery results in significant reductions in abdominal pain and disability, and improvements are maintained at 6 months. Guided imagery is low in cost, easily administered, is well liked by both children and parents, and can be applied as first line treatment. One 11 year old girl reported: "I used to use medications for my stomachaches. But now, guided imagery is my medication and it doesn't even taste bad."

Pilot Study on the Feasibility and Efficacy of a School Nurse Guided Imagery Program for Childhood Recurrent Abdominal Pain

Nader N. Youssef, MD, MBA
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Nader Youssef

Our research (Youssef 2006) has shown that children's self-reported quality of life (QoL) scores are significantly impacted by their symptoms of Recurrent Abdominal Pain (RAP). Parents have emotional and social concerns about their children's QoL when they suffer from RAP. Children suffering from recurrent abdominal pain are less likely to participate in weekly social activities, and they are more likely to miss 10 or more days of school.

When school nurses are asked about children with RAP (Youssef 2007), 47% believe the children are faking their symptoms, 38% believe the children are lazy, 23% believe they are seeking attention, and 35% believe they are sad. School nurse recommendations for RAP were: rest in the office (94%), go to the bathroom (90%), go back to class (68%), or send the child home (48%). We found that 81% of school nurses were lacking education about RAP, and that communication with the child's physician about the RAP was poor in 84% of cases.

The aims of our study are to assess: (1) the feasibility of guided imagery administered at the school nurse level, and (2) the efficacy of guided imagery as compared to traditional rest in the reduction of RAP pain in children. We aim to assess the impact of treatment on (1) abdominal pain, (2) disability and quality of life, and (3) anxiety and depressive symptoms. The study design entails the recruitment of 20 children with RAP, ages 8-17 years. All subjects will be consented and baseline data collected on pain, Qol, and psychosocial scores. Subjects will then be randomized to two equal arms (10 each) – school nurse guided imagery (SNGI) or routine reassurance and rest (RRR). Subjects will be assessed once a week for 3 months with regard to pain, Qol and psychosocial scores.

To date, 13 RAP patients have been enrolled: 6 males, mean age 9.2 years (range 7-11), and mean duration of RAP pain 7.8 months. No patient was sent home during protocol or 3-month follow up. SNGI patients completed all sessions. Our preliminary finding is that abdominal pain has decreased for both groups, but more significantly for the SNGI group. Functional disability has decreased for the SNGI group, but not for the RRR group.

Findings from our research will be used for Community Outreach Research Partnership to: (1) increase awareness about RAP in the community, (2) maximize resources for effective treatment strategies, (3) provide direct care at initial point of contact, (4) decrease the socioeconomic burden on families with children who suffer from RAP, and (5) improve the quality of life for children with RAP. Directions for further research include approaching the State Department of Education for funding to establish a countywide program within elementary and middle schools. We hope to recruit district-specific lead school nurse researchers/educators and to establish a web-based program for community research/education.

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State of the Art: Enteric Neurodegenerative Disease

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Jackie Wood

My interest, as a basic scientist, was stimulated during a visit to David L. Wingate, M.D., FRCP at London/Guys Hospital in March 1983 when we discussed a patient who at the moment was being taken to surgery to explore signs of mechanical bowel obstruction. The patient, Mrs. P.N., DOB 12/03/1943, was diagnosed with LES achalasia at age 32, had onset of constipation at age 36, severe constipation associated with diminished enteric ganglia in biopsies at age 37, and recurrent subacute bowel obstruction. The exploratory surgery culminated with total colectomy. The astonishing observation at surgery was hyperactive small intestinal motility rather than ileus during laparotomy when the bowel was "exposed out on the drapes". Full thickness histology revealed total absence of the enteric nervous system (ENS) in the small intestine. Mrs. P.N. is alive and subsisting on TPN in 2009. Her case is an example of neuropathic intestinal pseudoobstruction and the impact of loss of the enteric nervous system (ENS); in particular, the loss of inhibitory motor innervation of the musculature, which leaves uncontrolled contractile behavior reflecting the autogenic-functional electrical syncytial properties of the smooth muscle in the absence of inhibitory control. The gut does not work in the absence of the ENS!

In 2004, I received the following letter from Dr. xxxxxx: "Dear Dr. Wood: My personal medical condition may hold some interest for you and I am writing in the hope that it does. I am a professor of neurology at xxxxxx, was formerly the chair there and now I am chief of neurology at the VAMC in xxxxxx, the site of half the xxxxxx neurology residency program. By interest, training, and experience I am an expert in Parkinson's disease, other movement disorders and in neuro-behavioral disorders, especially violence. I am not sophisticated in diseases of the blood or GI system but think I have an illness that is right up your alley. I have had MGUS for 25 years without symptoms. Starting about 2-3 years ago, strange symptoms started: ankle swelling, proteinuria (nephrotic syndrome), achalasia, and increasingly severe attacks of diarrhea. I began to lose weight and dropped 25 pounds, ending with a blaze of diarrhea and injections of sandostatin (that prevented pancreatic enzymes from getting to the foods I ate). I felt weak. Not knowing what I had and seeing your articles that postulate an antibody that can attack the myenteric plexus, I wrote to you. Kindly, you accepted a sample of blood, tested it against guinea pig intestine and you found that it had significant antibody activity that was directed against the myenteric plexus. Subsequently, Dr. xxxxxx, a first class GI man in DC diagnosed amyloidosis. He biopsied my upper, lower and mid GI tract and the slides were subtly disordered. They were called normal at Sibley Hospital here but at Mayo they were called positive for amyloidosis, same with a subcutaneous fat biopsy and a bone marrow. The amount of amyloid was tiny. I have a lot of symptoms and not much amyloid. Why? Autonomic neuropathy: diarrhea, sexual difficulties, postural hypotension, proteinuria, swollen ankles, and the sense of energy loss. The small amount of amyloid that I have seems to be acting like an antibody directed against my myenteric plexus, disinhibiting my parasympathetic nerves so the sympathetics have predominance, a terrific gastro-cholic reflex every time I eat. I pay with a long bout of diarrhea for each delicious meal."

