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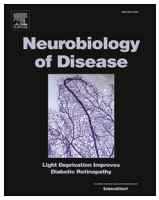

Impact of intestinal disorders on central and peripheral nervous system diseases

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ABSTRACT

Brain injuries and neurological diseases have a significant impact on the gut microbiome and the gut barrier. Reciprocally, gut disorders, such as Inflammatory Bowel Syndromes (IBS), can affect the development and pathology of neurodegenerative and neuropsychiatric diseases, although this aspect is less well studied and is the focus of this review. Inflammatory Bowel Syndrome (IBS) is a chronic and debilitating functional gastrointestinal disorder afflicting an estimated 9–23% of the world's population. A hallmark of this disease is leaky gut, a pathology in which the integrity of the gut blood barrier is compromised, causing gut contents such as immune cells and microbiota to enter the bloodstream leading to low-grade systemic inflammation. The increased levels of inflammation associated cytokines in circulation has the potential to affect all organs, including the brain. Although the brain is protected by the blood brain barrier, inflammation associated cytokines can damage the junctions in this barrier and allow brain infiltration of peripheral immune cells. Central inflammation in the brain is associated with various neurodegenerative disease such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and neuropsychiatric disorders, namely, depression, and anxiety. Neurodegenerative diseases are of particular concern due to the anticipated rise in the population of the elderly and consequently, the prevalence of these diseases. Additionally, depression and anxiety are the most common mental illnesses affecting roughly 18% of the American population. In this review, we will explore the mechanisms by which IBS can influence the risk and severity of neurological disease.

1. Introduction

Common neurological and neurodegenerative diseases are associated with complex pathologies including inflammation in both the central (Amor et al., 2010) and autonomic nervous system (Takahashi, 1991; Probst et al., 2008; Affoo et al., 2013; Femminella et al., 2014; Racosta et al., 2015), leading to a myriad of dysfunction across different organ systems. Moreover, these diseases are often characterized by poor gut health due to the loss of gut-barrier integrity (Mulak and Bonaz, 2015; Liddle, 2018; Fujii et al., 2019; Morais et al., 2021), which underscores the role of the brain-gut axis. The role of the gut brain axis is to monitor and integrate gut functions, link affective and cognitive centers of the brain with peripheral intestinal functions and mechanisms such as immune activation, gut permeability, enteric reflex, and enteroendocrine signaling. Both clinical and pre-clinical models over the last two decades suggest that the enteric nervous system or "the second brain" plays a crucial role in the regulation and maintenance of homeostasis. However, the reciprocal aspect of the gut-brain axis, namely the development and progression of neurological diseases resulting from prior inflammatory bowel syndromes, is not well explored. Therefore this review will provide an introduction to bowel disease followed by an overview of the current evidence to link inflammatory gut diseases/leaky gut with the onset of chronic neurological diseases. It will include evidence from studies of irritable bowel syndrome (IBS) and inflammatory bowel diseases (IBD). Irritable bowel syndrome (IBS) is a group of symptoms including abdominal pain and changes in bowel habit, which can occur without any visible signs of damage or disease in the digestive tract, although it is frequently accompanied by inflammation. IBD is characterized by chronic inflammation and immune activation, and destructive changes to the bowel, including Crohn's Disease and Ulcerative Colitis. The review concludes with possible mechanisms underlying the link between intestinal disorders and neurological disease.

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2. Irritable bowel syndrome

Irritable Bowel Syndrome (IBS) is a chronic and debilitating functional gastrointestinal disorder. Worldwide, it is estimated that 9–23% of the population has IBS (Quigley et al., 2009). Approximately 12% of patients are seen in a primary care setting while the majority of patients are seen in gastroenterology primary clinics (Saha, 2014). IBS Symptoms can range from moderate to serious impairment of ability to function (Enck et al., 2016). The hallmark of IBS in children and adults is abdominal pain bloating, gassiness, diarrhea, constipation, and diarrhea alternating with constipation and altered bowel habits. The current symptom based diagnostic criteria for IBS, called the Rome IV criteria (Saha, 2014; Lacy and Patel, 2017) consist of abdominal pain associated with an alteration in either stool form or frequency, occurring for at least 6 months. IBS can be classified into four types based on the symptoms and stool. IBS with pain or discomfort and predominant constipation (IBS-C), IBS with diarrhea (IBS-D), mixed IBS (IBS-M) and unsubtyped IBS (IBS-U) (Drossman, Dumitrascu et al., 2006; Enck et al., 2016). Nearly 25% of IBS-D patients have increased levels of total fecal bile acids caused by increased excretion and synthesis of serum C4 (7α-hydroxy-4-cholesten-3-one; a surrogate for bile acid synthesis), which enhances bowel habit through the acceleration of colonic transit and permeability and diarrhea, and visceral hypersensitivity in IBS (Camilleri, 2021).

