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Review Article

Inflammatory Bowel Disease and Neurodegenerative Diseases

Jin Sun Kim[1], Mu-Hong Chen[2,3,4], Hohui E. Wang[5], Ching-Liang Lu[4,6,7], Yen-Po Wang[4,6,7], and Bing Zhang[1]

[1]Division of Gastrointestinal and Liver Diseases, Department of Medicine, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA, [2]Department of Psychiatry, Taipei Veterans General Hospital, [3]Division of Psychiatry and [4]Institute of Brain Science, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, [5]Department of Psychiatry, University of California San Francisco, San Francisco, CA, USA, [6]Endoscopy Center for Diagnosis and Treatment, and [7]Division of Gastroenterology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

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Corresponding Author
Yen-Po Wang
ORCID https://orcid.org/0000-0002-3769-0020
E-mail ulnafu@gmail.com

Bing Zhang
ORCID https://orcid.org/0000-0002-3377-0963
E-mail bing.zhang@med.usc.edu

A growing body of evidence has demonstrated an intricate association between inflammatory bowel disease (IBD) and neurodegenerative conditions, expanding beyond previous foci of comorbidities between IBD and mood disorders. These new discoveries stem from an improved understanding of the gut-microbiome-brain axis: specifically, the ability of the intestinal microbiota to modulate inflammation and regulate neuromodulatory compounds. Clinical retrospective studies incorporating large sample sizes and population-based cohorts have demonstrated and confirmed the relevance of IBD and chronic neurodegeneration in clinical medicine. In this review, we expound upon the current knowledge on the gut-microbiome-brain axis, highlighting several plausible mechanisms linking IBD with neurodegeneration. We also summarize the known associations between IBD with Parkinson disease, Alzheimer disease, vascular dementia and ischemic stroke, and multiple sclerosis in a clinical context. Finally, we discuss the implications of an improved understanding of the gut-microbiome-brain axis in preventing, diagnosing, and managing neurodegeneration among IBD and non-IBD patients. **(Gut Liver 2023;17:495-504)**

Key Words: Inflammatory bowel diseases; Dementia; Parkinson disease; Multiple sclerosis; Gut-brain axis

INTRODUCTION

Inflammatory bowel diseases (IBD) are characterized by pathologic immune activation against microbiome dysbiosis in a genetically susceptible individual.[1] Manifesting mainly as either ulcerative colitis (UC) or Crohn's disease (CD), both present as chronic relapsing and remitting gastrointestinal and systemic inflammation. The two diseases demonstrate distinct phenotypes, encompassing different patterns of gastrointestinal involvement, depths of inflammation, impact on surrounding organs, in addition to endoscopic, histologic, and radiographic characteristics.

Recently, increasing evidence suggests an association between chronic inflammatory disorders and neurodegeneration. This was demonstrated by the ARIC (Atherosclerosis Risk in Communities) study, which established that systematic inflammation was associated with increased cognitive decline among patients followed for up to 20 years.[2] Furthermore, patients with IBD or rheumatologic diseases have higher incidence of multiple sclerosis (MS) and vice versa.[3-5] While epidemiologic and clinical evidence are robust, pathophysiology remains uncertain.

Until recently, research on brain disorders among IBD patients has focused primarily on depression and anxiety, two highly prevalent comorbid mental illnesses linked with worse IBD clinical outcomes.[6-8] Two research publications from 2018 and 2019 examined and found positive correlation between IBD and development of Parkinson disease (PD), prompting investigation between IBD and chronic neurodegeneration beyond mood disorders.[9,10] Our team subsequently investigated the risk of dementia among IBD patients using the Taiwan National Health Insurance Research Database and found increased risks for both overall dementia and Alzheimer disease (AD), and both diagnosed at younger ages among IBD patients compared to matched controls.[11] These associations were supported by

subsequent findings from the United States,[12] while studies from Korea and Denmark reported significant but less dramatic risks,[13,14] and the U.K. Biobank study reported lack of association.[15]

Several plausible mechanisms link IBD with neurodegeneration, including genetic factors, gut microbiome dysbiosis, and environmental factors which may affect both the enteric nervous system (ENS) and central nervous system (CNS).[4,5] Moreover, there is an increased risk of vascular dementia given the high thromboembolic risk in IBD patients.[16] This paper reviews the current literature to present the incidence, pathophysiology, and risk factors of neurodegenerative diseases in IBD. We also discuss the clinical impact of these associations and implications for the management of neurodegenerative diseases in IBD patients.