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At Ohio State, we responded by testing Dr. xxxxxx's serum sample on two separate occasions and sent him the following report on 08/27/2004. "Dear Dr. xxxxxx: We analyzed the blood sample you sent for anti-enteric antibodies. Two changes we note since the analysis done in August 2002 are the much stronger reaction limited to neuronal nuclei and reaction with small blood vessels (perhaps arterioles) in regions around ganglia in the submucosal lamina propria. The attached PowerPoint file includes both August 2002 and 2004 results. Sincerely, Jackie D. Wood, MSc, PhD, AGAF, Professor of Physiology and Internal Medicine."

These are two examples from my experience with multiple ad hoc studies of serum samples from patients with functional GI symptoms, which suggest that degenerative enteric neuropathy caused by autoimmune attack in the ENS underlies the symptoms. There is little doubt now that there is a subset of patients with functional GI symptoms who have anti-enteric neuronal antibodies in their blood, which makes it highly likely that their symptoms emerge from progressive damage to the ENS. A current challenge is to establish the size of the subset of patients who suffer from a functional gastrointestinal disorder that reflects an anti-enteric degenerative neuropathy.

Enteric Nervous System

Minute-to-minute behavior of the gastrointestinal tract reflects the integrated functioning of its musculature, mucosal epithelium and blood-lymphatic vasculature. The enteric nervous system (i.e., the brain-in-the-gut) organizes and coordinates the activity of the three effector systems to generate functionally effective patterns of behavior that are adaptive for differing digestive states. The ENS is a local minibrain that contains a library of programs for the necessary patterns of intestinal behavior. Mixing in the digestive state, the migrating motor complex in the interdigestive state and emetic patterns of small intestinal motor behavior and haustral formation in the large intestine are examples of outputs from four of the neural programs in the ENS library.

The ENS has as many neurons as the spinal cord. The large number of neurons, required for program control of digestive functions, would overly expand the CNS if housed there. Rather than crowding the neural control circuits exclusively within the skull or vertebral column and transmitting nerve impulses over long transmission lines to the gut, vertebrate animals have evolved with most of the neural networks, required for automatic feedback control, spatially distributed along the digestive tract close to the effector systems (e.g., muscles, secretory glands and blood vessels) that must be controlled and integrated for whole organ function.

Like the spinal cord, the ENS has interneurons and motor neurons that are interconnected by chemical synapses into functional neural networks. Motor neurons in the ENS are excitatory or inhibitory motor neurons. Enteric inhibitory motor neurons have central importance in consideration of ENS degenerative neuropathy because their loss is manifest as profound pathological changes in contractile behavior of the intestinal musculature. The pathological changes in motor behavior associated with degeneration of inhibitory motor neurons reflect the specialized physiology of the musculature. The gastrointestinal musculature is a self-excitable electrical syncytium consisting of interstitial cells of Cajal (ICCs) that function as pacemakers for the intestinal circular muscle coat. The term "electrical syncytium" infers that pacemaker potentials and action potentials spread by way of gap junctions from smooth muscle fiber to muscle fiber in three dimensions. The action potentials trigger contractions as they spread through the bulk

of the musculature. The ICCs are a non-neural pacemaker system of electrical slow waves that are electrically coupled to the musculature and account for the self-excitable characteristics of the muscle. The electrical slow waves, in this construct, are an extrinsic factor to which the circular muscle responds. Consideration of these functional aspects of the musculature raises the question of why the circular muscle fails to respond with action potentials and contractions to each and every pacemaker cycle and why action potentials and contractions do not spread in the syncytium throughout the entire length of intestine whenever they occur at any point along the bowel. The answer is that the circular muscle in a segment of bowel can only respond to invading electrical slow waves from ICCs when the inhibitory motor neurons in the ENS of that segment are inactivated by input from the control circuits formed by interneurons. Likewise, action potentials and associated contractions can propagate only into regions of musculature where the inhibitory motor neurons are themselves "turned-off" by inhibitory synaptic input. Therefore, activity of inhibitory motor neurons determines when the omnipresent electrical slow waves initiate a contraction, as well as the distance and direction of propagation once the contraction has begun.

