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EFFECTS OF ADVERSE CHILDHOOD EXPERIENCES ON SEROTONIN LEVELS IN THE PATHOGENESIS OF IRRITABLE BOWEL SYNDROME

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ABSTRACT

Irritable Bowel Syndrome (IBS) is a common and chronic functional gastrointestinal (GI) disorder with a poorly understood pathogenesis that presents with visceral hypersensitivity, gut microbiota alterations, and dysfunction of the brain-gut-microbiome axis. Early adverse life events causing alterations in the brain-gut-microbiome axis has been proposed as a possible etiological factor of IBS. The aim of this literature review is to investigate if early adverse life events (EALS) specifically cause the alterations in serotonin levels and the correlation to IBS type that is seen in the possible pathogenesis of IBS. In order to investigate this proposal, the case files of patients who were diagnosed with IBS when < 18 years old were pulled and the participants had their serum serotonin levels measured and were given questionnaires to retrospectively look at the correlation between serotonin, EALS, and IBS. In conclusion, findings indicate there is a strong correlation between EALS causing alterations in serotonin levels in the gut leading to the development of IBS. As research continues, the exact correlation between severity of IBS symptoms, type of IBS, serotonin fluctuations, gender, and other microbial factors in relation to serotonin need to be investigated.

KEYWORDS: Irritable bow syndrome, gastrointestinal, microbiome axis

1. INTRODUCTION

Irritable Bowel Syndrome (IBS) is a common and chronic functional gastrointestinal (GI) disorder that presents with visceral hypersensitivity, gut microbiota alterations, and dysfunction of the brain-gut-microbiome axis. IBS prevalence is estimated at 10-15%

throughout the globe with a range of 1.1 to 35.5% worldwide (Mishima et al., 2020). Women were found to have IBS 1.67 times more than men (Xiao et al., 2021). There are four different types of IBS: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), IBS with a mixed pattern (IBS-M), and unclassified IBS (IBS-U). Questionnaires regarding GI symptoms based on the Rome IV Criteria along with fecal condition and bowel habits are used to diagnosis IBS. Details pertaining to the pathogenesis of IBS remains unclear, there are multiple aspects including genetics, low-grade mucosal inflammation and immune activation post-GI infection, aberrant bile salt metabolism altered central nervous system (CNS), abnormal neurotransmitter pathways, alterations in gut microbiota, environmental factors, psychology, and increased gut mucosal permeability that could potentially play a role in the etiology of IBS (Mishima et al., 2021). Due to the heterogenous nature of IBS, it is most likely a mixture of genetic and environmental factors that play a role in the multifactorial etiology of IBS. This literature review serves to investigate if early adverse life events specifically cause the alterations in serotonin levels seen in the possible pathogenesis of irritable bowel syndrome.

Early Adverse Life Events

One of the most common risk factors for the development of IBS is early adverse life events (EALS), but the molecular mechanisms for how EALS causes IBS is unclear. EALS are anything that can cause trauma such as abuse, domestic violence, and mental illness (Joshee et al., 2022). Mental illness is defined as health conditions involving changes in emotions, thinking or behavior and can be associated with distress and functioning problems (American Psychiatric Association, 2023). Within the trauma category, EALS and the neurocognitive association with GI abnormalities have been discussed and provide a potential rationale for the disease-modifying effects of IBS.

Some studies have reported a higher prevalence of EALS in IBS patients compared to healthy controls while other studies have found no associations (Joshee et al., 2022). Studies with more structured and standardized questionnaires showed a stronger association between EALS and IBS while more subjective measures like self-reporting has a lower association (Joshee et al., 2022). One study found that a history of EALS was associated with two-fold higher odds of developing IBS and has a correlation with the severity of IBS symptoms such as poorer daily function, abdominal pain, and more healthcare services utilized. Another study found perceived severity of traumatic events and type of trauma increases odds of IBS

while confiding in others about your EALS was a protective factor (Ju et al., 2020). Most patients don't disclose EALS history to others, especially their doctors, and there is potentially no benefit in confiding EALS history due to the limitation on interpersonal barriers. Further research needs to be held on the factors (amount, depth, characteristics) associated with confiding in others that are most beneficial. Also, since this information was mainly taken from retrospective self-report studies, the results are based on associations, can't directly infer causality, and don't give a clear picture of the role EALS have in prenatal or infancy.