GUT-BRAIN AXIS

The gut-brain axis consists of the CNS, ENS, autonomic nervous system, and the hypothalamic pituitary adrenal pathway.[17] Through these connections, the gut-brain axis plays an essential role in the crosstalk between the gastrointestinal system and the CNS. There are many pathways of communication between the gut and the brain including neuronal, immune, endocrine, and metabolic methods of communication.[18] This gut-brain bidirectional communication system has mostly been explored to understand the pathophysiology of irritable bowel syndrome patients, although more recent literature has begun to explore its role in IBD patients.[19]

The balance of microbial diversity and richness influences neurons and neurotransmitters of the ENS including dopamine, serotonin (5-HT), and catecholamines.[20] These neuropeptides induce vasodilation, leukocyte migration, and plasma extravasation to regulate colonic inflammation. They also function as signaling molecules of the autonomic nervous system, thus serving as neuromodulators and neurohormones to mediate between the nervous system and the gut.[21] Disturbance of normal intestinal flora in IBD patients induce a pro-inflammatory effect in the intestines that is relayed to the nervous system (Fig. 1). Spore-forming bacteria in the gut produce short-chain fatty acids (SCFAs) and secondary bile acids that stimulate 5-HT production and secretion from the enterochromaffin cells (ECCs) of the gut epithelium. ECCs have neuropod-like extensions that allow them to communicate with the vagal afferent fibers, which ultimately project to the nucleus tractus solitarius in the brainstem.[19,22] On the other hand, central regulation of the intestine is also present. The autonomic nervous system can activate ECCs to release 5-HT into the gut. ECCs have more than 90% of the body's 5-HT and are uptaken by 5-HT receptors of the intestinal system.[19] Cholinergic signals from the vagal efferent fibers can also exert anti-inflammatory effects by inhibiting cytokine release from macrophages.[22]

Immune and endocrine pathways of communication are also important components of the gut-brain axis. Stress such as local infection, food antigens, and dysbiosis will trigger intestinal inflammation as microbial cell wall components such as lipopolysaccharide (LPS), flagellin, and