Some of the inhibitory motor neurons to the circular muscle fire continuously and continuously release inhibitory neurotransmitters at their junctions with the muscle. This results in ongoing inhibition of contractile activity. Action potentials and contractions of the muscle are permitted only when the active inhibitory neurons are inactivated by input from the interneuronal control circuitry. The behavior of inhibitory motor neurons to smooth muscle sphincters (e.g., lower esophageal, sphincter of Oddi and internal anal sphincter) is opposite to that of the intestinal circular muscle coat. Inhibitory motor neurons to the sphincters are normally silent and are switched to firing mode with timing appropriate for coordinated opening of the sphincter with physiological events in adjacent regions. When inhibitory motor neurons fire, they release inhibitory neurotransmitters that relax ongoing muscle contraction in the sphincteric muscle and prevent excitation-contraction in the musculature on either side of the sphincter from spreading into and closing the sphincter.

In non-sphincteric circular muscle, the activity state of the inhibitory innervation determines the length of a contracting segment by controlling the distance of spread of action potentials within the three-dimensional electrical geometry of the smooth muscle syncytium. Contraction can occur in segments in which ongoing inhibition is inactivated while adjacent segments with continuing inhibitory input cannot contract. The boundaries of the contracted segment reflect the transition zone from inactive to active inhibitory motor neurons. The directional sequence in which the inhibitory motor neurons are inactivated establishes the direction of propagation of the contraction. Normally, inhibition is progressively inactivated in the aboral direction, resulting in contractile activity that propagates in the anal direction. During emesis, the inhibitory motor neurons must be inactivated in a reverse sequence to account for small intestinal propulsion that travels toward the stomach. In general, any treatment or condition that ablates the intrinsic inhibitory neurons (e.g., autoimmune neuropathy) results in spastic-uncoordinated contractile behavior of the intestinal circular muscle coat reminiscent of the behavior of Mrs. P.N.'s bowel during exploratory surgery for obstruction.

The inhibitory neuromuscular relations in the intestine predict that spasticity and "achalasia" (i.e., failure to relax) will accompany any condition where inhibitory motor neurons are rendered inactive or destroyed. Without ENS inhibitory neural control, the self-excitable smooth muscle contracts continuously and behaves as an obstruction. This occurs because the muscle responds

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to each and every ICC-generated electrical slow wave with contractions that propagate in all directions without any control of amplitude or distance of propagation. Contractions spreading in the uncontrolled syncytium collide randomly resulting in chaotic-ineffective behavior in the affected intestinal segment is ways which are reminiscent of fibrillation in the myocardium.

Loss or malfunction of inhibitory motor neurons is the pathophysiological starting point for disinhibitory enteric motor disease, which includes several forms of chronic intestinal pseudoobstruction and sphincteric achalasia. Neuropathic degeneration of the ENS includes loss of the pool of inhibitory motor neurons along with the interneuronal pool and is a progressive disease that in its early stages may be manifest as symptoms that are interpreted as a functional gastrointestinal disorder (e.g., IBS). Recognition of the brain-like functions of the ENS suggests that early stages of a degenerative enteric neuropathy might be expressed as IBS-like symptoms. Early symptoms in these patients can be lower esophageal sphincter achalasia, which reflects loss of inhibitory innervation of the sphincter, and postprandial cramping abdominal pain and diarrhea. The disease in these individuals appears to progress from IBS-like symptoms to symptoms of chronic intestinal pseudoobstruction in parallel with progressive loss of neurons from their ENS.

Prevalence of Anti-Enteric Neuronal Antibodies in IBS

Results of a collaborative study in progress between the University of North Carolina Center for Functional Gastrointestinal and Motility Disorders and my ENS laboratory at The Ohio State University suggest that the prevalence of autoimmune degenerative enteric neuropathy, in patients with functional gastrointestinal disorders, exceeds by far what we might have expected. The UNC Center collected serum from each of 78 symptomatic patients, who had received a diagnosis of IBS based on Rome III symptom-based criteria and shipped the serum to the ENS laboratory at Ohio State University for analysis during 2008. Analysis of the serum found that 43 of the 78 patients had, in their blood, antibodies that interacted with neurons in the ENS of guinea pig intestine. Our results showing the presence of anti-enteric neuronal antibodies in such a high proportion (55%) of patients, who have a Rome III diagnosis of IBS, was unexpected and surprising.

The epidemiological data suggesting that 10-20 percent of the population worldwide is impacted by IBS spotlights the significance of the large percentage of IBS patients we found to have circulating anti-enteric neuronal antibodies. The impact, if it should indeed turn out to be the case for a larger study sample, is huge. According to the U.S. Bureau of the Census, the resident population of the United States was projected in 01/21/09 to be 305,659,487. If 10% of the current US population were diagnosed with IBS, then the number with an autoimmune anti-enteric neuronal degenerative neuropathy as an identified factor in their illness would be predicted to be about 17 million, if 55% of the serum samples contained anti-enteric neuronal antibodies. The numbers become staggering for larger populations, such as in China. The prevalence of IBS in Beijing is reported to be 10.5% in the city and 6.14% in the surrounding rural population. According to Google, the population of mainland China in 2008 was estimated to be 1,330,044,600. If 6.1-10.5% of the 1.3 billion Chinese were diagnosed with IBS in 2008, then the number with an autoimmune anti-enteric neuronal degenerative neuropathy as an identified factor in their illness could be more than 100 million.