Increased odds of IBS with traumatic events could be due to the fear association with EALS. Peritraumatic fear was found to be an independent factor of IBS which has shown to cause dysregulated abdominal pain-related fear learning and memory processes mediated by the amygdala, cingulate cortex, prefrontal areas, and hippocampus. This in turn is associated with a greater emotional and physiological stress response leading to decreased resilience when recovering and adapting to stress positively. Stress via an altered autonomic nervous system (ANS) has shown to mimic the symptoms of IBS (Ju et al., 2020).

There is no known critical age of exposure that increases the risk of IBS development and there is a lack of data on temporal association between EAL and IBS symptom onset. Animal studies have helped to identify possible mechanisms that show the potential time period in which EALS are more likely to affect IBS development such as altered emotional state, increased stress response, and heightened visceral pain perception. As mentioned before, IBS is more common in women than men, but less is known about the sex differences in EALS and IBS. This could be due to lower sample size of men compared to women in studies or that men may underreport traumatic events or be less likely to confide in others (Ju et al., 2020). There is also no significant difference found in the levels of depression and anxiety among different IBS subtypes, but IBS patients have higher levels of depression and anxiety compared to controls; adequate psychological screening and psychotherapy need to be investigated for IBS patients (Hu et al., 2021).

About 50% of individuals who meet the diagnostic criteria for anxiety disorders have IBS and individuals with IBS have a threefold risk of meeting the criteria. In majority of IBS patients, CNS-related precipitants in early and adult life such as psychological trauma, stress, abuse, and maternal neglect have been identified. It has also been implied that gut dysfunction can precede mood disorders and even be a driver for them. The gut-brain axis plays an important

role in maintaining homeostasis throughout our bodies. There are a multitude of intrinsic and extrinsic factors that influence signaling along this axis and modulate both the functions of the enteric (ENS) and central nervous system (CNS). One study used the Hospital Anxiety and Depression Scale (HADS) to investigate the altered interaction between the gut microbiome, systemic neurohormonal activity, and stress in IBS patients, and no associations were found with anxiety and depression. The questionnaire has its limitations and doesn't cover the full spectrum of symptoms so further surveys and questionnaires need to be developed to fully investigate the correlation and causation (Mujagic et al., 2022).

Brain-Gut-Axis

Most aspects of GI physiology are under neural control via neurons and glia that span throughout the ENS. Although the ENS can regulate peristalsis in the gut independently from CNS input, there are factors extrinsic to the ENS like the brain, ANS divisions, gut microbiome, and gut associated immune system that modulate GI motility. It has been hypothesized that adequate gut function is critical for brain-gut homeostasis, but how the gut-brain communication occurs in health and disease remains an area of investigation in humans (Margolis, K.G, et al. 2021). Pathways of communication between the microbiota and brain to be investigated include endocrine (cortisol), immune (cytokines), and neural (Vagus, ENS, spinal nerve) pathways. Several gut microbes capable of synthesizing neurotransmitters (GABA, serotonin, noradrenaline, and dopamine) that act on target cells in the gut should be investigated. Lastly, neuroactive microbial metabolites like affecting epithelial cells, enteroendocrine cells and dendritic cells that modulate brain and behavior need to be investigated. Although there has been evidence in germ free mice supporting the concept of the microbiome being involved in the brain processes involved in stress hormone signaling, neural function, and neuroprotection, there is significant limitations to human translation of these findings. (Margolis, K. G., et al, 2021).

Aside from the evidence (or lack thereof) from strength and consistency of association, there is reasonable biological plausibility on how EALS might result in IBS development. For example, it is known that exposure to EALS affects the hypothalamic–pituitary–adrenal (HPA) axis directly or through the accumulation of epigenetic markers. Some animal studies show EALS-mediated methylation of glucocorticoid receptor promoters leads to HPA axis dysregulation (prolonged elevation of corticosteroids) and the development of hallmark features of IBS such as visceral hyperalgesia, reduced somatic analgesia, and increased

colonic motility development (Joshee et al., 2021). There is a possibility that these epigenetic changes may be passed onto any future offsprings of affected individuals – translating the effect of EALS into permanent genetic predispositions.

Serotonin

One of the most studied neurotransmitters in the IBS physiology is serotonin. Serotonin is a chemical messenger that plays a key role in our digestion, mood, learning, memory, happiness, and body temperature regulation. Around 90% of our serotonin is produced in our gastrointestinal tract while the other 10% is produced by the brain (Serotonin: What is it, Function & Levels, 2022), specifically, the 90% is produced in our Enterochromaffin cells (ECCs) (Margolis, K.G, et al. 2021). Alterations in the enteric mucosal and blood serotonin signaling has been demonstrated in adults and children with IBS which indicates a GI-initiated serotonergic dysregulation.