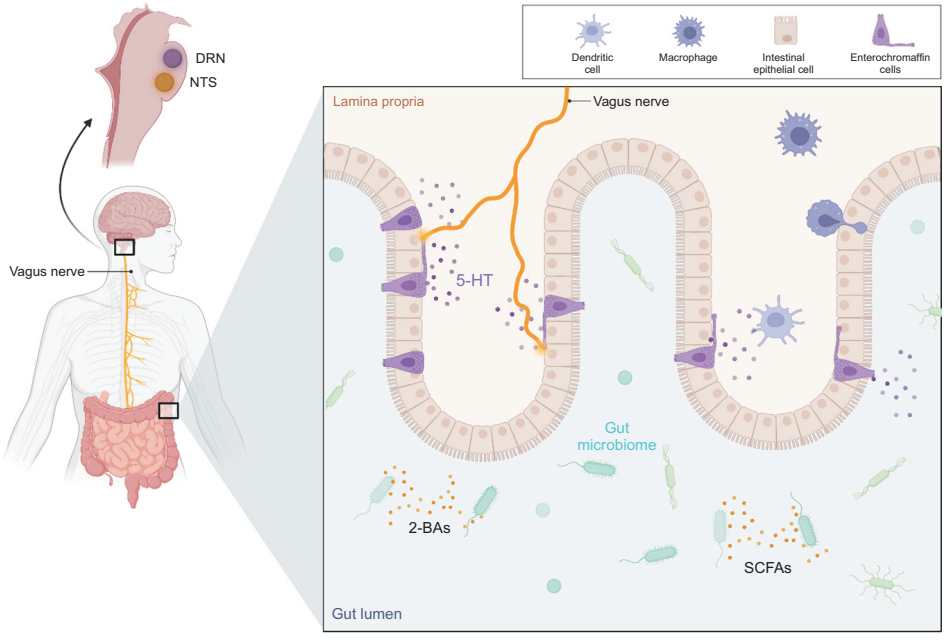

Fig. 1. The gut microbiome produces molecules such as SCFAs and 2-BAs that simulate enterochromaffin cells to release 5-HTs. 5-HTs communicate via the vagus nerve, traveling to the nucleus tractus solitarius in the brainstem. The autonomic nervous system also communicates via the vagus nerve and can activate enterochromaffin cells to release 5-HT into the gut.
SCFAs, short-chain fatty acids; 2-BAs, secondary bile acids; 5-HTs, serotonins; DRN, dorsal raphe nucleus; NTS, nucleus tractus solitarii.

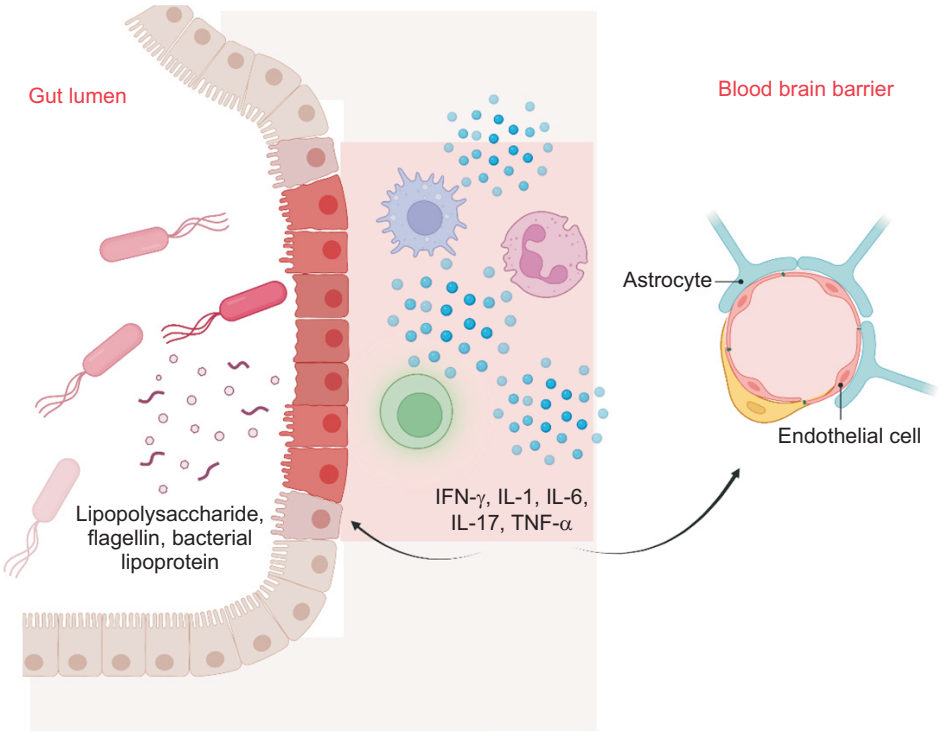

Fig. 2. Microbial components such as lipopolysaccharide, flagellin, and bacterial lipoprotein encounter immune cells and activate them. The activated immune cells release pro-inflammatory cytokines and modulators such as IFN-γ, IL-1, IL-6, IL-17, and TNF-α, which alters the gut epithelium and blood-brain barrier, leading to increased intestinal and blood-brain barrier permeability.
IFN-γ, interferon gamma; IL, interleukin; TNF-α, tumor necrosis factor alpha.