Are Enteric Neuropathies Found in a Subset of IBS?

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In a previous study of inflammation and enteric neuropathy in patients with Irritable Bowel Syndrome (IBS), full thickness jejunal biopsies were collected from 10 IBS patients. Infiltration of lymphocytes in and around enteric ganglia was found in 9 out of 10 patients, and neuronal degeneration was seen in 6 out of 91. In a review, De Giorgio and colleagues2 speculated that inflammation of enteric ganglia is responsible for a spectrum of severe motility disorders including IBS, and that circulating antineuronal antibodies may be a diagnostic biomarker. Mechanisms may include viral invasion of enteric ganglia or autoimmunity.

Di Giorgio and colleagues2 speculated that steroids or immunosuppressants might be helpful for the treatment of IBS and other motility disorders. In animal models, corticosteroids and selective COX-2 inhibitors attenuate inflammatory-mediated motility effects, and surveys show a lower incidence of IBS in asthma patients on steroids3. However, in a clinical trial prednisolone showed no benefit in Post Infectious IBS patients with diarrhea4.

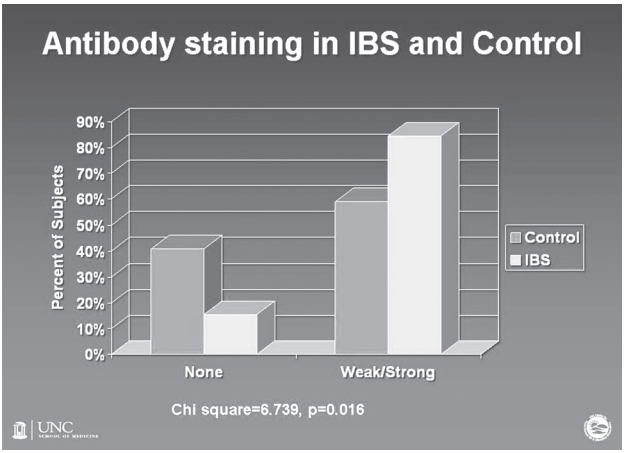
We first conducted a pilot study to test the feasibility of identifying antibodies to enteric neurons using plasma withdrawn from a peripheral vein. Six plasma samples collected from IBS patients in an ongoing study were sent to colleagues at Ohio State University. These samples included 3 patients with severe symptoms on the IBS Symptom Severity Index (IBSS) and 3 with excessive amounts of phasic colonic motility. When these serum samples were added to the medium in sections of guinea pig ilium, two of the 6 serum samples yielded definitive evidence of antibodies to enteric neurons. Based on these preliminary data we undertook the following larger study:

The primary aim of this expanded pilot study was to determine whether Hu antibodies (indicative of enteric inflammation) are found in a greater proportion of IBS patients compared to healthy controls. Secondary aims were to determine whether antibody patients have (1) greater IBS symptom severity, (2) more motility abnormalities, and/or (3) greater visceral hypersensitivity. Study subjects were drawn from our on-going study and included 75 Rome II positive and clinically confirmed IBS patients and 25 healthy controls. Frozen serum samples were sent to Ohio State University for blinded Hu antibody assays, and antibody titers were compared to (1) the IBS symptom severity index (IBSS), (2) colon motility in response to graded distention, (3) visceral pain thresholds, and (4) proportion of bowel movements that were described as hard vs. loose and watery.

Figure 1 shows the primary results: 84.6% of IBS patients exhibited staining for Hu antibodies in enteric ganglia compared to 59.1% of healthy controls (Chi square=6.739, p=0.009), supporting the hypothesis that enteric inflammation is associated with the development of IBS. However, there was a substantial overlap, suggesting that Hu antibodies in enteric ganglia are not uniquely associated with IBS. When the presence and/or intensity of Hu antibody staining was compared to clinical and physiological characteristics of subjects, Hu antibody was found to be uncorrelated with IBS Symptom Severity, motility index, or sensory thresholds for pain or urgency to defecate. However, the presence of Hu antibody was significantly associated with having loose stools at least 25% of the time (Chi square=5.561, p=0.018).

W. Whitehead, J. Wood, O. Palsson, continued

In conclusion, these data support the hypothesis that inflammation of enteric neurons plays a role in the etiology of IBS and/or related motility disorders for at least a subset of patients. The data also suggest that diagnostic tests based on plasma from the systemic circulation can be used to identify these patients. Further research is needed to confirm these results and to determine why approximately 60% of healthy controls also show positive antibody tests.



Reference List

1. Tornblom H, Lindberg G, Nyberg B, Veress B. Full-thickness biopsy of the jejunum reveals inflammation and enteric neuropathy in irritable bowel syndrome. Gastroenterol 2002;123:1972-1979.

2. De Giorgio R, Guerrini S, Barbara G, Stanghellini V, De Ponti F., Corinaldesi R, Moses PL, Sharkey KA, Mawe GM. Inflammatory neuropathies of the enteric nervous system. Gastroenterol 2004;126:1872-1883.