Patients with irritable bowel frequently report symptoms of other functional gastrointestinal disorders including chest pain, heartburn and nausea or dyspepsia (Almansa, Rey et al., 2009). Patients may also experience symptoms unrelated to the intestine such as headache, functional dyspepsia, fibromyalgia, temporomandibular joint disorder, interstitial cystitis/painful bladder syndrome, and chronic fatigue syndrome, collectively known as functional pain syndromes (Alagiri et al., 1997; Kim, Chang et al., 2012). In addition, bowel motor impairment, visceral hypersensitivity, or the abnormal processing of sensations are also observed in IBS patients (Posserud et al., 2006).

3. Gut features in IBS

3.1. Intestine barrier

IBS are characterized by intestinal inflammation that compromises the integrity of the epithelial barrier leading to increased permeability and infiltration of pathogens (Teshima et al., 2012). The epithelial gut lining is in constant contact with the environment and with billions of bacteria that constantly challenge the intestinal immune system (Bischoff et al., 2014). In addition to regulating fluid and nutrient intake, the intestinal epithelial barrier plays a critical role in controlling the passage of pathogens. These functions are regulated by luminal as well as internal components, such as bacteria or immune cells, and emerging evidence indicates that two cell types of the enteric nervous system (ENS), enteric neurons and enteric glial cells, are also potent modulators of intestine epithelial barrier (Neunlist, Van Landeghem et al., 2013).

Histological examination of colonic biopsies showed an abnormal cellular distribution of the tight junction proteins claudins, ZO-1 and occludin in IBS patients as compared to healthy controls (Kong et al., 2007; Cheng et al., 2015), indicative of increased intestinal permeability. This is an early event in IBS that leads to low-grade immune cell infiltration of the gut mucosa. Increased epithelial permeability has been observed mainly in IBS-D category, although other categories, such as IBS-C and IBS-M may also exhibit an increase the intestine epithelial permeability (Bischoff et al., 2014). Interepithelial tight junction changes are probably the result of both bacterial and proteasome-mediated degradation triggered by low-grade inflammation (Coëffier, Gloro et al., 2010), and the presence of inflammatory mediators including eicosanoids, histamine and proteases (Berkes et al., 2003).

3.2. Enteric nervous system

The ENS is the intrinsic nervous system of the GI tract, capable of autonomous function (Hansen, 2003). It consists of several networks including the myenteric/submucosal nerve plexus, intrinsic neural network, and intrinsic primary neurons. The myenteric plexus is located between the longitudinal and circular muscle layers and regulates the movement of gut contents and peristalsis, migrating motor complex, accommodation reflex, and transit through the stomach, small bowel, and colon (Furness, 2000). The submucosal plexus is located in the submucosal layer and regulates secretory function and sensory-motor function (Hansen, 2003). Intrinsic Primary Afferent Neurons are located in between the myenteric and submucosal plexuses and are essential for the regulation of local and peripherally mediated reflexes (Langley, 1921). In rats exposed to chronic and acute stress, there is an acceleration of intestinal transit time, accompanied by an increase in the number of secretomotor cholinergic neurons and peptidergic neurons in the submucosal plexus, and decreased inhibitory musculomotor neurons such as nitric oxide synthase immunoreactive neurons in myenteric plexus (Jahng and Kim, 2016). These data suggest that structural change in the ENS underlies the pathophysiology of stress-related IBS-D symptoms (Li et al., 2010).

Many neuropeptides and neurotransmitters are governed by the immunological functions of discrete subsets of immune cells (Neunlist et al., 2003; O'Connor et al., 2004; Mashaghi, Marmalidou et al., 2016). In experimental colitis models using trinitrobenzene sulfonic acid, loss of myenteric neurons (20%) is associated with infiltration of neutrophils (Boyer et al., 2005; Linden, Couvrette et al., 2005). Inflammation markedly affects the cholinergic neurons, the major excitatory phenotype of the rodent ENS, causing changes in the expression of the synaptic vesicle proteins necessary for the release of acetylcholine (Collins, Blennerhassett et al., 1992; Villanacci, Bassotti et al., 2008). The neuropeptide Substance P which mediates ENS signaling, immune cell proliferation, and cytokine production, is also altered in IBD. Substance P-positive neurons are increased in numbers in the myenteric plexus of ulcerative colitis patients (Neunlist et al., 2003, O'Connor et al., 2004, Mashaghi, Marmalidou et al., 2016). In Crohn's disease patients, vasoactive intestinal peptide (VIP)-positive neurons are elevated in the submucosal region (Schneider, Jehle et al., 2001; Boyer et al., 2007). Enteric neuron damage may be caused by bacterial lipopolysaccharide and the presence of pro-inflammatory agents, which promotes tryptophan metabolism into the kynurenine pathway (Fritscher-Ravens et al., 2014; Kennedy et al., 2017). Enteric neuron apoptosis and oxidation promotes mast cell activation and initiates a detrimental cycle of inflammatory and cell loss. Moreover, inflammation in the colon could activate the enteric nervous system and facilitate communication to the afferent nerve fibers projecting to the brain to trigger the release of vasoactive neurotransmitters, which could eventually dysregulate the blood brain barrier.

