REVIEW ARTICLE

Bridging Gut Inflammation and Cognitive Decline: Exploring the Pathogenesis of Inflammatory Bowel Disease-associated Dementia

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Abstract

Dementia, characterized by a progressive decline in cognitive functions such as memory, thinking, problem-solving, language, and behavior, is most commonly associated with Alzheimer's disease, a prevalent neurodegenerative disorder. Recent epidemiological evidence suggests a potential link between inflammatory bowel disease (IBD) and dementia, prompting investigations into this association. This abstract reviews current research on the pathogenesis of IBD-associated dementia, focusing on animal model studies that mimic chronic intestinal inflammation similar to IBD. The pathogenesis of IBD is related to dysbiosis of the gut microenvironment, and various epidemiological studies show that patients with IBD are more likely to have dementia in future. Thus, targeting IBD as a potential therapeutic approach for dementia has garnered increasing attention. Furthermore, IBD-induced neuroinflammation affects brain function and contributes to dementia. In this review, we highlight the role of microbiota and their metabolites in mediating the pathogenesis of IBD-associated dementia. Disruptions in gut microbiota can lead to altered metabolite profiles that may influence neuroinflammatory pathways and exacerbate cognitive impairment. Furthermore, immune-mediated mechanisms play a critical role in this process. The microbiota-gut-brain axis, which links gut microbiota with brain function, has emerged as a significant pathway through which IBD-related changes in microbiota and metabolites contribute to dementia. Overall, the research underlines the complex interplay between chronic intestinal inflammation, microbiota alterations, and immune responses in the development of dementia associated with IBD.

Key words: Dementia, gut–brain axis, inflammatory bowel disease, immune-mediated mechanisms, microbiota

INTRODUCTION

Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), represents a group of chronic, relapsing inflammatory conditions primarily affecting the gastrointestinal (GI) tract. CD can involve any part of the GI tract, with a preference for the terminal ileum and colon, and is marked by transmural inflammation, skip lesions, and granuloma formation. In contrast, UC is confined to the colon and rectum, presenting as continuous mucosal and submucosal inflammation.[1] Both disorders significantly impact patient's quality of life and healthcare systems globally. The pathogenesis of IBD is multifactorial, driven by an intricate interaction of genetic, environmental, microbial, and immune factors. Genetic predisposition, including mutations in genes such as NOD2, ATG16L1, CARD9, and IL23R, impairs microbial sensing, autophagy, and immune regulation. Environmental triggers such as a Western diet, antibiotic exposure, smoking, and increased hygiene contribute to gut microbial dysbiosis.[2] This dysbiosis compromises the intestinal epithelial barrier, facilitating the translocation of luminal contents and triggering inappropriate immune responses. Both innate and adaptive immune pathways are implicated in IBD pathophysiology. Disruption of the epithelial barrier permits microbial antigens to activate pattern recognition receptors (PRRs), including toll-like receptors

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(TLRs) and NOD-like receptors (NLRs), on innate immune cells such as macrophages and dendritic cells.[3] This leads to the release of pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, and IL-6. The adaptive immune response further drives inflammation through aberrant T-cell activation. CD is predominantly associated with Th1/Th17 responses, characterized by elevated interferon gamma (IFN-γ) and IL-17, whereas UC is linked to a Th2-skewed response involving IL-4, IL-5, and IL-13. Impairment in regulatory T-cells (Tregs) exacerbates chronic immune activation.[4] Several intracellular signaling pathways orchestrate the inflammatory milieu in IBD. The nuclear factor kappa B (NF-κB) pathway is a central regulator of inflammatory gene transcription. Similarly, the Janus kinases/ Signal transducer and activator of transcription (STAT) axis, especially via STAT3 activation by IL-6 and IL-23, promotes immune cell survival and proliferation. The mitogen-activated protein kinase pathway (ERK, JNK, and p38) responds to cellular stress and cytokines, enhancing pro-inflammatory cytokine production and epithelial damage. The NLRP3 inflammasome also plays a crucial role by activating caspase-1, which processes pro-IL-1β and pro-IL-18 into their active inflammatory forms.[5] Chronic intestinal inflammation in IBD may also trigger genetic and immunological pathways shared with neurodegenerative conditions, particularly dementia.[6]