3. Huerta C, Garcia Rodriguez LA, Wallander MA, Johansson S. Users of oral steroids are at a reduced risk of developing irritable bowel syndrome. Pharmacoepidemiol Drug Saf 2003;12:583-588.

4. Dunlop SP, Jenkins D, Neal KR, Naesdal J, Borgaonker M, Collins SM, Spiller RC. Randomized, double-blind, placebo-controlled trial of prednisolone in post-infectious irritable bowel syndrome. Aliment Pharmacol Ther 2003;18:77-84.

Stress, corticotropin releasing factor, and colon dysfunction

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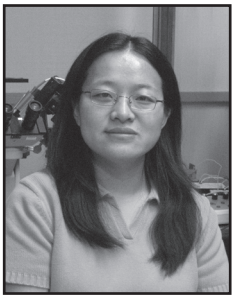
Sumei Liu

Stress has long been known to disrupt normal gastrointestinal (GI) functions, including: (1) inhibiting gastric emptying, (2) slowing down small intestinal transit, (3) accelerating colon transit, (4) stimulating intestinal mucosal secretion, and (5) disrupting intestinal epithelial barrier function. The mechanisms of stress-related GI dysfunction are not well understood. However, corticotropin releasing factor (CRF) is implicated in various stress-induced functional abnormalities, including changes in GI functions.

CRF is a 41 amino acid peptide, which was first isolated from the hypothalamus in 1981. It stimulates the activity of the hypothalamic–pituitary–adrenal (HPA) axis during stress. It also mediates behavioral, endocrine, autonomic, and immune responses to stress through actions in the brain and periphery.

The mammalian CRF peptide family includes CRF, urocortin (Ucn) 1, urocortin2 and 3. CRF and urocortins exert their biological actions by stimulating two G protein-coupled receptors, CRF1 and CRF2, which display different ligand specificity. CRF has high affinity for the CRF1 receptor subtype and lower affinity for the CRF2 receptor. Ucn1 has equal affinity for both receptor subtypes. Ucn2 and Ucn3 interact only with CRF2 receptor subtype.

Several non-selective and selective CRF receptor antagonists are available right now. Alpha-helical CRF(9-41), D-Phe12CRF(12-41), astressin, and astressin-B are non-selective CRF receptor antagonists. CP-154,526, antalarmin, NBI 27914, NBI 35965, NBI 30775/R121919, DPM 696, CRA 1000, SN003, and SR125543A are selective CRF1 receptor antagonists. Antisauvagine-30 and astressin2-B are selective CRF2 receptor antagonists.

CRF is involved in stress-related gastrointestinal dysfunctions. A stressful event (physical or psychological) perceived by the brain triggers the release of CRF from the brain. Centrally released CRF activate the autonomic nervous systems (including both the parasympathetic and sympathetic nervous systems), which then sends information to the enteric nervous system (ENS) within the gut wall. The ENS determines to stimulate or inhibit motility (depending on the region) and stimulate secretion, causing the symptoms of diarrhea, cramping, bloating, abdominal pain, and urgency. These symptoms mimic the symptoms of irritable bowel syndrome.

Most studies concern central mechanisms whereby a stressful event influences the gut. Recent studies showed that peripherally administered CRF and Ucns also mimic the effects of stress on gastrointestinal functions. Peripherally injected CRF and Ucns can't pass blood brain barrier, thus they more likely act at the peripheral sites, e.g. the ENS. However, the peripheral mechanisms of CRF action and whether it plays a role in stress-induced gastrointestinal dysfunction are largely unknown.

S. Liu, continued

The aims of our study are: (1) to use double-stranded RNA (dsRNA)-mediated RNA interference (RNAi) to silence the expression of CRF in the rat colon and generate a tissue-specific CRF knockdown phenotype; (2) to determine the effect of CRF knockdown on colonic motility, mucosal secretion, and mucosal permeability under normal conditions; and (3) to determine the effect of CRF knockdown on stress-induced changes in gastrointestinal motility, mucosal secretion, and mucosal permeability.

Laser capture microdissection (LCM) was used to capture myenteric ganglia from cross-sections of the rat colon. Forty myenteric ganglia were captured and used for RT-PCR. CRF mRNA expression was found in the myenteric ganglia of the proximal and distal colon. Beta-actin was used as an internal control. During LCM, it was possible that contaminating cells (i.e. smooth muscle cells) might also been captured. To rule out the possibility that CRF mRNA was from smooth muscles, circular muscles were collected and used for RT-PCR. No CRF mRNA was found in circular muscles. The relative CRF mRNA levels in the myenteric ganglia were similar in the proximal and distal colon.

CRF-immunoreactivity was found in the cell bodies of the enteric neurons and varicose nerve fibers in both the myenteric and submucosal plexuses in the rat, mouse and guinea pig colon.

DsRNA-mediated RNA interference was used to silence CRF expression in the rat colon. DsRNA for beta-globin serves as a control. On day 0, rats were anesthetized with isoflurane. A midline laparotomy was performed. The proximal colon was exteriorized. A reference suture was placed in the colon wall at about 5 cm away from the ileocecal junction. DsRNA (20 μg) for either beta-globin or CRF was mixed with 1.5 ul lipofectamine 2000 and was injected intramuscularly into the colon wall. DsRNA was injected at two sites, each was 1.5 cm away from the reference suture. The abdomen was closed and rats were allowed to recover. On day 4, rats were sacrificed. Two colon segments were collected from the regions proximal and distal to the suture. One segment was processed for immunofluorescence analyses for CRF protein expression. The other segment was snap-frozen for real-time RT-PCR analysis of CRF mRNA levels. All other functional studies were also carried out on Day 4.