3.3. Immune cells

Increased infiltration of T cells and mast cells is seen in the mucosa of the small and large intestine of some IBS patients (Barbara, Cremon et al., 2011). Biopsy from IBS patients had high level of mast cell mediators, including proteases histamine, and polyunsaturated fatty acid metabolites (Cenac et al., 2015). Mucosal immune activation and gene expression alters of the host mucosal immune response to microbial pathogens, suggesting that the microbiota might contribute to the observed immune activation (Barbara, Cremon et al., 2011). In addition, supernatants from mucosal biopsies from IBS-D patients influence the activation and abnormal signaling patterns of human ENS neurons. These patterns were inhibited by antagonists to the histamine receptor and the serotonin receptor, as well as protease inhibitors. These mucosal samples had high levels of mast cell density, suggesting that the ENS-stimulating factors may be derived from this immune cell type

(Buhner et al., 2009). Moreover, high levels of serine and cysteine proteases are present in the mucosa and stool of patients with IBS (Annaházi et al., 2009).

3.4. Gut microbes

In IBS patients, gut microbes like Clostridiales and *Ruminococcus torques* were significantly decreased and increased respectively (Saulnier et al., 2011) and positively correlated with bowel symptoms (Malinen et al., 2010). Changes in the normal microbiota composition and disturbed colonic fermentation in IBS patients may play an important role in development of IBS symptoms. Firmicutes and Bacteroidetes are major gut phyla and the ratio between the two (F:B) is frequently used as an estimator of gut health. Elevated F:B levels, for example are seen in obesity (Ley et al., 2006) and aging (Spychala et al., 2018) and after stroke in aging animals (Spychala et al., 2018; Park et al., 2019). A two-fold increase in the ratio of Firmicutes to Bacteroidetes has been reported in IBS patients (Kerckhoffs et al., 2011; Ponnusamy et al., 2011; Duan et al., 2019).

4. Effect of IBS on the brain

The gut-brain axis is bidirectional, thus messages from the gastrointestinal tract may be conveyed to brain regions, where these signals may influence higher level functions such as behavior, cognition and emotion regulation, both in normal and disease states (Baj et al., 2019). Population studies have shown significant associations between IBS and occurrence of both peripheral and central nervous system type disorders. Many of these associations have sex specific differences as well. The exact mechanisms of this are not completely understood, however, there are several ways by which this could occur including microbiota/metabolite dysregulation, the effect of IBD on immune cell populations and vagus nerve signaling. In this section we will discuss the ways by which IBD can disrupt brain function and the clinical implications of these disruptions in a sex specific manner.

4.1. Blood brain Barrier function

Biological barriers are essential to maintain the homeostatic environment in the tissue/body, and therefore, any disruptions in the integrity of these barriers play a crucial role in the onset and progression of pathological processes (Grossman, 1979; Bloom, 1980; Rhee et al., 2009). Evidence from both clinical and experimental studies suggests that chronic inflammatory diseases of the gut disrupt the interaction between the neural, endocrine, and immune systems of the enteric nervous system and central nervous system, which can affect the blood brain barrier and consequently elevate the risk for neuroinflammation (Westfall et al., 2017; Dopkins et al., 2018; Russo et al., 2018).

The blood brain barrier (BBB), a molecular barrier present at the interface between blood and the brain parenchyma is composed of specialized endothelial cells surrounded by pericyte embedded basal lamina and ensheathed by astrocytic endfeet on the abluminal side (Ballabh et al., 2004; Abbott et al., 2006; Zlokovic, 2008). BBB dysfunction is an important hallmark of a variety of neurological and neurodegenerative diseases such as Alzheimer's disease (Zlokovic et al., 2010; Sweeney et al., 2018) and multiple sclerosis (Minagar and Alexander, 2003; Farrall and Wardlaw, 2009) with increased trafficking of peripheral inflammatory mediators and immune cells through disrupted endothelial tight junctions. While it is very clear that increased BBB permeability is associated with the progression of AD and MS, very little is known about how chronic gut inflammation contributes to the onset of these disorders. This section of the review will provide an overview of the mechanisms that link leaky gut to BBB dysfunction, and subsequently trigger neuroinflammation that culminates in neurodegenerative diseases.

Chronic inflammatory conditions of the gut like IBD cause increased intestinal permeability (Bischoff et al., 2014) (described above), which in turn can induce the release of cytokines by peripheral immune cells, leading to elevated systemic inflammation (Rivera et al., 2019). This excessive stimulation of the innate immune system can directly activate the BBB endothelial cells, through which peripheral T-cells can gain access to the brain parenchyma. Additionally, another major consequence of leaky gut is endotoxemia (LPS), which can also promote BBB hyperpermeability and activation of Toll-like Receptors (TLRs) on the endothelial surface (Abdul et al., 2018; Johnson et al., 2018). BBB dysfunction is one of many important mechanisms by which altered gut function/increased gut permeability can activate inflammatory processes in the brain through glial cell activation (Sofroniew, 2015; Park et al., 2020). High levels of circulating pro-inflammatory cytokines are shown to increase the endothelial permeability at BBB (Varatharaj and Galea, 2017), through disrupted tight junctions ((Huber et al., 2002, Wolburg et al., 2003, Zhou et al., 2014) leading to increased immune cell invasion (Banks, 2012). Consistent with this hypothesis, in an experimental model of colitis in rabbits, there was a 75–1110% increase in fluorescein extravasation in the brain (Hathaway et al., 1999). Research focusing on the direct linkage between gut permeability and BBB permeability is very limited, which could be due to the well-known impact of systemic inflammation on BBB permeability as shown in previous studies (Ericsson et al., 1995; Nadeau and Rivest, 1999; Prat et al., 2005).