One study showed patients with IBS scored higher for anxiety, depression, and in increased stress response (IBS symptoms triggered by stress); 66% of IBS patients noted a strong relation between daily psychological stress and GI symptoms while 38% indicated IBS development after a stressful life event. In this same study, alterations in serotonin levels were found compared to healthy controls. In one of their previous studies, serotonin's metabolite, 5-hydroxyindoleactic acid (5-HIAA) was lower compared to healthy controls in all of IBS subtype as well as a lower 5-HIAA/5-HT ratio. The mechanisms behind altered plasma serotonin levels are still misunderstood but it's known that they modulate the CNS and by proxy, psychological and behavioral processes as well as key modulatory functions of the ENS such as motility, visceral perception, and intestinal secretion co-regulation (Mujagic et al., 2022). Most of the research has focused on the $5\text{-}HT_3$ and $5\text{-}HT_4$ serotonin receptors, which have shown effects on mood, motility, and abdominal pain (Margolis, K. G., et al, 2021).

In the intestinal epithelium, the termination of serotonin (5-HT) signaling relies almost exclusively on the serotonin reuptake transporter (SERT)-dependent translocation of 5-HT from the lamina propria. In biopsy specimens from patients with IBS compared to healthy individuals, there was a significant decrease in SERT expression. SERT is needed to deactivate serotonin that is released from ECCs (Vahora I.S., et al, 2020). Decreased SERT expression results in elevated serotonin levels in IBS patients which ultimately causes the diarrhea and discomfort (Vahora I.S., et al, 2020). Elevated SERT expression was seen in

IBS-C compared to IBS-D, causing a decrease and increase in serotonin levels of the gut, respectively (Vahora I.S., et al, 2020). There are a multitude of different factors like our microbiome and psychological factors that can also account for the increase and decrease of SERT and serotonin and more studies need to hone in on the possibly correlation (Vahora, I.S, et al., 2020). A lack of SERT expression in mice has shown increased intestinal motility, enhanced colonic secretion, and visceral hypersensitivity. (Gao J., et al, 2022).

In some patients, inadequate SERT expression causes serotonin to stay around longer inside, and trigger bowel changes seen in IBS. 5HT3 receptors found extrinsically are also critical for sending signals from gut to brain; if the bowels are exposed to painful stimuli like excessive stretching or contraction, patients with IBS are failing to use CNS down-regulating mechanisms which lead to the visceral pain and other IBS symptoms (GI Society, 2020). There is also a possibility that SERT may affect the metabolism of IBS due to polymorphisms although there is still controversy between the relationship of 5-HT, SERT gene, and IBS (Xiao, 2021). Throughout the literature, the exact mechanism for which SERT is expressed and regulated in the setting of IBS is unknown.

Another source talked about increased plasma levels of 5-HT in IBS patients throughout a series of meta-analyses which could be associated with a possible pathogenesis of IBS (Xiao et al., 2021). As we know, enteric 5-HT regulates gut peristalsis and secretion, inflammation and development of neurons and interstitial cells of Cajal while being related to pain, sensitivity, and reflexes via the activation of enterochromaffin and enteroendocrine cells (ECC) (Xiao, 2021). ECCs, mast cells, and 5-HT levels are significantly up-regulated in IBS patients compared with healthy controls and the degree of visceral pain and hypersensitivity is correlated with 5-HT release (Xiao, 2021). Other studies have shown possibilities of 5HT3 increasing motility and 5HT4 decreasing motility, but the exact mechanisms need to be studied (Vahora, I.S, et al., 2020).

Related to serotonin, there has been some interaction between tryptophan (TRP) metabolism, gut microbiota, and host immunity that has been researched regarding IBS. There is growing evidence showing TRP and its metabolites (kynurenines, serotonin, and melatonin) and its microbiome-modulated metabolites (indole, indolic acid, skatole, and tryptamine) have effects on the gut microbial composition, function, interface, and interactions between the host immune system and intestinal microbiota. Plasma serotonin levels were found to be decreased and TRP increased in germ free mice compared to normal animals. Stress-induced

increases in serotonin levels released by the brain is related to TRP Hydroxylase expression (Gao et al., 2018). There has also been a proposed hypothesis that the gut microbiota of IBS patients with depression may favor the TRP/serotonin metabolism along the KYN-produced pathway. This in turn would affect the TRP availability and serotonin levels in the brain; but this hypothesis is based on literature only and is poorly understood (Han et al., 2022).