bacterial lipoprotein come into contact with the Toll-like receptors of immune cells (Fig. 2).[17] Activated immune cells release pro-inflammatory cytokines and modulators such as interferon gamma, interleukin (IL)-1, IL-6, IL-17, and tumor necrosis factor alpha (TNF-α). These pro-inflammatory mediators disturb epithelial tight junctions, both increasing intestinal permeability and disrupting the blood-brain barrier (BBB).[22] The "leaky gut" and compromised BBB allows for translocation of systemic immune cells and cytokines to travel from the gut to the brain.[22] Moreover, intestinal inflammation from stressors triggers activation of the hypothalamic pituitary adrenal axis, increasing release of glucocorticoids. Glucocorticoids affect intestinal function and immune activity, which may help restore intestinal homeostasis. However, the balance is nuanced given multiple factors. Blunting of the hypothalamic pituitary adrenal axis with microbiota deficiency and dampening of the corticotropin release hormone (CRF) gene associated with chronic colitis may counteract the release of glucocorticoids.[22,23]

Lastly, microbe derived neuroactive molecules such as microbial metabolites play a key role in the gut-brain communication. SCFAs, which regulate intestinal motility, secretion, and production of 5-HT as mentioned above, are produced by fermentation of dietary fiber by microbes in the gut.[17,19] Bile acids, which are synthesized and conjugated from cholesterol in the liver, are metabolized by gut microbes. Primary bile acids are deconjugated and dehydroxylyzed into secondary bile acids.[17] Secondary bile acids bind to farnesoid X receptor and G protein-coupled receptor 5, which are expressed in ECCs, intrinsic and extrinsic nerves, as well as immune cells.[24] They have many different roles in gut homeostasis including glucose metabolism, 5-HT production, and immune response modulation.[19,25,26] The gut microbiome also produce tryptophan metabolites such as 5-HT, kynurenine, and ligands for aryl hydrocarbon receptor.[17,21] Increased production of kynurenine associated with various local stress and dysbiosis can cross the BBB and exert neuroinflammatory effects.[19] Taken together, several physiologic mechanisms serve to relay intestinal inflammation reflecting IBD to the CNS. Focused discussions of the gut-brain-axis' role in specific neurodegenerative diseases are described below.

PARKINSON DISEASE

Increased risk of PD in IBD patients has been reported. Several of these studies revealed significantly increased incidence of IBD before and after the PD diagnosis, suggesting a bidirectional relationship.[27-29] These findings were also supported by research utilizing several population-based health databases including the Taiwanese, Korean, Sweden, and Danish databases.[9,29-31] Specifically, higher risk of developing PD were identified among IBD patients who were older (>65 years) and those who did not undergo

treatment with anti-TNF-α agents or azathioprine. There were no differences between men and women.[27]

Several theories have been speculated to explain the relationship between IBD and PD. Genetic overlap in the pathogenesis of IBD and PD has been one. Specifically, mutations in the LRRK2 gene, the most identified genetic cause of PD, are also associated with an increased risk of CD.[32] The study of Hui *et al.*[33] demonstrated that a variant of this gene increased risk of CD in PD patients, while another haplotype of the gene was likely protective. LRRK2 plays a role in α-synuclein phosphorylation and is expressed in neurons, glial cells, and immune cells; therefore, LRRK2 mutations may induce α-synuclein accumulation in the gut that spreads to the brain, leading to neurodengeration.[34,35] Increased LRRK2 activity is also associated with both gastrointestinal and systemic inflammation, reflecting CD development and disease activity. Other than the LRRK2 gene, six other loci were strongly associated between IBD and PD, with the strongest pleiotropic associations found between CD and PD.[36]