4.2. Microbiota and metabolites

The metabolism of undigested carbohydrates, proteins and lipids by microbiota leads to the production of SCFAs, bile acids, tryptophan and indole, among other metabolites. The most researched metabolites are the SCFAs which bind GPCRs on the surface of epithelial cells and immune cells and can alter their function and induce secretions of gut hormones that signal to the brain. SCFAs can act directly on central receptors due to their ability to diffuse passively or actively (via monocarboxylate transporters) across the BBB (Vijay and Morris, 2014).

In the case of IBD, the microbiota composition is perturbed, leading to altered metabolite production. One of the most predominant SCFAs, butyrate, has been shown to have a therapeutic effect in IBD as it repairs the tight junction lesions which have been associated with the disease. Butyrate can also repair tight junction lesions in the gut blood barrier (Geirnaert et al., 2017). SCFAs also influence the BBB as germ-free mice exhibit a leaky BBB likely due to the lack of SCFAs and this permeability can be rectified with a fecal microbiota transplant of the butyrate producer *Clostridium tyrobutyricum* (Braniste et al., 2014). Propionate and butyrate exert an influence on the intracellular potassium level, which implicates SCFAs in the operation of neuronal signaling systems (Oleskin and Shenderov, 2016). Given the HDAC inhibition property of SCFAs, several animal studies have focused mainly on the use of butyrate to elevate histone acetylation in the brain during a critical phase of memory formation (Silva et al., 2020). Elevated histone acetylation modulates glial cells in an anti-inflammatory and neuroprotective manner. Since inflammation is heavily implicated in neurodegenerative disease and neurological injuries, the abundance of SCFAs like butyrate could be critical for outcomes. Additionally, it has been shown that certain SCFAs, such as butyric acid, are capable of interfering with protein-protein interactions necessary for the process of Aβ assembly which plays a role in AD pathogenesis (Ho et al., 2018). In stroke, fecal transplants from young donors, which contain much higher levels of SCFAs, ameliorate behavioral deficits as well as central and peripheral inflammation in aged mice (Lee et al., 2020). SCFAs have also been shown to play a role in experimental autoimmune encephalomyelitis (EAE), an experimental model for MS, as they have been shown to ameliorate the symptoms of EAE (Haghikia et al., 2015; Mizuno et al., 2017). In addition to SCFAs, tryptophan has also gained considerable attention. Tryptophan is an essential amino acid derived from diet. Changes in its metabolism have been linked to the development of

inflammatory responses in the gut (Bosi et al., 2020) and it is also a precursor to bioactive molecules that influence multiple gut-brain axis pathways (Kennedy et al., 2017) and also neuroendocrine transmitters such as serotonin and melatonin.

The most compelling evidence that metabolites from the gut may play a role in neurological disease is the observation of altered levels of said metabolites in diseases like Autism, mood disorders and Alzheimer's disease. Specifically, children with Autism Spectrum Disorder had higher levels of propionic acid and acetic acid but lower levels of butyric acid (De Angelis et al., 2013). The comparative increase and decrease of certain SCFAs is to be expected as there is an overall shift in microbiota composition. Lower microbiota composition of butyrate producing species have been noted in depressive disorder (Capuco et al., 2020). Similarly, in AD, SCFA production was reduced as microbiota composition of SCFA producing bacteria is perturbed in the disease (Zhang et al., 2017). Tryptophan is transported across the BBB for the production of central serotonin. There is clear evidence that alterations in gut microbial tryptophan metabolism, resulting from altered microbiota composition, influences tryptophan availability which influences central serotonin levels (Gao et al., 2019). Altered neurotransmitter levels have implications in anxiety and depression but have also been seen to play a role in cognition and thus diseases such as Alzheimer's and Parkinson's (Chen et al., 2021).

4.3. Immune cells impact on the brain

Low-grade systemic inflammation in older adults is commonly associated with leaky gut and gut dysbiosis. Intestinal diseases, such as IBD, where the disease hallmark is leaky gut, are characterized by persistent and uncontrolled inflammation (Cui et al., 2010). Common inflammatory cytokines such as TNFa and IFNy, which are elevated in IBD's, such as ulcerative colitis and Crohn's, have been shown to downregulate tight junction proteins ZO-1, claudin-1 and occludin and thus increased BBB permeability. This allows peripheral immune cells to infiltrate the brain (Larochelle et al., 2011). Once immune cells are in the brain, they can destroy healthy brain tissue and disrupt the function of glial cells. An inflammatory environment in the brain is associated with increased risk of brain disorders such as Alzheimer's (Seo and Holtzman, 2020). Brain inflammation has also been shown to be a precursor to depression (Slavich and Irwin, 2014).