Microbiome

Looking at our microbiome, the human GI tract has trillions of microorganisms that influence both health and disease. Our microbiota has key enzymes and metabolites that help absorb essential nutrients and vitamins that are important for development and function of our mucosal immune system. As a function overall, our microbiome has microorganisms that prevent invasive pathogens and maintain the gut microbial ecosystem. One study showed a common observation that microbial diversity in fecal samples from IBS patients are lower than healthy control subjects. There were also lower levels of fecal Lactobacillus and Bifidobacterium and higher levels of Escherichia coli and Enterobacter. Resident bacteria of our gut like Corynebacterium spp., Streptococcus spp., and Enterococcus spp., produce serotonin while other indigenous spore-forming bacteria regulate host serotonin biosynthesis. 5-HT was also found to play an important role in quorum sensing (QS), which is a density-dependent signaling mechanism in the microbiota, while 5-HT stimulates a QS-dependent virulence factor and biofilm production in pathobionts, and expands infection (Mishima et al., 2020).

Overall, these findings show that abnormalities in bowel transit and stool consistency in IBS patients alter gut microbial richness, composition, metabolic profile, and low-grade mucosal inflammation (Mishima et al., 2020). Another important implication worth noting for the IBS diagnosis is related to data showing nearly 50% of serum metabolites exhibit significant changes even when adjusting the linear influence of dietary habits. This means that there are some certain associations between metabolic dysregulation and IBS pathogenesis (Han et al., 2022).

Pharmacology

Next, the pharmacological and non-pharmacological treatments for IBS can help clue into pathogenesis. Some pharmacological agents targeting serotonergic pathways including 5-HT3 agonists, 5-HT4 antagonists, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and serotonin norepinephrine reuptake inhibitors (SNRIs). Other gut

microbiota interventions include probiotics, prebiotics, synbiotics, nonsystemic antibiotics, and elimination diets like the low FODMAP diet. Questions that can be answered related to the treatment include whether there is a specific therapy that can be used to regulate 5-HT or it's pathway in IBS patients (Mishima et al., 2021). Since there has been increasing attention on the use of probiotics, prebiotics, and synbiotics, the option of a fecal microbiota transplantation has been emerging but there are controversial results. This observation leads to the need for further evaluation because there can possibly be multiple different mechanisms for the pathogenesis of IBS if one person responds while another person doesn't in terms of treatment (Bonetto et al., 2021).

2. METHODS

The case files of male and female patients who were diagnosed with IBS when < 18 years old were pulled and contacted from GI clinics to see if they would participate in multiple questionnaires to see whether there is a potential correlation between serotonin, IBS, and early adverse life events. Subjects were compensated $100 for answering the questionnaires and getting their blood drawn to measure serum serotonin levels. The questionnaires given were the Retrospective Questionnaire, the Early Trauma inventory Self-Report Short Form (ETISR-SF), the Childhood Trauma Questionnaire-Short Form (CTQ-SF), Patient Health Questionnaire (PHQ-9) and General Anxiety Disorder (GAD-7). Patients were then asked if their serotonin levels could be taken via blood sample.

The ETISR-SF (Figure 1) is a 27-item questionnaire that assesses general traumatic experiences before the age of 18 as well as physical, emotional, and sexual abuse. Three other additional questions are at the bottom of the questionnaire which ask the reader to choose the event that had the greatest impact on their life and the other two measure their subsequent reactions to the event. Each question answered yes is given 1 point and each no is given 0 points.

The CTQ-SF (Figure 2) is a 28-item retrospective self-report questionnaire. It focuses on well-known child abuse and neglect and assesses the five dimensions of childhood maltreatment: sexual abuse, physical abuse, emotional abuse, physical neglect and emotional neglect. Questions are scored from 1 to 5 (1 being never true to 5 being very often true).