Dementia is a progressive clinical syndrome that includes various neurodegenerative disorders like Alzheimer's disease (AD), vascular dementia (VaD), Lewy body dementia (LBD), frontotemporal dementia (FTD), and Parkinson's disease dementia (PDD).[7] Although these subtypes exhibit overlapping clinical symptoms such as memory impairment, disorientation, and behavioral changes, each is distinguished by specific neuropathological signatures. AD is associated with amyloid-β plaques and tau tangles, VaD with vascular-induced cerebral damage, LBD with α-synuclein accumulation, FTD with degeneration in the frontal and temporal lobes, and PDD with motor and cognitive dysfunction arising from Parkinsonian pathology.[7]

Emerging data suggest a potential pathophysiological overlap between IBD and dementia, underpinned by shared mechanisms including chronic systemic inflammation, immune dysregulation, and gut–brain axis (GBA) disruption. In addition, microRNAs (miRNAs) are implicated as key regulators in both diseases. In this review, we investigated the potential link between IBD and neuroinflammation as well as the mechanism through which chronic inflammation may exacerbate the onset of dementia.

PREVALENCE OF IBD ASSOCIATED DEMENTIA

The epidemiological studies across the globe have revealed a correlation between pro-inflammatory cytokines and chemokines with neuroinflammation. Particularly, individuals suffering from gut inflammation or IBD show higher susceptibility to dementia.[8] A study by Zhang *et al*. utilized the Taiwanese National Health Insurance Research database to analyze 1,742 patients aged 45 and older with IBD to evaluate their risk of developing dementia. The results demonstrated markedly elevated dementia prevalence among patients with IBD, with an incidence rate of 5.5% compared to 1.4% in the control cohort. Furthermore, the hazard ratio (HR) for dementia development in IBD patients was calculated at 2.54 (95% confidence interval [CI]: 1.91–3.37). Researchers have also observed that youngsters with IBD exhibit minor difficulties with language and memory, but they do not experience significant cognitive impairments.[9] Zingel *et al*. conducted a nationwide retrospective cohort study in Germany which involved individuals aged 60 years and older diagnosed with IBD. The research involved 3,850 individuals diagnosed with IBD and an equivalent number of non-IBD controls. Results indicated that IBD was associated with a 1.22-fold increased likelihood of dementia development (95% CI: 1.07–1.39). Specifically, patients with UC faced a 1.25-fold increased risk of dementia (95% CI: 1.07–1.46). However, there was no significant association found between CD and dementia risk (HR: 1.17, 95% CI: 0.93–1.47).[10] Administering TNF-α inhibitors to individuals with IBD was found to significantly decrease the occurrence of dementia.

Inflammatory biomarkers common in IBD and dementia

Several inflammatory biomarkers commonly elevated in IBD have also been implicated in the pathogenesis of various dementia conditions, highlighting a potential immunological link between GI and neurodegenerative disorders. Among the most prominent biomarkers, TNF-α, IL-6, and IL-1β are consistently elevated in both IBD and neurodegenerative dementias.[11] These pro-inflammatory cytokines contribute to sustained systemic inflammation, blood-brain barrier disruption, and activation of microglia, thereby promoting neuronal damage and cognitive decline.[12] C-reactive protein, a nonspecific acute-phase protein frequently elevated in IBD, has also been associated with increased risk and severity of cognitive impairment in dementia. Additionally, IL-17 and IFN-γ, which are involved in Th17 and Th1 immune responses, respectively, have been linked to both IBD pathophysiology and neuroinflammation in dementia, particularly in vascular and frontotemporal subtypes.[13] The dysregulation of these biomarkers reflects a shared inflammatory network between the gut and the brain, suggesting that chronic peripheral inflammation in IBD may exacerbate neurodegenerative processes. This common biomarker profile underscores the importance of systemic immune modulation as a potential therapeutic strategy in managing both IBD and associated dementia conditions.