Another potential mechanism for the pathogenic mechanism of PD among IBD patients is the Braak hypothesis, which states that accumulation of α-synuclein in the gastrointestinal tract from gastrointestinal inflammation is slowly transported to the CNS via the vagus nerve.[36,37] This was supported by studies using mouse models, which showed that when α-synuclein preformed fibrils were injected to the intestine, there was spread of phosphorylated α-synuclein in the brain with associated loss of dopaminergic neurons.[38] Moreover, when vagotomy was performed, spread of phosphorylated α-synuclein in the brain was prevented and cognitive deficits were not observed.[38] Clinically, patients who underwent truncal vagotomy were suggested to have a lower risk of developing PD, further supporting the spread of α-synuclein via the vagus nerve.[39]

One theory to explain similar pathologic inflammation characteristic of IBD and PD is the transference of intestinal inflammation to the brain. Inflammation in IBD is characterized by increased activity of CD4 T cells, mainly Th1 and Th17 cells and attenuated activity of Treg cells which have suppressive effects on inflammation.[36] The Treg cells also have anti-inflammatory effects in the CNS, and hence, decreased Treg activity in IBD may contribute to increased CNS inflammation seen in PD.[40] IBD and PD are also both characterized by increased intestinal permeability, which in combination with the systemic inflammation in IBD and PD have been associated with BBB dysfunction and enhanced brain inflammation.[36,41] Increased intestinal permeability results in increased passage of bacteria and bacterial products such as LPS into the bloodstream, which in turn activates immune cells. LPS and activated cytokines may enter the BBB to induce CNS inflammation. LPS has also been associated with degeneration of dopaminergic neurons.[36] Furthermore, gut dysbiosis and inadequate signaling and metabolites from the gut microbiome is associated with enhanced neuro-inflammation and dysregulation of dopamine in IBD and PD patients. Altered gut microbiome and especially SCFA producing bacteria are found in both IBD and PD patients. SCFAs are known to have anti-inflammatory effects by regulating oxidative stress in the colonic mucosa and its decrease has been associated with accumulation of α-synuclein.[32,36]

Literature providing evidence of association between IBD and PD continues to increase, providing mechanistic possibilities linking the two seemingly unrelated diseases. The shared common theme of pathogenesis is the bidirectional spread of inflammation between the gut and brain, which is secondary to genetic polymorphisms, increased intestinal barrier permeability, and gut dysbiosis. Early exposure to anti-TNF therapy has been shown to reduce incidence of PD in IBD patients,[10,27] supporting that unchecked systemic inflammation is pathologic for both diseases. Clinician awareness of the association between IBD and PD may enable earlier diagnoses, leading to improved medical outcomes.

ALZHEIMER DISEASE

In recent years, several studies have reported increased risk of dementia among IBD patients.[11,12,42,43] Our team first showed IBD patients were diagnosed with dementia at an earlier age compared to matched controls (mean age 76 vs 83) and risk was elevated with increased chronicity of IBD diagnosis.[11] Numerous studies demonstrated an increased risk of dementia in IBD patients regardless of age, while one retrospective study revealed specifically increased risk of dementia in IBD patients aged 60 to 70 years old.[42-44] Of note, incidence of dementia before IBD diagnosis and comorbidity rate of dementia in IBD patients were not significantly different from those without IBD, suggesting unidirectional relationship,[45] which may reflect the differences in age of onset for IBD and dementia. While most studies demonstrated no significant differences in dementia risk between CD and UC patients, some reported mixed results.[14,44,46]

While majority of studies demonstrate positive associations between IBD and dementia, few recent studies failed to or only identified minimal association.[14,15,47] Specifically, Sun *et al.*[15] are following IBD and non-IBD patients for a mean of 11.58 years and demonstrated no significant difference in the hazard ratio of dementia. They also studied

the brain structures via brain magnetic resonance imaging and found no statistical difference in anatomic and tissue-specific volumes. Two-sample Mendelian randomization utilizing large-scale genome-wide association studies by Guo *et al.*[48] surprisingly showed a decreased risk of Alzheimer's disease in genetically-determined IBD. A third report from Denmark showed minimal association, which the authors explained was likely due to increased healthcare contact.[14] These results show that the association is likely complex and cannot be explained by genetics or healthcare policies alone. Taken together, existing meta-analyses demonstrate positive unidirectional relationship between IBD and dementia, with most studies reporting the hazard ratio to be greater than 1 and less than 2.[42,43]