4.4. Vagus nerve

Nerve fibers in the vagal nerve can also participate in gut to brain signaling and can be stimulated by microbial compounds and metabolites and hormones from enteroendocrine cells (Durgan et al., 2019). The altered microbial composition and metabolites in IBD would lead to dysregulated vagus nerve signaling and constitute another way by which the gut can affect the nervous system. Recent studies have shown that peripheral cytokines induce alterations in vagus nerve activity (Steinberg et al., 2016) meaning that conditions, such as IBD, that influence peripheral inflammation have a direct effect on this nerve's activity. The gut bacteria *Lactobacillus rhamnosus*, which can regulate GABA receptors in mice, is shown to reduce depressive behaviors. Severing the vagus nerve, however, negated the beneficial effects of L. *rhamnosus* in mitigating depressive behavior (Bravo et al., 2011), suggesting that an intact vagal nerve is necessary for transducing the effects of this bacterium. Another example is traumatic brain injury, where it was shown that in rats, vagus nerve stimulation resulted in improved recovery attributed to increased neural plasticity and norepinephrine release (Smith et al., 2005). In contrast, in the case of stroke, vagotomy improves stroke outcomes likely due to the prevention of immune cell trafficking from the gut to the brain (Naseh et al., 2020). Overall, these studies suggest a complex interaction between vagal nerve integrity and the type of disease state.

Collectively, these elements of gut disease can impact the central and peripheral nervous system. While gut-mediated inflammatory changes may be common to both, the mechanisms are likely to be different. Inflammatory gut metabolites such as LPS are well known to cause peripheral neuropathies, while CNS damage may include disruption of the blood brain barrier, thus exposing vulnerable brain circuits to inflammatory mediators.

4.5. IBD and peripheral neuropathies

Peripheral neuropathies (PN) result from damage to nerves outside of the brain and result in pain, numbness, tingling and weakness, usually in the hands and feet but could be anywhere in the body. Parasthesias and increased threshold for temperature detection (which could be indicative of early PN) are common in patients with Crohns Disease, in untreated (19%) or metronidazole treated (21–39%) patients (Stahlberg et al., 1991). In the two largest retrospective studies the incidence of peripheral neuropathy associated with IBD varied from 0.9 (Lossos et al., 1995) to 3.6% (Elsehety and Bertorini, 1997), although a recent population-based study concluded that neuropathy is uncommon in the IBD patient population (Figueroa et al., 2013)). Neurological disorders other than PN were observed in 67% of the Crohn's Disease and 53% of the Ulcerative Colitis patients with PN and these included small vessel disease, transient ischemic attacks, transient diplopia, strokes and intracerebral hemorrhage, seizures, ocular myositis, Bell's palsy, bilateral optic neuritis, tremor, 'central serous retinopathy', migraine and sleep apnea (Gondim et al., 2005). The precise cause of these neuropathies is not known, although nutritional deficiencies such as Vitamin B12 have been implicated, as well as side effects from anti–tumor necrosis factor-α (anti-TNF) therapy or treatment with the antibiotic metronidazole.

5. Effect of IBS on chronic neurodegenerative diseases

Several psychiatric comorbidities are seen in patients with IBS, including anxiety disorders and mood disorders (Fadgyas-Stanculete et al., 2014), as well major CNS disorders such as Multiple sclerosis (MS), AD, and Parkinson's disease (PD). A common theme linking these neurological disorders are degenerative changes in the blood brain barrier, which exposes CNS tissue to toxic proteins and cells. Below we will review the data of common neurodegenerative conditions that are exacerbated by bowel disease.

5.1. Multiple sclerosis

This chronic inflammatory demyelinating disease of the central nervous system, causes a wide array of symptoms due to the involvement of the somatic and autonomic nervous systems. These include bowel problems, incontinence, fatigue, blurred vision, numbness and tingling in the extremities, trouble walking, anxiety, depression among others (Preziosi et al., 2018). Despite the influence of geographic location on occurrence of MS, several studies have reported a consistently high female preponderance in the incidence of MS (Orton et al., 2006; Alonso and Hernán, 2008; Kingwell et al., 2013), particularly in patients under the age of 20 (Cossburn et al., 2012). Furthermore, a retrospective study using a large-scale national administrative data set from 2008 to 2012, estimated that females are 3 times more likely to develop MS than males (Dilokthornsakul et al., 2016). The disease progression is categorized into an acute relapsing-remitting primary progressive and secondary progressive stages and all these stages are characterized by disrupted blood brain barrier function. The BBB endothelial cells play a key role in MS pathology. The higher levels of circulating inflammatory cytokines and immune cells activate the endothelium (Barreiro and Sanchez-Madrid, 2009; Ricci et al., 2009; Wilson et al., 2010) to upregulate the adhesion receptors for the leukocytes to make contact with the vessel wall, and to facilitate the tethering and rolling of leukocytes across the barrier (Hernandez-Pedro et al., 2013), a phenomenon seen

with conditions that are associated with high peripheral levels of inflammation associated cytokines. In EAE models, endothelial tight junction proteins such as claudin5 and occludin are downregulated and is correlated with increased inflammatory infiltrates (Wolburg et al., 2003), suggesting that the inflammatory cells disrupt the blood brain barrier to promote neuroinflammation.