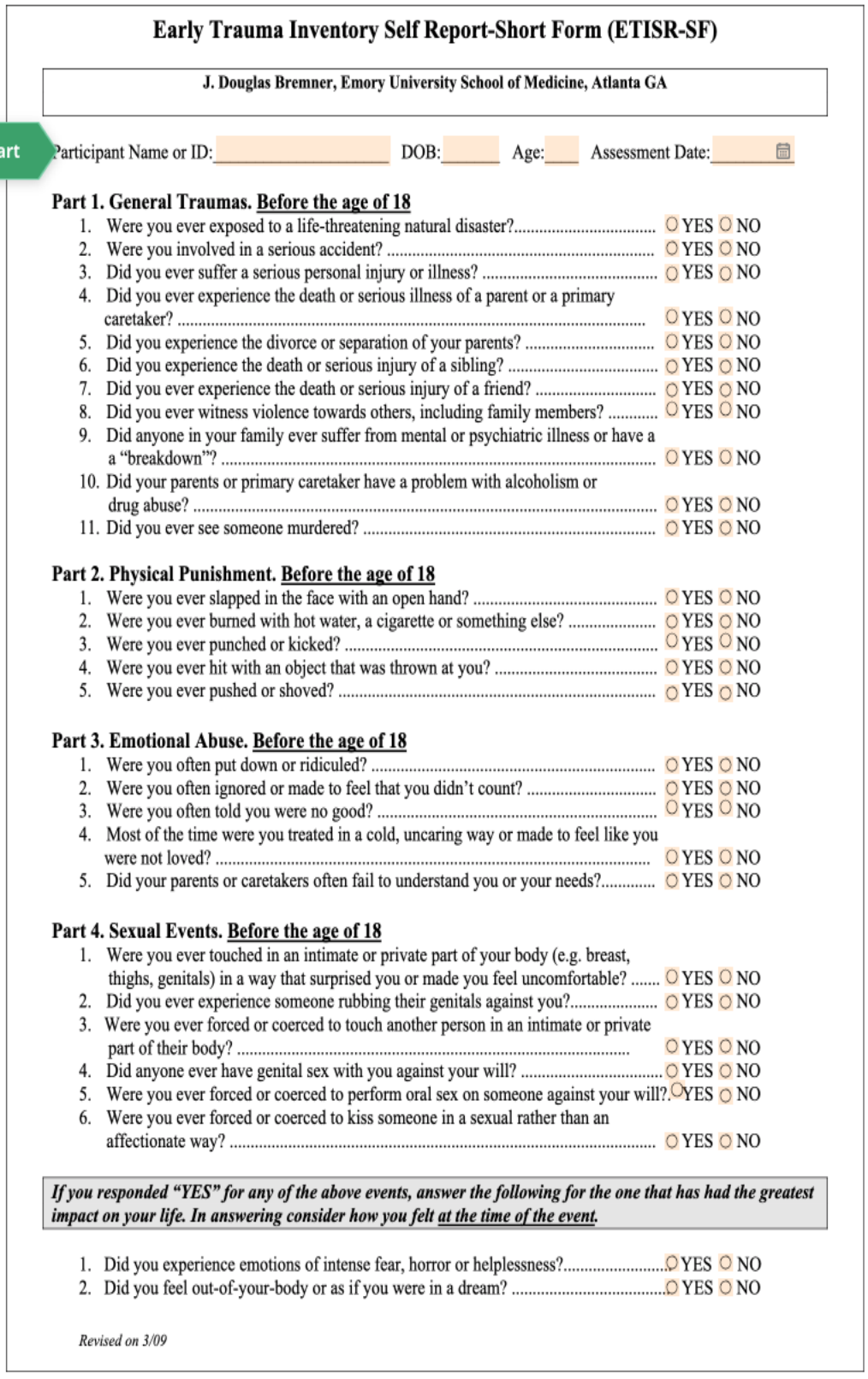
The PHQ-9 (Figure 3) consists of 9 items representing the criteria for Major Depressive Disorder (DMM) by the DSM-5. The questions determine how much each depressive symptom has bothered the reader over the past 2 weeks. It is graded on a scale of 0 to 3 (0

being not at all and 3 being nearly every day). Higher scores represent depression symptomatology.

The GAD-7 (Figure 4) consists of 7 items representing the criteria for Generalized Anxiety Disorder (GAD) by the DSM-5. The questions determine how much each anxiety symptom has bothered the reader over the past 2 weeks. It is graded on a scale of 0 to 3 (0 being not at all and 3 being nearly every day). This questionnaire helps identify probable cases of GAD and possibly cases of panic, social anxiety, and PTSD as well as measure the anxiety symptom severity. Higher scores represent anxiety symptomatology.

Lastly, a sample retrospective questionnaire (SRQ) as shown in Figure 5 has been created to help identify early life factors in IBS patients. The questions that were developed in this questionnaire aim to gain more insight on the development and background of each participant. This questionnaire will be helpful to see if there are any correlations in early life between all the participants.