Neurocognitive degeneration and AD among IBD patients may reflect changes in the gut microbiome. The exact pathogenic process remains clandestine, but one hypothesis is that gut dysbiosis and increased intestinal permeability in IBD leads to increased neuronal inflammation from transference of intestinal inflammation.[45,49] One potential way is via the vagus nerve, which serves as a liaison between the ENS and the CNS. Sun *et al.*[50] showed that beta-amyloid injected in the intestinal tract of mice was found in the vagus nerve and brain one year later and accompanied concomitant cognitive dysfunction. Hence, chronic inflammation in IBD may lead to beta-amyloid plaque formation in the intestinal tract that spreads to the brain via the vagus nerve.[49] Studies of decreased beta-amyloid and Tau lesions following vagotomy and restoration of impaired memory further support this hypothesis.[51]

Another possibility linking IBD and dementia is intestinal microbiota dysbiosis, a prominent feature of IBD.[45,52] Both IBD and AD patients were found to have decreased microbiome diversity.[49] The gut microbiome is capable of producing anti-inflammatory metabolites such as SCFAs, certain bile acids including tauroursodeoxycholic acid, and ligands for aryl hydrocarbon receptor, which are capable of crossing the BBB to modulate inflammation in the CNS.[49,53] Decreases in the production of these beneficial metabolites are secondary to diminished microorganisms responsible for their production often associated with decreased microbiome diversity. Conversely, several studies have also noted that chronic systematic inflammation in IBD accompanies the production of neurotoxic metabolites which in turn promote inflammation in the CNS via activation of microglia and astrocytes. These intestinal metabolites include kynurenine and certain bile acids, and inflammatory biopolymer substances such as LPS and enterotoxins. The biopolymer substances in particular damage the intestinal lining and the resulting "leaky gut" potentiates the capacity of neurotoxic metabolites to migrate from the gut lumen into circulation and possibly the CNS.[17,49,53,54]

Although the exact mechanisms of pathogenesis of AD in IBD patients remain unclear, several studies have suggested clinical implications in IBD patients in respect to prevention of AD. The study of Kim *et al.*[13] showed that female sex and age ≥65 years experienced increased AD risk, while those living in an urban area had decreased risk. Dementia screening strategies in IBD patients, and especially those harboring other risks, are recommended. Furthermore, control of IBD activity likely protects against inflammation-associated neurodegeneration.[12] Finally, healthy lifestyle behavior including exercise, maintaining a healthy weight and diet, and cessation of tobacco and alcohol may improve IBD and prevent chronic neurodegeneration.[55,56] Microbiome-based research on dementia and AD potentiate the future development of novel diagnostic and therapeutic modalities for dementia through manipulation of the intestinal flora.[49]

VASCULAR DEMENTIA AND ISCHEMIC STROKE

Current literature suggests association between vascular dementia and IBD given overall 2- to 3-fold increased risk of venous thromboembolisms (VTEs) among IBD patients, which is an established independent risk factor for thromboembolic events.[16,57-59] Although the pathogenesis is multifactorial,[60-62] recent focus on "vascular hypothesis" suggests micro- and macrovascular endothelial dysfunction secondary to elevated inflammatory cytokines in IBD leads to increased VTE risk.[60,61] While most thromboembolic events are deep vein thromboses or pulmonary embolisms, several cases have also described cerebral arterial infarction in IBD patients.[63,64]