Injection of CRF dsRNA caused 53% decrease in CRF mRNA levels in the rat colon within 4 days of CRF dsRNA injection. Injection of CRF dsRNA resulted in dramatic decrease of CRF immunfluorescence intensity in both the myenteric (81%) and submucosal (85%) plexuses. These results confirmed that treatment with CRF dsRNA effectively knocked down CRF expression in the rat colon.

Previous studies suggested that systematic administration of CRF stimulates colonic motility and fecal pellet outputs. Thus, we measured fecal pellet outputs over 24 hours every day for 4 days after dsRNA injection. Surprisingly, knockdown of endogenous CRF had no effect on the total number of fecal pellet output over 24 h after dsRNA injection. This suggested that CRF might not participate in regulation of colonic motility under basal conditions.

To determine the effect of CRF knockdown on stress-induced changes in colonic motility, mucosal

S. Liu, continued

secretion, and mucosal permeability, four days after dsRNA administration, half of the animals were exposed to restraint stress for 2 h and the other half of the animals were kept in control environment. Fecal output was monitored as a measurement of colonic transit. In rats treated with control dsRNA, restraint stress induced a significant increase in fecal output when compared to non-stressed animals. Treatment with CRF dsRNA did not change fecal output during the 2h period under non-stress condition; however, it prevented restraint stress-induced increases in fecal output.

In Ussing flux chambers, baseline values for the short-circuit current were measured as an indicator of ion secretion. In rats treated with control dsRNA, restraint stress increased baseline Isc. Treatment with CRF dsRNA did not change baseline Isc under non-stress condition, however, it significantly inhibited restraint stress-induced increases in baseline Isc.

Trans-epithelial tissue conductance was measured as an indicator of ion permeability. In rats treated with control dsRNA, restraint stress increased baseline tissue conductance, indicating increased colonic ion permeability. Treatment with CRF dsRNA did not change baseline tissue conductance under non-stress condition, however, it significantly inhibited restraint stress-induce increases in tissue conductance.

To summarize, neurons in the myenteric and submucosal plexuses of the rat colon express CRF mRNA and immunoreactivity. Injection of dsCRF into the rat colonic wall effectively silences basal CRF expression. Control dsRNA treatment does not affect CRF expression. Knockdown of CRF has no effect on colonic motility, ion secretion, and ion permeability under basal conditions. Knockdown of CRF attenuates restraint stress-induced acceleration of colon transit and increase of mucosal secretion and ion permeability.

Post Infectious-IBS and IBD-IBS: A Conceptual Model

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Michigan State University

It is not uncommon for clinicians to encounter conditions that defy the traditional distinction between functional and organic disorders. This "blurring of boundaries" can occur with post-infectious irritable bowel syndrome (PI-IBS), a subset of irritable bowel syndrome (IBS), and a newly recognized entity called inflammatory bowel disease-irritable bowel syndrome (IBD-IBS). Characteristic symptoms include pain and diarrhea that are disproportionate to the observed pathology, microscopic inflammation, and often a co-association with psychological distress. A previous initiating gastrointestinal (GI) infection is required for PI-IBS and can be assumed for IBD-IBS. We discuss the growing evidence for the overlapping features of these two disorders in terms of alteration of gut flora, immune dysregulation, and the role of stress. A unifying model of PI-IBS and IBD-IBS is proposed that may have important clinical and research implications.

PI-IBS develops in 3 to 30% of bacterial gastroenteritis (GI) cases and usually manifests itself as diarrhea predominant IBS (IBS-D). The development of PI-IBS is associated with: (1) the severity of the gastroenteritis, (2) the patient's psychological distress (anxiety, depression, hypochondriasis, adverse life events), (3) the persistent presence of inflammatory cells (CD 3/8 T-lymphocytes, IL-1 beta expression, mast and EC cells), and (4) microscopic inflammation but normal endoscopic appearance. It serves as an ideal example of brain-gut interactions, as infection-induced physiologic changes (such as mucosal inflammation and dysmotility leading to visceral hypersensitivity) are not sufficient to explain GI symptoms experienced in PI-IBS. In fact, psychologic distress at the central nervous system level in addition to physiologic dysfunction is necessary for the development of PI-IBS. Psychosocial factors have an overarching modulating effect on symptom development in PI-IBS.

