



Major Depressive Disorder and the “Leaky Gut” Post Cholecystectomy

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Abstract

Major Depressive Disorder (MDD) is the most common mental health disorder in the United States as well as all over the world. According to the CDC, MDD affects more than 16.1 million American adults, or about 6.7% of the U.S. population age 18 and older in a given year. People suffering from MDD experience sadness, anhedonia, feelings of guilt, loss of energy, lack of concentration, loss in appetite, and psychomotor symptoms with possible suicidal ideation. It is a mental disease that unfortunately is still marginalized and ostracized in society today. We wrote this case report in hopes of raising awareness for depression and how it can affect individuals through secondary pathways.

Background

The role of the gut microbiome and its correlation with the production and dissemination of serotonin is still a relatively novel concept and one that has not been given its due amongst the scientific community. By showing how intrinsic the enteric nervous system and its maintenance is to promoting the production of various neurotransmitters involved in mental health diseases, we hope to make its role intricate to the understanding of mental illness and its potential treatment going forward. Gastric acid is involved in the primary function of preparing food for digestion and absorption by the intestine. Acid production is a central component of the stomach's contribution to digestion. Low gastric acid means higher susceptibility to food poisoning. Proton pump inhibitors use can cause diarrhea, enteric infections, and alter the gastrointestinal bacterial population by suppressing the gastric acid barrier leading to Small Intestinal Bacterial Overgrowth (SIBO) [1]. Normally when food leaves the stomach, it is acidic, and it leads to changes in pH and the pancreas and gallbladder release pancreatic juice and bile but if the stomach is not producing gastric acid, the gallbladder stops releasing bile. Prolonged PPI treatment produces bowel symptoms and symptoms such as cramps, hypotension and hypomagnesemia. The gallbladder has a very important role to play as the same nutrients that work in the gallbladder produce bile. Therefore, when a patient undergoes cholecystectomy, they develop an imbalance of neurotransmitters. Bile makes glycine and taurine and when it is depleted we cannot absorb calcium and this leads to hypocalcemia. Gallbladder bile rinses bacteria off the intestinal lining and the bacteria sticks to the wall increasing its bowel population leading to gastrointestinal symptoms such as malabsorption. This now increasing enteric bacterial population leads to the formation of the “leaky gut” bacteria causing inflammation and depression by increased intestinal permeability associated with an upload of Lipopolysaccharide (LPS) translocation which induces depression symptoms [2]. Hence gut microbiota and probiotics alter behavior and brain neurochemistry.

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Case Presentation

In the case of our patient we had a 62-year-old female who had suffered from years of Gastroesophageal Reflux Disease (GERD) as well as obesity class 1 with a BMI of 33. Our patient also complained of alternating bowel movements, abdominal cramps, dyspepsia, and years of H2 receptor blockers and PPI use, as well as recurring cholecystitis and its affiliated symptoms. In March of 2017 our patient underwent a cholecystectomy after feeling months of gastric discomfort and dyspepsia and had finally had enough and could no longer further prolong her discomfort. Her ultrasound imaging and lab results pointed to a diagnosis of cholelithiasis with concurrent cholecystitis and she presented to the ER with intractable abdominal pain in the right upper quadrant. After initial stabilization with fluids, antibiotic treatment, and pain management, the patient in agreement with the consulting Gastrointestinal (GI) physician, decided to have a cholecystectomy

performed as she had been struggling with cholecystitis for years now. The procedure was done laparoscopically with no post operational complications. Three months later the patient presented with severe fatigue and weight gain and the recurrence of her pre-cholecystectomy symptoms. Additionally she did not feel like leaving her house, stopped socializing with her friends, felt a loss of energy and just seemed to stop caring about things. She was taken to her primary care physician, who referred her back to her GI doctor, and recommended a psychiatry consult. After standard imaging and pertinent lab results conducted by the GI physician failed to show any causal gastro intestinal factors that could be contributing to our patients state she visited a psychiatrist who, based on her presenting symptoms, diagnosed her with moderate depression secondary to the life stresses compounded by her recent surgery. The purpose of this report is to theorize how her enteric system undergoing chronic inflammation along with her cholecystectomy further exacerbated the inflammation and ultimately lead to her depression, highlighting the “Leaky Gut” phenomenon.