Among IBD patients, higher risk for VTEs is associated with active and severe disease, corticosteroids use, extensive colonic involvement, hospitalization, surgery, and pregnancy.[59,65,66] Given these additional risk factors, IBD patients hospitalized for flare should be initiated on deep vein thromboses prophylaxis medications unless otherwise contraindicated.[16] Use of prophylactic anticoagulation has been deemed safe and the risk of gastrointestinal bleeding is not higher among those receiving anticoagulation.[67] For postoperative patients, including those who underwent colorectal surgery, standard prophylactic dosages of anticoagulation may be inadequate, and higher doses with longer period may be more beneficial.[68] Managing other known risk factors by maintaining the state of remission and avoiding use of steroids, hormone replacement therapy, immobilization, and smoking also help prevent VTEs.[16]

Lastly, although outpatient use of prophylactic anticoagulation has been associated with decreased lifetime risk of VTEs, its use is not recommended due to lack of cost-effectiveness.[69]

MULTIPLE SCLEROSIS

The association of MS, a demyelinating disorder of the CNS, and IBD has been well established. While difficult to ascertain which condition precedes the other, there is higher prevalence of MS among IBD patients and vice versa. Specifically, meta-analyses have reported relative risk of >1.5 for the comorbidities.[4,5] Interestingly, patients with both MS and IBD were found to have milder neurological course compared to patients with only MS. Zéphir *et al.*[70] showed MS-IBD patients had lower Expanded Disability Status Scale compared to MS-only patients and a lower proportion transitioned from relapsing-remitting MS to secondary-progressive MS after a median of 12 years of disease follow-up.

Many hypotheses attempt to explain the correlation between MS and IBD. Both are classified as immune-mediated inflammatory diseases.[71] MS patients have reduction in the phyla Bacteroidetes and Firmicutes, which are associated with production of anti-inflammatory SCFA.[71] Other studies have elucidated dysbiosis relating to the development of experimental autoimmune encephalomyelitis (EAE), the murine equivalent of MS.[72] Increased intestinal permeability associated with increased pro-inflammatory Th1 and Th17 cellular responses and reduced anti-inflammatory Treg activity precedes and worsens with development of EAE.[73-75] Conversely, germ-free or antibiotic-treated mice with altered microbiome exhibited attenuation of EAE disease severity corresponding to normalization of Th1 and Th17, while the regulatory effect of Treg was heightened leading to increased release of IL-10 and IL-13.[76,77] Taken together, the gut microbiome and its metabolism have a clear role in the pathogenesis and severity of EAE/MS.

Beyond the gut-microbiome-brain axis, shared genetic and environmental risk factors are found in patients with MS and IBD. Environmental variables include vitamin D deficiency, smoking, cold climate, and high socioeconomic factors.[4] Several experimental studies have shown that vitamin D is required for the normal development of T cells, and supplementation has a protective effect against MS and IBD through suppressing Th1 autoimmune responses while activating anti-inflammatory Treg cells.[78,79] Genetically, three single-nucleotide polymorphisms were found to be associated with IBD and MS. Greater correlation was found between MS and UC patients (commonly harboring the single-nucleotide polymorphism rs116555563) than between MS and CD patients (commonly harboring the single-nucleotide polymorphisms rs13428812, rs9977672). However, a causal relationship could not be established.[80] In IBD patients with concomitant MS, anti-TNF agents are avoided given concerns of drug-induced demyelination.[81] Several case reports have shown development of MS after treatment with anti-TNF agents.[82,83] Clinical studies reported 1.43 to 2 times increased risk of MS in IBD patients who underwent anti-TNF therapy compared to IBD patients who did not.[84,85] Although the exact mechanism of drug-induced demyelination is unclear, one hypothesis is that anti-TNF agents stop the apoptosis of autoreactive T cells, which subsequently cross the BBB to induce demyelination. Moreover, anti-TNFs cannot cross the BBB and thus may lead to paradoxical increased TNF-α level in the CNS promoting an inflammatory environment.[85] On the other hand, TNF-α can also have anti-inflammatory effects by promoting Treg cells. Hence, another theory is anti-TNF agents may systemically induce autoimmunity by decreasing TNF-α associated upregulation of Treg cells.[85]