Co-occurrence of IBS symptoms in mild or inactive IBD has been observed when symptoms of bloating, diarrhea, anorectal pain, and fecal incontinence occur with minimal or no observable inflammation. From an epidemiological standpoint, an estimated 10 to 15% of the population has IBS, and the same proportion with IBD can have IBS. In addition, infection can trigger PI-IBS in the IBD population. During IBD remission, IBS symptoms persist at a rate that is 2 to 3 times higher than for the normal population. At least one functional GI disorder (FGID) has been found in 82% of patients with inactive IBD over the last year. In one study, about half the patients thought to have pouchitis after surgery in ulcerative colitis (UC) were later diagnosed as "irritable pouch syndrome". Functional GI symptoms can occur in IBD patients before disease onset, during active disease when symptoms are out of proportion to inflammation, and during periods of quiescence or even remission. Also, the severity of symptoms in active IBD may not always correlate with severity of disease, and patients may report symptoms out of proportion to the IBD disease activity. Abnormal motility, visceral hypersensitivity, and psychosocial factors all may play a role in the development of functional GI symptoms in IBD patients. In UC, there is reduced colonic activity with meals and opiate stimulation, associated with functional constipation. In celiac disease (CD), there is increased small intestinal motility beyond active disease, associated with functional diarrhea. CD patients in remission who experience IBS-like symptoms when compared with those without these symptoms have persistently increased levels of colonic tryptophan hydroxylase, suggesting a possible role of persistently increased serotonin in the visceral hypersensitivity of patients with IBD-IBS.

M. Grover, continued

Serotonin plays a pivotal role in the clinical expression of IBS. The pathogenesis can also include other issues related to IBD, such as sub-acute obstruction, fibrous obstruction, and bile salt malabsorption.

The relationship of psychologic factors to IBD is complex. The general thinking among physicians has been that stress contributes to the exacerbation of IBD but not to the etiology or onset of the condition. However, more recent studies suggest that psychologic stress or depression may play a role in the overall natural course of IBD. The presence of IBS-like symptoms in patients with IBD can be predicted by the degree of anxiety, depression, and general well being. Patients with CD have been shown to have greater psychologic disturbances than those with UC. Up to three fourths of IBD patients believe their psychological state contributes to the course of their disease. Stress can affect illness behaviors, such as physician visits independent of disease activity. In a study of 1000 patients with IBD, the frequency of physician visits was predicted primarily by psychosocial factors, whereas disease activity and symptom ratings were not predictive of such visits. As the biological mechanisms resulting from psychological stress are evolving, stress is becoming a more or less accepted risk factor in IBD.

Given these observations, we propose a unified understanding of PI-IBS and IBD-IBS which suggests: (1) both are triggered by bowel infection, (2) the etiology involves altered mucosal immune function, (3) stress activates immune response (increased permeability, effects on HPA axis via CRF, dysautonomia), (4) involves altered bacterial flora, and (5) psychosocial factors affect the disease process. By using a biopsychosocial construct, we propose a unifying hypothesis for the development if IBD-IBS and PI-IBS. There may be a common genetic predisposition that contributes to enhanced responses to life stress via alteration of HPA (hypothalamic–pituitary–adrenal) function and its possible effects on susceptibility to gut infection. The altered response to life stress and the development of infection can both produce immune dysfunction and alter microbial flora, which can lead to increased inflammation via serotonergic and/or mucosal cytokine activation. These physiological effects on gut mucosa can then produce the symptoms of pain and diarrhea consistent with these conditions. Finally, the presence and degree of these symptoms are influenced by life stress, abuse, maladaptive coping, and other psychosocial factors that amplify the symptom experience via alterations in central pain regulatory systems such as the anterior cingulate cortex.

The therapeutic implications of these findings are (1) to avoid mislabeling patients as “refractory IBD” and potentially escalating IBD therapy, which may have minimal or no effect on the functional symptoms; and (2) to consider using antidepressants and behavioral treatments (cognitive behavioral therapy, hypnosis) for IBD, which is already well known in the field of IBS. As the evidence for the commonality of these two conditions grows, we need to move away from the limitations of the functional-organic dichotomy toward a more integrated biopsychosocial construct that will ultimately improve physician and patient satisfaction.

[I would like to thank Drs. Douglas A. Drossman and Hans Herfarth for their valuable insight in this area and help in preparation of the manuscript, which has been published in the perspective section of the journal Clinical Gastroenterology and Hepatology.]

Gene Environment Interactions in IBS: A Prospective Study of Post-Infectious IBS

Reuben Wong, MD; William Whitehead, PhD

Post-Infectious IBS (PI-IBS) has been previously documented in studies of patients following bacterial gastroenteritis (GE) and incidences range from 9-30%. Factors favoring the development of PI-IBS include severity of the infectious episode, host factors, and psychological factors within individual patients. Furthermore, several studies into the genetics of IBS have identified a number of genes, such as IL10-1082, TNF-a, and SCN5A. A pilot project using a gene chip consisting of 3,300 SNPs across approximately 320 genes that mediate pain and inflammation has identified a number of genetic loci that also exist in IBS patients.

Our hypothesis is that, in PI-IBS patients, it is a combination of the environment (in this case, a pathogen that caused the inflammatory process in the GE) and predisposing genes (very likely those that mediate inflammation) that need to be present together to result in the phenotype that is PI-IBS.