Figure 1: ETISR-SF ***Number of IBS patients exposed to general, physical, emotional, and sexual trauma.***



Early Trauma Inventory Self Report-Short Form (ETISR-SF)

J. Douglas Bremner, Emory University School of Medicine, Atlanta GA

Start Participant Name or ID:_____ DOB:_____ Age:___ Assessment Date:_____

Part 1. General Traumas. Before the age of 18

1. Were you ever exposed to a life-threatening natural disaster?..... O YES O NO
2. Were you involved in a serious accident? ..... O YES O NO
3. Did you ever suffer a serious personal injury or illness? ..... O YES O NO
4. Did you ever experience the death or serious illness of a parent or a primary caretaker? ..... O YES O NO
5. Did you experience the divorce or separation of your parents? ..... O YES O NO
6. Did you experience the death or serious injury of a sibling? ..... O YES O NO
7. Did you ever experience the death or serious injury of a friend? ..... O YES O NO
8. Did you ever witness violence towards others, including family members? ..... O YES O NO
9. Did anyone in your family ever suffer from mental or psychiatric illness or have a a "breakdown"? ..... O YES O NO
10. Did your parents or primary caretaker have a problem with alcoholism or drug abuse? ..... O YES O NO
11. Did you ever see someone murdered? ..... O YES O NO

Part 2. Physical Punishment. Before the age of 18

1. Were you ever slapped in the face with an open hand? ..... O YES O NO
2. Were you ever burned with hot water, a cigarette or something else? ..... O YES O NO
3. Were you ever punched or kicked? ..... O YES O NO
4. Were you ever hit with an object that was thrown at you? ..... O YES O NO
5. Were you ever pushed or shoved? ..... O YES O NO

Part 3. Emotional Abuse. Before the age of 18

1. Were you often put down or ridiculed? ..... O YES O NO
2. Were you often ignored or made to feel that you didn't count? ..... O YES O NO
3. Were you often told you were no good? ..... O YES O NO
4. Most of the time were you treated in a cold, uncaring way or made to feel like you were not loved? ..... O YES O NO
5. Did your parents or caretakers often fail to understand you or your needs?..... O YES O NO

Part 4. Sexual Events. Before the age of 18

1. Were you ever touched in an intimate or private part of your body (e.g. breast, thighs, genitals) in a way that surprised you or made you feel uncomfortable? ..... O YES O NO
2. Did you ever experience someone rubbing their genitals against you?..... O YES O NO
3. Were you ever forced or coerced to touch another person in an intimate or private part of their body? ..... O YES O NO
4. Did anyone ever have genital sex with you against your will? ..... O YES O NO
5. Were you ever forced or coerced to perform oral sex on someone against your will?..... O YES O NO
6. Were you ever forced or coerced to kiss someone in a sexual rather than an affectionate way? ..... O YES O NO

If you responded "YES" for any of the above events, answer the following for the one that has had the greatest impact on your life. In answering consider how you felt at the time of the event.

1. Did you experience emotions of intense fear, horror or helplessness?..... O YES O NO
2. Did you feel out-of-your-body or as if you were in a dream? ..... O YES O NO

Revised on 3/09

Figure 2: CTQ-SF ***Number of IBS patients exposed to emotional, physical, sexual abuse and emotional and physical neglect.***

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Childhood Trauma Questionnaire—Short Form
CTQ-SF

Items
I. Emotional abuse
Called names by family
Parents wished was never born
Felt hated by family
Family said hurtful things
Was emotionally abused
II. Physical abuse
Hit hard enough to see doctor
Hit hard enough to leave bruises
Punished with hard objects
Was physically abused
Hit badly enough to be noticed
III. Sexual abuse
Was touched sexually
Hurt if didn't do something sexual
Made to do sexual things
Was molested
Was sexually abused
IV. Emotional neglect
Felt loved (R)
Made to feel important (R)
Was looked out for (R)
Family felt close (R)
Family was source of strength (R)
V. Physical neglect
Not enough to eat
Got taken care of (R)
Parents were drunk or high
Wore dirty clothes
Got taken to doctor (R)

Note. Items presented in abbreviated form. (R) = reverse-scored item. Range of all variables = 1–5. 1 = never true; 2 = rarely true; 3 = sometimes true; 4 = often true; 5 = very often true.

Figure 3: PHQ-9 ***Number of IBS patients with none to severe depression.***

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

ID #: _____ **DATE:** _____

Over the last 2 *weeks*, how often have you been bothered by any of the following problems? *(use "✓" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
	add columns		+	+
(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card).		TOTAL:		

10. If you checked off *any problems*, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all _____ Somewhat difficult _____ Very difficult _____ Extremely difficult _____

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Figure 4: GAD-7 ***Number of IBS patients with minimal to severe anxiety.***

GAD-7 Anxiety

Over the last two weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid, as if something awful might happen	0	1	2	3

Column totals _____ + _____ + _____ + _____ =

Total score _____

If you checked any problems, how difficult have they made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Source: Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD-PHQ). The PHQ was developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues. For research information, contact Dr. Spitzer at ris8@columbia.edu. PRIME-MD® is a trademark of Pfizer Inc. Copyright© 1999 Pfizer Inc. All rights reserved. Reproduced with permission

Scoring GAD-7 Anxiety Severity

This is calculated by assigning scores of 0, 1, 2, and 3 to the response categories, respectively, of "not at all," "several days," "more than half the days," and "nearly every day."
GAD-7 total score for the seven items ranges from 0 to 21.