Interestingly, the association between IBD and MS was first identified when ulcerative colitis patients showed a three-fold increase in MS incidence after having undergone colectomy for treatment (Rang et al., 1982). Subsequently, more studies have reported that the incidence of MS is higher in patients with Crohn's disease and ulcerative colitis (Gupta et al., 2005; Pokorny et al., 2007; Kosmidou et al., 2017). Conversely, patients with MS show a higher incidence of IBS (12.2%) as compared with general population (6.8%) (Marrie, Yu et al., 2013). Both IBD and MS share many common mechanisms, for example, dysregulated immune responses and uncontrolled peripheral inflammation are the major players in the pathophysiology of these diseases. Importantly, alteration in gut microbial population and their metabolites is linked to the initiation and progression of MS (Ochoa-Repáraz et al., 2009; Glenn and Mowry, 2016; Shahi et al., 2017). Moreover, this gut dysbiosis is characterized by a less microbial diversity (fewer Bacteriodetes phyla) and overexpression of proinflammatory species (more Actinobacteria, Bifidobacteria and Streptococcus) in the gut of MS patients (Cantarel et al., 2015; Miyake et al., 2015; Cox et al., 2021), suggesting that compromised microbial diversity contributes to reduced levels of beneficial SCFAs, which have been shown to be altered in the serum of MS patients (Olsson et al., 2021; Trend et al., 2021) and exacerbates inflammation in both gut-blood barrier and blood brain barrier. Interestingly, female MS patients showed a reduction in fecal SCFA levels whereas males did not, which is consistent with the increased prevalence of MS in women, however, there was no observed active intestinal inflammation (Becker et al., 2021).

5.2. Alzheimer's disease

This neurodegenerative disorder is characterized by progressive cognitive decline and is the primary cause of dementia. The clinical symptoms include memory loss, confusion, weight loss, inability to communicate, loss of bowel and bladder control, difficulty swallowing, etc. AD primarily affects older adults and, two-thirds of patients are females (Seshadri et al., 1997; Babapour Mofrad and van der Flier, 2019). In the US, of the total 5.2 million AD patients, women account for 3.3 million (Oveisgharan et al., 2018). This pronounced sex difference is attributed to the longer life expectancy in women compared to men. Several clinical and pathological studies have shown that AD is associated with inflammation induced vascular changes in the blood brain barrier (Iadecola, 2004; Kapasi and Schneider, 2016). Blood brain barrier dysfunction contributes to the onset and progression of AD (Kalaria, 2002; Deane and Zlokovic, 2007; Cai et al., 2018), as indicated by damaged endothelium and collapsed microvessels with defective BBB transporters such as Glut-1 and P-gp (Zlokovic et al., 2010; Winkler et al., 2015). Furthermore, AD brains are characterized by deposition of amyloid-β (Zlokovic et al., 2010; Carrano et al., 2011; Erickson and Banks, 2013) and tau (Kovac et al., 2009; Blair et al., 2015) in the perivascular spaces in the neurovascular unit and also in the surrounding parenchyma, suggesting that leaky vessels contribute to proinflammatory events and cytotoxic events. Moreover, higher levels of inflammatory mediators like nitric oxide, prostaglandins, MMPs have been found in AD brain microvessels (Grammas, 2011), revealing proinflammatory role of the vasculature. Additionally, other BBB components such as astrocytes also contribute to AD pathology, for example, transgenic mice with Artic and Swedish APP (Arc/SweAβ) mutations showed reduced expression of GLUT1 transporters in astrocytic end feet (Merlini et al., 2011) and also relocation of AQP4 from end feet membrane to non-end feet regions (Yang et al., 2011, Park, Park et al., 2014) Previous studies have shown that pericytes also facilitate transmigration of neutrophils through upregulation of ICAM1 and RAGE receptors in AD brains (Yan et al., 1996; Wilhelmus et al., 2007; Zenaro et al., 2015).