Past medical history

Hyperlipidemia, Gastroesophageal Reflux Disease, Hypertension, Gastritis and Obesity

Past family history

The patient’s father and mother both had a history of hypertension, gastroesophageal reflux disease and hyperlipidemia. Both parents now deceased, died of cardiac causes.

Past social history

Patient denies use of alcohol, nicotine and illegal drugs.

Differential diagnosis

- Social Anxiety
- Gastroesophageal Reflux Disease
- Post-cholecystectomy Syndrome
- Cholecystitis
- Cholelithiasis
- Factitious Disorder
- Munchausen Syndrome
- Major Depression Disorder
- Generalized Anxiety Disorder
- Panic Disorder
- Primary Hypertension
- Secondary Hypertension

Treatment

The patient besides mild pain following surgery felt well post-surgery and had hoped her symptoms of abdominal pain, continuous GERD, IBS, and nausea would get better. She was prescribed cholestyramine and esomeprazole to deal with any residual symptoms post-surgery. The patient was also scheduled to follow up with a dietician who prescribed a course of medical nutrition therapy individualized to our patient, and to follow up with her PCP to better manage her other chronic medical concerns and for medication reconciliation. The patient was advised to limit fat intake, increase dietary fiber gradually, and to avoid caffeinated and carbonated

drinks, chocolate, citrus products, spicy foods and to eat small meals. Due to a combination of factors including non-compliance with proposed dietary restrictions and inability to comply with her PCP’s instructions pertaining to maintaining a healthier lifestyle, our patient experienced a return of pre-surgical symptoms as well as a sudden loss of interest in activities of daily living and was diagnosed with moderate depression by a psychiatrist. The psychiatrist after a careful review of the patient’s file suggested a thorough course of Cognitive Behavioral Therapy (CBT), a modified and realistic diet in consultation with a dietician, a workout routine and therapy sessions relating to the patient’s depression and eating habits. After two months of little improvement, the patient was started on Wellbutrin XL by her psychiatrist keeping the associated weight gain with other antidepressants in mind. The patient was instructed to take Wellbutrin XL 150 mg once daily in the morning for the first 4 days after which she would start on Wellbutrin XL 300 mg once daily.

Outcome and Follow-Up

Although our patient was given the appropriate post-op care, she initially did feel better but then began to deteriorate to her pre-surgery levels in terms of symptoms and in addition developed this new feeling of being depressed all the time which could have been related to her non-compliance with the physician ordered lifestyle recommendations in terms of her diet and other appropriate lifestyle changes. After a psychiatric consult and initial assessment, the patient tried to be more adherent to the recommendations and hoped her CBT sessions, therapy, and new dietary guidelines coupled with exercise would alleviate her concerns yet she continued to feel depressed and continued to have abdominal symptoms similar to what she felt before she had her cholecystectomy. The patient was then prescribed Wellbutrin XL and advised to continue her CBT and follow her dietary, exercise, and healthy lifestyle recommendations. After an intense and strict adherence to her diet/exercise/CBT routine together with the medication the patient experienced mild relief within five months post-surgery, her abdominal symptoms had disappeared, and she had started to lose weight and felt happier. The patient started to socialize more and took up a proactive approach to bettering her eating habits and other lifestyle choices. The Wellbutrin XL initially started at 150 mg once a day was increased to 300 mg once today after the initial four day period and then maintained as the patient did not feel like there was any need for an adjustment.

