Fatigue and Co-occurring Symptoms in Women with Irritable Bowel Syndrome

1. Summary of Project Aims

Introduction

Irritable bowel syndrome (IBS) is a common functional gastrointestinal (GI) disorder that is characterized by abdominal pain or discomfort and changes in bowel movement (Hungin, Chang, Locke, Dennis, & Barghout, 2005; Drossman & Dumitrascu, 2006; Yao et al., 2012). Complex symptoms such as abdominal pain, psychological distress and fatigue are experienced in patients with IBS (Hulisz, 2004). To date, the etiology of IBS is poorly understood. Multiple factors including genetics have been implicated in symptom phenotypes, all of which may be part of the pathophysiology of IBS (Saito, 2011).

Fatigue is one of the most common symptoms reported by patients with IBS (Lackner, Gudleski, DiMuro, Keefer, & Brenner, 2013). In patients with IBS, fatigue frequently co-occurs with abdominal pain, depression, and anxiety (Han & Yang, 2016; Lackner et al., 2013). Strategies for patients with IBS that specifically focus on fatigue management are lacking. The challenge is separating fatigue from the other co-occurring symptoms (i.e., abdominal pain, depression, and anxiety). It has been suggested that fatigue is part of a symptom cluster in individuals with IBS—a cluster that also includes abdominal pain and psychological distress (Lackner et al., 2013; Simren, Svedlund, Posserud, Bjornsson, & Abrahamsson, 2008; Hausteiner-Wiehle & Henningsen, 2014; Witthoft, Hiller, Loch, & Jasper, 2013). One potential etiologic factor that could explain the clustering of symptoms is genetic polymorphisms makeup of the individual (Dinan, Cryan, Shanahan, Keeling, & Quigley, 2010; Saito, 2011).
GI and psychological distress symptoms are associated with serotonin and catecholamine pathways in IBS (Dinan et al., 2010; Fukudo & Kanazawa, 2011; O’Mahony, Clarke, Borre, Dinan, & Cryan, 2015). In the serotonin pathways, tryptophan hydroxylase (TPH) as the rate-limiting enzyme in serotonin biosynthesis (Allegri, Costa, Ragazzi, Steinhart, & Laresio, 2012; Brown et al., 2011) and serotonin transporter gene, as a gene of protein that is responsible for the reuptake of serotonin into the presynapse (SERT) (Canli & Lesch, 2007; van Kerkhoven, Laheij, & Jansen, 2007) are associated with IBS symptoms. In the catecholamine pathways, the catechol-O-methyltransferase (COMT), as one of several enzymes that degrade catecholamines (Bisogni, Pengo, Maiolino, & Rossi, 2015), is associated with symptoms in IBS. Although the mechanisms of fatigue in IBS remain largely unknown, serotonin and catecholamine-related genes are associated with fatigue as well as symptoms of IBS (Hickok, Morrow, McDonald, & Bellg, 1996; Parker, Wessely, & Cleare, 2001). Therefore, the polymorphisms of serotonin and catecholamine may be important to understand fatigue and its co-occurring symptoms (i.e., the symptom cluster of fatigue, abdominal pain, depression, and anxiety) in IBS patients.

For effective management of fatigue in IBS, a better understanding of its characteristics including biological mechanisms, together with its symptom clusters, is important. To the best of our knowledge, no other studies have conducted this line of research to date.

Study Aims
(1) if distinct latent classes of IBS patients could be identified based on categories of severity of the symptom cluster of fatigue, abdominal pain, depression, and anxiety.

(2) if these latent classes differed on patient characteristics (e.g., sociodemographics, clinical characteristics, symptoms, life impact variables).

(3) if genetic polymorphisms of TPH, SERT and COMT were associated with single symptoms (i.e., fatigue - exploratory, abdominal pain, depression and anxiety - confirmatory).

(4) if these genetic polymorphisms were associated with the latent class membership.

2. Theoretical/Conceptual Framework

The conceptual framework is the biopsychosocial model (Tanaka, Kanazawa, Fukudo, & Drossman, 2011, p. 133). This framework illustrates the relationships among personal/biological variables; psychosocial, physiological, and IBS symptom variables; and life impact variables.

3. Methods

Design, Procedures and Sampling

This study is a secondary analysis of a baseline symptom data collected over 28 days from two previous randomized controlled trials (Study-1 and Study-2) (Jarrett et al., 2016; Jarrett et al., 2009). Participants had to have a diagnosis of IBS, be between 18 and 70 years of age, and met the Rome-II (Study-1) and Rome-III (Study-2) criteria for IBS. Rome II criteria included - at least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two or more of the following: improvement with defecation, onset associated with a change in frequency of stool, onset associated with a change in form of stool; while Rome III criteria included - recurrent abdominal pain or discomfort at least 3 days/month in last 3 months associated with two or more of the symptoms aforementioned above (Drossman & Dumitrascu, 2006). Participants were excluded for co-existing GI pathology (e.g.,
inflammatory bowel disease) or surgery; renal or reproductive pathology (e.g., endometriosis); or select medications (e.g., antibiotics, anticholinergics, narcotics, iron supplements). After participants were recruited, orientation to questionnaires was given at the first study visit, and each participant underwent a screening for eligibility. After obtaining informed consents including genetic data collections from participants, eligible participants came to the research office and they were oriented to the study, and completed baseline questionnaires. Participants had blood drawn for genomic analyses. At home they completed the daily diary each evening for 28 days.