In addition to the blood brain barrier, the blood gut barrier also plays a significant role in the etiology of AD. Recent evidence indicates that IBD has a positive correlation with development of dementia, such that the risk for AD in IBD patients is six times more than the non-IBD individuals (Zhang et al., 2021). This elevated risk is linked to IBD-induced dysregulation of the immune system and gut dysbiosis. More specifically, elevated proinflammatory cytokines increase oxidative stress, cause blood brain barrier dysfunction and accelerates the amyloid-β accumulation in the brain (Jiang et al., 2017; Kesika et al., 2021). This possibility is strengthened by evidence from studies of the ADLP^{APT} mice (which carries 3 human transgenes for amyloid precursor protein, presenilin-1 and tau), which displays gut microbiota composition alterations, gut barrier dysfunction and chronic gut and systemic inflammation. AD pathology is usually seen at 8 months of age in this model, while gut dysbiosis is noted as early as 2 months, indicating that the gut dysfunction precedes AD pathology. In another AD mouse model, Tg2576, one study showed that gut dysregulation preceded cerebral Aβ aggregation (Honarpisheh et al., 2020). This was associated with increased inflammatory plasma cytokines, possibly contributing to the disease etiology. Moreover, oral fecal microbiota transfer from wild type donor mice to transgenic mice, reduced gut permeability, decreased hippocampal amyloid-β and tau accumulation (Kim, Kim et al., 2020). A human cross-sectional study from a memory clinic in Japan presented that the concentration of gut microbiome-associated metabolites was related to dementia risk. Specifically, increased fecal ammonia was associated with increased risk and lactic acid was associated with decreased risk (Saji et al., 2020). As discussed previously, IBD impacts gut metabolites as well as peripheral inflammation which may explain why it elevates the risk of dementia. Relatedly, stroke, which is a risk factor for vascular dementia, is increased in patients with IBD (Xiao et al., 2015). In addition, specific memory functions, unrelated to dementia, such as amygdala mediated emotional cognitive alterations and hippocampus mediated visuospatial episodic memory alterations may occur in IBS (Kennedy et al., 2014).

5.3. Parkinson's disease

This movement disorder, is the second most prevalent neurodegenerative disease that affects the aging population. Unlike MS and AD, PD affects more men than women (2:1), and men are more likely to show early onset of the disease. The symptoms range from sleep disturbances, loss of smell, difficulty swallowing, constipation, bladder control issues, fatigue, tremor in the hands or legs, gait disturbances to cognitive deficits. This progressive neurological disorder is characterized by loss of dopaminergic neurons in the mesencephalon, particularly in the substantia nigra pars compacta (Hirsch et al., 1998). Previous studies demonstrate that these vulnerable neurons are very sensitive to inflammation (McGeer et al., 1988; Blum-Degen et al., 1995; Banati et al., 1998). Importantly, the blood brain barrier integrity is compromised in the ventral mesencephalon of Parkinson's patients (Kortekaas et al., 2005). In a mouse model of PD, systemic inflammation induced by peripheral administration of LPS elevated blood brain barrier permeability (Al-Bachari et al., 2020), and increased the number of galectin expression in microglia, followed by loss of dopaminergic neurons in the MPTP treated animals (Garcia-Dominguez et al., 2018). Moreover, astrocytes also play a key role in neuroinflammation in PD (Episcopo et al., 2013; Rizor et al., 2019). In addition to the above-mentioned changes in blood brain barrier and PD, recent studies highlight the direct association between IBD and PD in both clinical studies and in animal models. For example, a retrospective study indicates that there is 35% increased risk for PD in Crohn's disease patients (Lin, Lin et al., 2016). In fact, a 2006 study found alpha-synuclein, whose protein aggregates in dopaminergic neurons play a key role in PD, also aggregates in the Meissner's and Auerbach's plexus in the stomach of different stages of PD patients

(Braak et al., 2006), providing first evidence to link the neuronal dysfunction in the gut and PD. Another study showed that experimental colitis caused increased expression of inflammatory markers and phopshorylated-alpha-synuclein in marmosets with colitis (Resnikoff et al., 2019) suggesting that immune activation and peripheral inflammation plays a critical role in PD pathology. Similarly, higher expression of CD8+ T-cells and NF-kappaB p65 were reported in the colon of PD patients (Houser et al., 2018). The same study showed that depletion of CD8+ T-cells in male mice reduced the colitis-induced reduction of dopaminergic neurons. Additionally, microbial dysbiosis, characterized by reduction of beneficial microbes such as prevotellacaea and its metabolites are observed in the fecal samples of PD patients (Unger et al., 2016; Sun and Shen, 2018). The heightened inflammatory response coupled with low levels of beneficial gut metabolites associated with IBD can increase the blood brain barrier permeability and elevate the risk of dopaminergic neuronal loss in PD brain.

5.4. IBD and neuropsychiatric disorders

In addition to neurodegenerative disease, neuropsychiatric disorders such as schizophrenia and autism are associated with IBS-like symptoms (Catassi, 2015).

Anxiety and depression are higher in IBD patients versus healthy controls. They are also higher in active disease IBD patients when compared to inactive IBD patients (Mikocka-Walus et al., 2016). Additionally, IBD is associated with a later increase in abnormal anxiety scores while baseline anxiety makes more aggressive IBD therapy necessary as it decreases chance of remission (Gracie et al., 2018). Clinically, this implies that IBD patients should be regularly screened for psychological disorders. The link between IBD and depression and anxiety is largely attributed to the proinflammatory systemic profile that accompanies IBD. Consequently, inflammation associated diseases of the nervous system also show an increased incidence with IBD.