Discussion

A dysbiotic state leads to increased intestinal permeability and allows contents such as bacterial metabolites and molecules as well as bacteria themselves to leak through the submucosa and into the systemic circulation, a phenomenon aptly named leaky gut syndrome [2]. In our digestive gut, sugar precursors *E. coli* & proteobacteria Bifidobacterial species act on the chorismite from where *E. Coli*, proteobacteria, *B. subtilis*, firm elves, mycobacterium and actinobacteria leads to formation of tryptophan which in the intestinal epithelial cells causes serotonin production in the gut. When the concentration of these bacteria is reduced due to antibiotics or PPI use, it decreases their quantity in the gut and the lack of bile post-cholecystectomy prevents the cleansing of the gut lining to get rid of the bad bacteria. This in part leads to less tryptophan and serotonin being produced in the enteric system, leading to depression. Tryptophan is synthesized from chorismite by members of several bacterial phyla including protein bacterium, actinobacterium & fircules. *E. Coli* can synthesize chorismite, a tryptophan precursor, which acts as a

branch point for microbial metabolic pathways consistent with this key role for bacteria. Antibiotics and PPI treatment alters tryptophan and undoes metabolism leading to less serotonin and melatonin in the brain. Tryptophan, tyrosine, and phenylalanine are made in the gut. When tryptophan is shuttled through the kynurenine pathway there is less tryptophan available to make serotonin and hence less serotonin in the gut available to be transported to the brain *via* the vagal nerve. Low bile, post-cholecystectomy, causes leaky gut as bile acid stimulates biliary lipid secretion due to their physical chemical properties. They can form mixed micelles together with biliary phospholipids which allows the solubilizing in bile of cholesterol and other lipophilic compounds. Mixed micelles also account for the emulsion of dietary fat and lip soluble vitamins in the gut, helping their absorption. Bile acids also facilitate intestinal calcium absorption. At the intestinal level, bile acids are known to modulate pancreatic enzyme secretion and cholecystokinin release. Moreover, they are potent anti-microbial agents that prevent bacterial over growth in the small bowel.

There is also a systemic IgM-mediated immune response in depression directed against LPS (which is part of the bacterial wall of gram negative bacteria) suggesting that bacterial translocation may play a role in the inflammatory and pathophysiology of clinical depression. Bacterial translocation indicates the presence of “leaky gut” or an increased permeability of the gut wall or loosening of the tight junction barrier [3]. Hyperactivity of the HPA axis is also one of the most reliable biological findings in patients suffering from major depression. Exposure to stress and cytokine responses may impair neuronal plasticity and stimulation of neurotransmission. Administration of exogenous IL-1b significantly enhances IL-1b levels in the Pre-frontal Cortex (PFC) and hippocampus and further increases Hypothalamic, Pituitary, and Adrenal (HPA) axis activity. Likewise, acute stress markedly increases IL-1b levels in the PFC, hippocampus and hypothalamus. Repeated stress sensitizes the HPA axis response to administration of exogenous IL-1b and possibly leads to depression [4].

The gut is composed of nerve tissues and uses neurotransmitters to communicate with the brain. The gut microbiota affects brain development and plasticity by secreting various neurotrophins and proteins, such as Brain-Derived Neurotrophic Factor (BDNF), synaptophysin and postsynaptic density [5]. Our brain has an

intimate connection with our gut *via* vagal nerve, which has hundreds of millions of nerves cells that regulate our digestive processes. This “second brain” in the gut is spread out throughout the entire length of the gut. This second brain has many sensors in the enteric nervous system. The connection between depression and the gut is integrative from serotonin in the gut and how it relates to serotonin in the brain. Many patients with depression complain of constipation. This might be due to 95% of our serotonin being produced and stored in the gut *via* enterochromaffin cells which leads to modulation of mood, appetite, and well-being. The serotonin in the gut is synthesized from the food that we ingest and the microbes that live in our gut that stimulate the production of serotonin. 60% of the production is due to the signals that come from the microbes in our gut. The serotonin cells are sandwiched between the cells that make the lining of the gut. The cells have vagal nerve association and the signal when the cell is activated goes to the brain *via* the vagal nerve from where it is delivered into the limbic system. This case study involves a patient with a long history of GERD treated with H2 antagonists, PPIs, and a host of other medications over the years who underwent a cholecystectomy. This was followed by symptoms of depression that required treatment with an antidepressant coupled with healthier lifestyle changes and dietary restrictions. This case study is being written to establish a possible connection between the gut microbiome and depression.

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