Since both randomized controlled trials (Jarrett et al., 2016; Jarrett et al., 2009) had similar protocols, recruitment approaches, and sample characteristics conducted by the same research team and in the same research settings, we combined data from both studies. Gender-related differences in abdominal pain, fatigue, and psychological symptoms are apparent in patients with IBS, but women experienced these symptoms more severely and frequently than men (Cain et al., 2009; Kroenke & Spitzer, 1998). Thus men were excluded in this study. In addition, to minimize racial/ethnic bias, only Caucasian women, which were the majority of participants, were included. A total of 249 eligible Caucasian women with IBS were included for this proposed sample.

**Measures**

- Demographics and symptom characteristic questionnaires.
- Daily diary to assess daily fatigue, abdominal pain, depression, and anxiety.
- Composite International Diagnostic Interview (CIDI) to assess previous major depression disorders, and global anxiety disorders.
- Brief Symptom Inventory (BSI) to assess current depression and anxiety.
- Cognitive Scale for Functional Bowel Disorders (CSFBD) to assess cognitive beliefs related to functional bowel disorder.
• Work productivity and activity impairment questionnaire (WPAI) to assess the impact of IBS on work and other regular activities.
• IBS Quality of Life (IBSQOL) to assess health-related QOL.
• Genes: DNA was isolated from blood using buffy coat preparation, Single nucleotide polymorphisms (SNP) were genotypes and candidate SNP were selected based on the previous literature. COMT Val158Met genes were selected. SNPs from existing dataset were rs4537731, rs684302, rs211105, and rs1800532 of TPH1; rs4570625 of TPH2; rs25531 of SERT; and rs4680 of COMT.

**Statistical Analyses**

Descriptive statistics were used to calculate the mean and standard deviation, and the total number and percentage of outcome variables. The z scores were used for all analyses. Data analysis was conducted with Mplus Version 7.4 for latent class profile analysis (LCPA) to identify latent class membership, and latent class group comparisons were conducted with Chi-square test and ANOVA. Data analysis was performed with IBM SPSS Statistics for Windows, version 19.0 (SPSS, Inc., Armonk, NY: IBM Corp, USA). A *p* value ≤ .05 was considered statistically significant. All tests were two-tailed.

**4. Summary of Findings**

**Latent Class Membership**

Using an LCPA, three distinct latent classes of IBS patients were identified. There was no clinical cut point for interpreting the levels of symptom severity, so the subgroups were assigned names based on tertiles of percentage of days with moderate to very severe symptoms (0 % ≤ low < 33%, 33% ≤ medium < 66%, and 66% ≤ high ≤ 100%). Class 1 (n = 158, 53.2% of total participants) was labeled “low severity,” Class 2 (n = 70, 23.6%) was labeled “medium severity,”
and Class 3 (n = 21, 7.1%) was labeled “high severity.” Classes 1 and 2 had a relatively low level of depression compared to fatigue, abdominal pain, and anxiety.

**Differences in Patient Characteristics**

Patients in Classes 1 and 2 had similar demographic characteristics, but patients in Class 3 (the high severity class) were less often married or partnered compared to patients in the low and medium severity classes ($p = .032$). In addition, annual personal income was higher among patients in Class 1 (low severity) than in Classes 2 and 3 ($p = .004$). Age, education, employment status, and type of job were not statistically significantly different across the classes.

**Severity of GI symptoms and psychological distress**

Significant differences between latent classes were observed for most of the symptoms. Of these, the symptoms of stress ($F = 98.9$), sleepiness ($F = 42.3$), and global severity index ($F = 61.6$) differed significantly across the latent classes.

**Life impact variables**

The most negative cognitive beliefs, the lowest QOL scores, and the highest work and life interference were found in Class 3 (high severity). Of note, the overall HRQOL score ($F = 33.1$) and the subscales for sleep ($F = 59.4$) and social role ($F = 49.4$) differed most significantly across the classes. The sleep and social role subscale scores were markedly poorer in the high severity class (Class 3) compared to the other two classes.

**Genetic Associations with Single Symptoms and with Identified Latent Class Membership**

There were significant mean differences in severity of fatigue by polymorphism of TPH2 SNP rs4570625. Fatigue severity was higher in patients with TT homozygous, compared to the G allele carriers (i.e., GG and GT genotype). Abdominal pain differed significantly by polymorphism of TPH1 SNP rs4537731. Abdominal pain was higher in G allele carriers (AG and
GG genotype) than in the patients with AA homozygous. No significant differences were observed in the severity of single symptoms (i.e., fatigue, abdominal pain, depression, or anxiety) by SERT and COMT genotype. None of the genetic polymorphisms of SERT, TPH, or COMT were significantly associated with identified latent class membership.

Conclusions

This is the first hypothesis-generating study in IBS (a) to identify three distinct subgroups of women with IBS based on the severity of fatigue, abdominal pain, depression, and anxiety using an LCPA; and (b) to explore the linkages of potential genetic markers with fatigue and with the latent class subgroups. This study uses an LCPA to provide strong support for presence of subgroups of IBS patients with fatigue and co-occurring symptoms and to explore genetic associations in IBS with both fatigue alone and in a symptom cluster that includes fatigue. The patients in the high severity symptom class had lower annual incomes; were less likely to be married or partnered; had more severe levels of psychological distress, more sleepiness during the day, and more stress; and were more likely to experience work and daily life interference as well as lower QOL.

5. Recommendations

This study suggests a comprehensive assessment for IBS patients with fatigue and co-occurring symptoms. In addition, understanding underlying biological mechanism of fatigue, and its symptom cluster are further required to manage fatigue in IBS. Lastly, development of effective fatigue management considering other co-occurring symptoms and QOL is recommended as future studies.

References


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