The use of sphingosine-1-phosphate (S1P) receptor modulators for treatment of coexisting IBD and MS is an area of ongoing research.[86-88] S1P is a lysophospholipid signaling molecule that regulates the immune system via S1P1, S1P4, and S1P5 receptors. Ozanimod, a selective S1P receptor modulator that specifically binds to S1P1 and S1P5 receptors, has been approved for the treatment of relapsing forms of MS,[86] and was recently approved for UC.[87,88] For moderately to severely active CD, the phase 2 trial has shown clinical, endoscopic, and histologic improvements and phase 3 trials are in investigation.[87] By decreasing lymphocyte activation via internalization of S1P receptors, S1P receptor modulators may specifically be considered for management UC and possibly CD in patients with coexisting MS.[88]

CONCLUSION

There continues to be a growing interest in the role of the gut-brain axis in IBD and neurodegenerative diseases. Current literature supports bidirectional associations between PD and MS with IBD, whereas increased risk of dementia and AD among IBD patients is more established with emerging evidence. Increased risk of VTEs associated with chronic inflammation accompanying IBD may contribute to the unidirectional association between IBD patients and dementia via heightened risk for vascular dementia.

While the phenotypes, clinical management and sequelae differ greatly among these chronic neurodegenerative diseases, several shared etiologic mechanisms are affiliated with IBD. Chronic systemic inflammation drives increased neuro-inflammation and higher permeability of the BBB. Intestinal microbial dysbiosis, a characteristic feature of IBD relapse, reflects decreased production of anti-inflammatory metabolites and potential increase in microbial-derived neurotoxic and neuromodulatory molecules. Gastrointestinal inflammation accompanying "leaky gut" increases the potential of these molecules to enter systemic circulation to eventually penetrate the CNS. Inflammatory signaling may also travel from the intestines to the CNS via the vagus nerve. Finally, shared genetic and environmental risk factors may contribute to both neurodegeneration and development of IBD, several of which have been described. These mechanisms may also play role in other brain disorders, including psychiatric manifestations.[89,90]

This review summarizes current knowledge regarding the relationship between IBD and neurodegenerative diseases. Existing research to-date rely largely upon animal models or observational studies from population-based cohorts, of which conclusions drawn from the former may not be directly applicable to humans, and the latter may contain biases and confounders. Large prospective observational studies will enhance the strength of available evidence; however, an increased mechanistic understanding of the gut-microbiome-brain axis and pathogenic mechanisms are needed to generate novel clinical diagnostics and therapeutics.

In conclusion, great strides have been made to study the role of the gut-brain axis in neurodegeneration and brain disorders. Existing evidence supports bidirectional crosstalk between the CNS and the ENS. Further experimental and epidemiological studies on IBD and less studied neurodegenerative diseases such as Lewy body dementia, frontotemporal dementia, and alcohol-related dementia may add to the current foundation of knowledge of the gut-brain axis. Moreover, clinical studies that are controlled and prospective would enhance current understanding of the precise methodology of the bidirectional crosstalk. Specifically, future research focusing on discriminating the contributions of each possible mechanistic pathway to neurodegenerative disorders from the gastrointestinal tract may lay the foundation for the development of novel diagnostics and therapeutics for the management of chronic neurodegeneration.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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ORCID

Jin Sun Kim https://orcid.org/0000-0002-1232-5326
Mu-Hong Chen https://orcid.org/0000-0001-6516-1073
Hohui E. Wang https://orcid.org/0000-0001-9486-8473
Ching-Liang Lu https://orcid.org/0000-0001-9335-7241
Yen-Po Wang https://orcid.org/0000-0002-3769-0020
Bing Zhang https://orcid.org/0000-0002-3377-0963

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