0–4: minimal anxiety

5–9: mild anxiety

10–14: moderate anxiety

15–21: severe anxiety

Figure 5: Sample Retrospective Questionnaire (SRQ): Given to all patients who have been diagnosed with IBS.

Demographics of each IBS patient

1. What is your gender?

2. What is your race/ethnicity?
   Hispanic Asian African American or Black White Decline to Answer Multiracial. Other_____.

3. What is your highest education level?

4. At what age did you first start noticing potential symptoms of IBS (excessive gas, bloating, diarrhea, constipation, stomach pain, etc) _____.

5. At what age were you diagnosed with IBS? _____ years.

6. What type of IBS do you have? Circle below.

   IBS-D. IBS-C. IBS-Mixed. IBS-U.

7. What symptoms do you experience? Circle all that apply.
   Gas Bloating Diarrhea Constipation Abdominal pain Cramps Mucus in stool Blood in stool Other _____.

8. Have you ever been diagnosed with a mental health disorder? If so, what? (Ex. Anxiety, depression, BPD, etc.)

9. Have you ever participated in psychotherapy?

10. List any health conditions or chronic illnesses you have been diagnosed with and add what year it was (Ex. Type 2 Diabetes 2012).

11. What triggers the symptoms of your IBS?
    Stress Gluten Dairy. Spicy foods. Coffee. Processed foods. Alcohol. Carbonated drinks. Legumes/Beans. Other _____.

12. Are you still experiencing IBS symptoms now? If not, what age did they go away or decrease in severity?

3. RESULTS

A total of 5 questionnaires has been handed out to IBS patients along with measurements of serum serotonin levels to determine if there is a correlation between the onset of IBS and early life stressors and the relation to serotonin in the gut. These questionnaires were the ETISR-EF, CTQ-SF, PHQ-9, GAD-7, and the SRQ. Looking at the table 1, it would be expected that a person diagnosed with IBS would say yes to at least 1 question in 1 part of the 4-part questionnaire. Next, it would be expected in the in table 2 that the reader would answer yes to at least 1 question in 1 part of the 5-part questionnaire. In the table 3, it would be expected that the reader would score at least 5+ and have mild depression. In the table 4, it would be expected that the reader would score at least 5+ and have mild anxiety. Lastly, in the table 5 it would be expected that majority of the readers had experienced IBS symptoms before the age of 18.

Table 1: ETISR-SF ***Percentage of IBS patients exposed to general, physical, emotional, and sexual trauma.***

	Yes (1 or >)	Yes (2 to 4)	Yes (5 or >)	None
General Trauma	(%)	(%)	(%)	(%)
Physical Punishment	(%)	(%)	(%)	(%)
Emotional Abuse	(%)	(%)	(%)	(%)
Sexual Events	(%)	(%)	(%)	(%)

*Note: (R) = reverse-scored item on the questionnaire; no means yes and vice versa.

Table 2: CTQ-SF ***Percentage of IBS patients exposed to emotional, physical, sexual abuse and emotional and physical neglect.***

	Yes (1 or >)	Yes (2 to 3)	Yes (4 to 5)	None
Emotional Abuse	(%)	(%)	(%)	(%)
Physical Abuse	(%)	(%)	(%)	(%)
Sexual Abuse	(%)	(%)	(%)	(%)
Emotional Neglect	(%)	(%)	(%)	(%)
Physical Neglect	(%)	(%)	(%)	(%)

Table 3: PHQ-9 ***Percentage of IBS patients with none to severe depression***

	Male	Female
None to Minimal (0-4)	(%)	(%)
Mild (5-9)	(%)	(%)
Moderate (10-14)	(%)	(%)
Moderate/Severe (15-19)	(%)	(%)
Severe (20-27)	(%)	(%)

Table 4: GAD-7 ***Percentage of IBS patients with minimal to severe anxiety.***

	Male	Female
Minimal (0 to 4)	(%)	(%)
Mild (5 to 9)	(%)	(%)
Moderate (10 to 14)	(%)	(%)
Severe (15 or more)	(%)	(%)