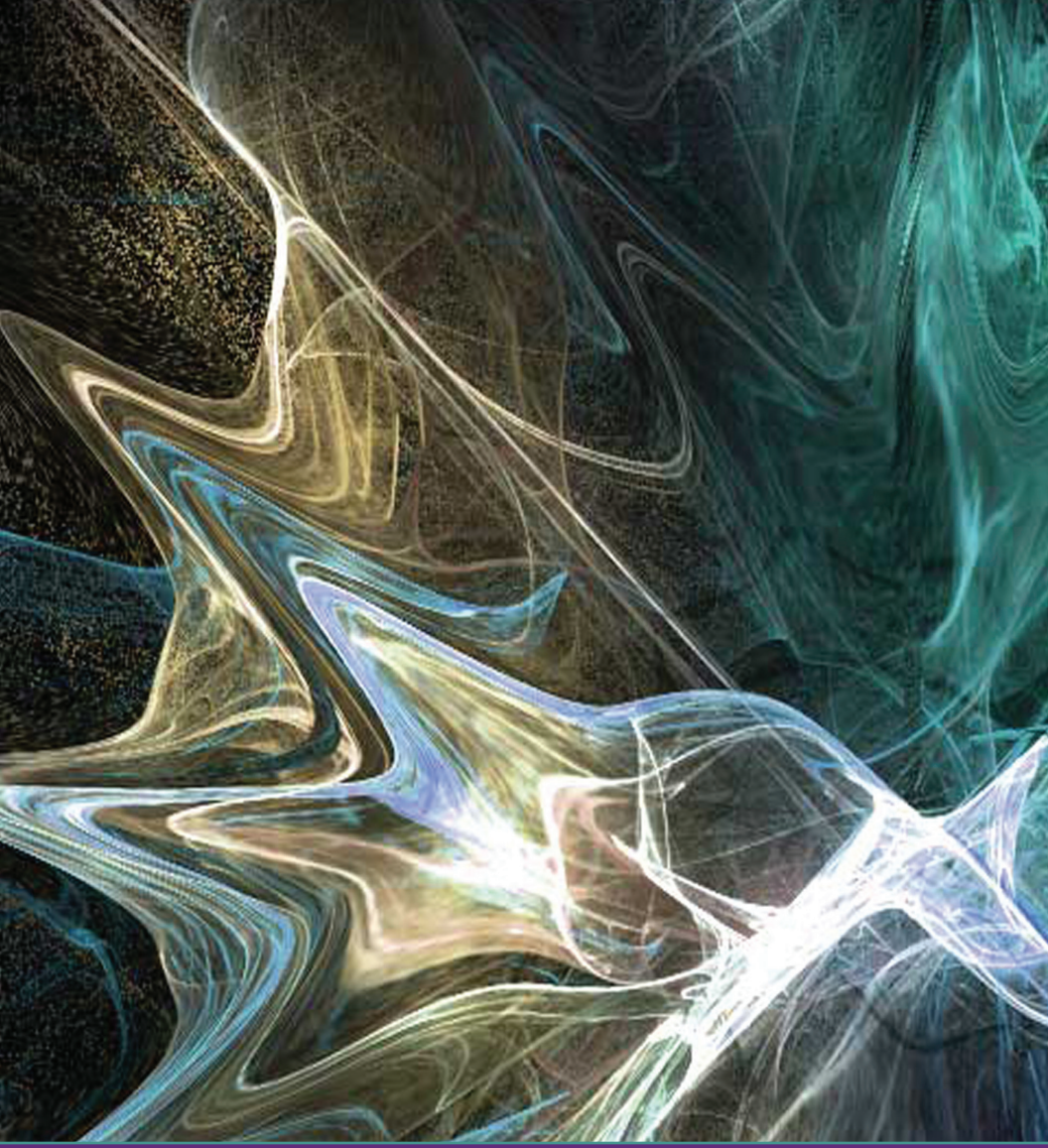
The aims of our study are: (1) to identify genetic markers associated with development of PI-IBS, (2) to evaluate the concept of gene-environment interaction, and (3) to investigate if there are other FGIDs triggered by a bacterial gastroenteritis.

We are using a prospective follow-up study design. In collaboration with the North Carolina Department of Public Health (NCDPH), we hope to contact 2000 individuals with a case of confirmed bacterial gastroenteritis. Controls for our study will be infected individuals who do not develop IBS.

At baseline, we will collect data on demographics, pre-existing illnesses, and acute GE symptoms. Questionnaires include: BSI-18 (psychological characteristics), Rome III (diagnosis of IBS), and IBS Severity Scale (symptom severity). DNA will be collected via a salivary specimen. We will follow the study subjects for one year for development of FGIDs (at 3, 6 and 12 months). All aspects of the study will be conducted by mail.

The outcome of primary interest is the identification of predisposing genes, by comparing patients with controls and identifying SNPs. We will also look for moderators of the gene-environment interaction: (1) psychological characteristics, (2) host characteristics (such as gender), and (3) characteristics of the gastroenteritis (such as clinical severity and bacterium involved). Finally, we will conduct exploratory analyses: (1) comparing genes identified in PI-IBS patients with those of de novo IBS patients (patients whose IBS is not considered post-infectious) and (2) looking for functional GI disorders other than IBS.

Our goal is to understand why some patients develop PI-IBS while others recover fully. Our hypothesis is that following an episode of GE there are genetic factors within individuals that might predispose or protect them from developing IBS. Hence, the idea of gene-environment interaction influencing disease development and expression.



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