5.5. Impact of sex and age on gut-brain disease

Due to the established effect of sex hormones on gut and brain functions, it is not surprising to note the sex difference in IBS occurrence as well as the sex specific dysregulation of the gut-brain axis. In Western countries, the female-to-male ratio of IBS occurrence is 2:1 (Camilleri, 2021). World-wide, that estimate rises to two-thirds of IBS patients being women (Shiotani et al., 2006). This shocking sex difference in prevalence has been largely attribute to sex hormones. Sex hormones have been shown to regulate mechanisms involving the gut-brain axis, stress response, intestinal barrier function, immune activation of intestinal mucosa, and gut microbiota. Not surprisingly, we see a similar sex difference in autoimmune diseases of the CNS such as multiple sclerosis where it is two to three times more common in women than men. Additionally, among men, IBS symptomatology tended to be inversely related to testosterone (Kim, Kim et al., 2018). Studies have also detailed that abdominal pain intensity was reported to be more severe in women with IBS following menopause than before menopause (Mulak and Taché, 2010; Meleine and Matricon, 2014). In response to a moderate visceral stimulus (inflation of the rectum), female patients showed greater activation in the ventromedial PFC, right anterior cingulate cortex, and left amygdala. In contrast, men showed greater activation of the right dorsolateral PFC, insula, and dorsal pons/periaqueductal gray (Naliboff et al., 2003), suggesting that brain circuits associated with IBS symptoms may be sexually dimorphic. Additionally, gray matter volume and cortical thickness changes have been identified in IBS patients (Labus et al., 2014). The sex differences in IBS are further observed in pain sensation where chronic pain conditions associated with IBS occur predominantly in female patients (Fadgyas-Stanculete et al., 2014).

In addition to sex differences in prevalence of IBS, there are differences in disease presentation between men and women. Women have been reported to have greater symptom severity (Yang et al., 2011; Choghakhori et al., 2017). The prevalence of IBS subtype, according to predominant stool pattern, seemed to vary between females and males with IBS. In females, IBS-C is significantly more common and IBS-D us significantly less common. IBS-M was shown to occur equally in both sexes (Lovell, Ford et al., 2012). Moreover, the serotonin transporter SLC6A4 and the S100A, a calcium binding protein that colocalizes with serotonin receptors are significantly higher in middle-aged female patients than in males (Katsumata et al., 2017). Additionally, prevalence of demyelinating and non-demyelinating peripheral neuropathies in association with IBD is higher in male patients although the difference is less pronounced for the demyelinating variety (Gondim et al., 2005).

5.6. Life span

Among children with IBD, 4% present before age 5 years and 18% before age 10 years, with the peak onset in adolescence. In approximately 25% of patients, IBD is diagnosed before age 20 years (Reed-Knight et al., 2016), and in approximately 50% of patients, symptoms began before age 35 (Canavan et al., 2014). One study reported that the 10–17 age subgroup was the major contributor to the rising pediatric IBD prevalence (Ye et al., 2020). Additionally, the incidence of IBD is bimodal; the first peak occurs in the second and third decades of life, with the second increase noted between the fifth and seventh decades (Kim and Ferry, 2004). It is worth noting that this distribution corresponds with the peak incidence of specific neurological diseases. For examples, the peak in the 2nd-3rd decade corresponds well with multiple sclerosis, which usually originates in younger individuals. The later peak during the 5th -7th decade corresponds with the development and progression of Alzheimer's disease and Parkinson's disease, which occur in aging but have a 10–20 year incubation period. There is also an increasing incidence and prevalence of IBD among the elderly as a consequence of the aging population (Arnott et al., 2018). With IBD patients belonging to many different age groups, research studies have focused on assessing age related differences in disease presentation.

Some population studies report no observed differences in the distribution of IBS subtypes between age groups (Tang et al., 2012) while another study claimed that among children, Crohn's disease was twice as prevalent as ulcerative colitis (45.9 vs 21.6). This study also noted that prevalence was higher in boys than girls for all forms of IBD, in contrast to the adult population where the prevalence was higher in women than men (Ye et al., 2020). The differing reports could be attributed to the challenge of diagnosing IBD later in life. Diagnosis in IBS patients can be confounded due to the large number of conditions that mimic IBD (NSAID induced colitis, Ischemic colitis,

Segmental Colitis Associated with Diverticulosis) (Prelipcean et al., 2013). Additionally, IBD diagnosis in the elderly can be particularly challenging because of the relative paucity of data often resulting from their exclusion from clinical trials and age-specific concerns such as impaired locomotor and cognitive function, co-morbid conditions, and consequent use of multiple prescriptions (Nimmons and Limdi, 2016; King et al., 2020).

6. Conclusion

This review offers a synthesis and summary of the current literature that has examined the neurological complications of IBS. Neurological manifestations of IBS are considered to be a major health problem, affecting disease morbidity. From the few clinical and preclinical studies covered in this review, it is clear that there is not a significant understanding of the pathogenesis of IBS-induced neurological manifestations, and much research is necessary. Such research will accelerate the development of therapeutics whose target is to decrease intestinal permeability or to repair bidirectional communication between the gut and the brain. The goal of this review is to serve as a comprehensive resource for researchers, physicians and pharmaceutical companies to use while developing novel gut-based therapeutics for neurological

conditions.

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