Table 5: Sample Retrospective Questionnaire (SRQ) ***Average demographics of each IBS patient.***

Gender (%)	Male	Female																		
Race (%)	White	Asian	African American		American indian/Native American			Native Hawaiian/Other Pacific Islander			Hispanic or Latino			Other						
Highest Education Level (%)	None	Nursery to 8th grade		Some High school, no diploma			High school graduate		Some college, No Degree		Trade/Technical/Vocational School			Associates Degree		Bachelors Degree		Masters Degree		Doctorate degree
Age of IBS development (%)	< 5 y/o	5 to 10 y/o	10 to 15 y/o	15 to 17 y/o																
IBS Type (%)	IBS-D	IBS-C	IBS-M	IBS-U																
Mental Health Diagnosis (%)	GAD	MDD	BPD	Bipolar	ADHD	PTSD	ASD	Other												
Psychotherapy Participation (%)	Yes	No																		
Chronic Illnesses (%)	Yes	No																		
IBS Triggers (%)	Stress	Gluten	Dairy	Fried Food	Spicy Food	Coffee	Ultra-Processed Foods		Alcohol	Carbonation	Legumes/Beans		Other							
IBS S/Sx now (%)	Yes	No																		
Symptoms (%)	Gas	Bloat	Diarrhea	Constipation	Vomiting	Abdominal Pain		Cramps	Mucus in stool		Blood in stool		Other							

Table 6: Serum Serotonin Levels ***Average serum serotonin levels among the 4 types of IBS patient.s.***

IBS Types vs. Serotonin Levels	Male	Female	Both
IBS-C			
IBS-D			
IBS-M			
IBS-U			

4. DISCUSSION

This literature review serves to investigate if there is a correlation between early adverse life events and alterations in serotonin levels seen in the possible pathogenesis of IBS. In order to look at the possible correlation between early adverse life events and IBS development,

multiple questionnaires in relation to early life and mental health were sent out to participants already diagnosed with IBS less than 18 years old. Participants also had their blood drawn in order to measure their serum serotonin levels.

It would be expected that people with IBS would have higher scores of stresses, anxiety and depression when compared to people without IBS. This expectation is due to the trauma the participants experienced in early childhood that has contributed to the development of IBS. Limitations with the questionnaires include a person's reluctant towards sensitivite topics being asked, difference in interpretation upon reader, and ignorance of questions. Also, since this data is being self-reported, there is potential issues with validity due to social desirability bias where the participant doesn't answer truthfully or answers in a way of what society expects them to.

Looking at serum serotonin levels, it would be expected that people with IBS-D would have increased serotonin levels that correlate with increased visceral hypersensitivity and increased motility while people with IBS-C would have decreased serotonin levels that correlate with decreased visceral hypersensitivity and decreased motility. People with IBS-M and IBS-U would potentially have mixed results of either increased or decreased serum serotonin levels. Further investigation needs to happen on following the serotonin levels of IBS participants throughout a period of at least 12 months and having the participant track their bowel movements and mood every day to gain more correlation between IBS, EALs and serotonin levels. This would allow to see if decreased serotonin, depression, and constipation go hand and hand or vice versa with increased serotonin, anxiety, and depression. It could also be a pinpoint if there is possible permanent changes in serum serotonin levels due to EALS or if serotonin levels remain situation and mood based.

5. CONCLUSION

Although there is a lot of research on IBS, there is not a lot of answers. Since the underlying mechanisms regulating the interaction between the gut microbiota and host remain unclear in IBS patients, there is no consensus on the relationship between specific microbiota derived metabolites and subtypes of IBS. Now, research has been moving away from relying on symptoms and experiences as a diagnostic and result based tool and moving towards understanding variations and fluctuations in the concentrations of host or microbiota-derived metabolites. This research can be used when trying to understand the process that is contributing to symptoms and severity of IBS. Since IBS is a disorder of dysfunction of the

brain-gut-microbiota, there is a possible link between ECs, enteric immune cells, intestinal epithelial cells, enteroendocrine cells, the microbiota, ENS, and CNS that could play a role in the pathogenesis of IBS. Unclear mechanisms that have been proposed need to have further research, especially the effect of EALS on serotonin levels in the gut. Specifically, if the increase or decrease in serotonin levels correlate with the symptoms of IBS, does the severity of EALS impact what type of IBS someone may develop? As research continues, the exact correlation between severity of IBS symptoms, type of IBS, gender, and other microbial factors in relation to serotonin need to be investigated.

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