Common miRNAs in IBD and dementia

The miRNAs have emerged as key molecular regulators common to both IBD and dementia conditions. Among them, miR-155 is prominently upregulated in IBD as well as in dementia, where it acts as a pro-inflammatory mediator by enhancing NF-κB signaling and suppressing anti-inflammatory responses.[14] miR-146a, another widely shared miRNA, functions as a negative regulator of innate immunity and is elevated in response to chronic inflammatory stimuli in both gut and brain tissues, targeting key adaptors like TRAF6 and IRAK1. miR-21, which is overexpressed in IBD and neurodegenerative conditions such as AD and PDD, contributes to immune cell survival, epithelial barrier integrity, and apoptosis regulation via pathways like PTEN/AKT.[15] In addition, miR-124 plays a critical role in maintaining microglial quiescence in the brain and modulating epithelial integrity in the gut, and its dysregulation has been linked to neuroinflammation in dementia and mucosal dysfunction in IBD.[16] Less broadly distributed but still significant, miR-7 and miR-126 is involved in α-synuclein regulation and endothelial function, respectively, and are implicated in LBD, PDD, and VaD, aligning with vascular and synucleinopathies in these diseases.[17] Collectively, these shared miRNAs provide a molecular bridge linking neurodegeneration and intestinal inflammation and may serve as potential biomarkers and therapeutic targets for both IBD and dementia [Table 1].

PRE-CLINICAL DATA OF IBD ASSOCIATED DEMENTIA

Research involving animal models was conducted to elucidate the connection between IBD and dementia. Numerous investigations have demonstrated that persistent inflammation associated with IBD can precipitate neuroinflammatory processes, thereby contributing as driving factor in the development of dementia. Numerous preclinical studies, particularly on rodents, have been employed to mimic the chronic intestinal inflammation characteristic of IBD. These models help in examining the subsequent effects on brain function and behavior. In the study conducted by Sohrabi *et al*., wild-type and App^{NL-G-F} mice aged 6–10 months were given 2% dextran sulfate sodium (DSS) for two cycles of 3 days each to induce IBD. Both groups of mice developed conditions resembling IBD. Histopathological and biochemical analyses of mice brain revealed elevated levels of insoluble $A\beta_{1-40/42}$ and a reduction in microglial CD68 in comparison with control. All of these findings suggest that IBD-induced inflammation exacerbates dementia.[28]

A research conducted by Chen *et al*., using 3xTg mouse model with induced intestinal inflammation via DSS, revealed that the C/EBPβ (transcription factor) and δ secretase pathway is activated over time in the gut of these mice. Activation of this pathway triggered the production of Aβ and τ fibrils, which subsequently propagated to the brain. Treatment with DSS enhanced intestinal permeability, promoting the dementia like pathologies in both the brain and gut of mice models, mediated through the C/EBPβ/δ-secretase signaling pathway.[29]

These findings underscore the vital role of gut-derived signals in the initiation and progression of neurodegenerative changes, prompting further exploration into how microbial metabolites and intestinal inflammation synergistically influence dementia pathology.

Table 1: Common miRNAs in IBD and dementia

Dementia type	Pathways connecting to IBD	Common cytokines	Common miRNAs	References
Alzheimer's disease	- Chronic systemic inflammation - Gut-brain axis dysregulation - Microbiota-derived neuroinflammation - Blood-brain barrier disruption	TNF-α, IL-6, IL-1β	miR-155, miR-146a, miR-21, miR-124	[18,19]
Vascular dementia	- Endothelial dysfunction - Inflammatory vascular injury in gut and brain - Shared oxidative stress mechanisms	IL-1β, TNF-α, IL-17	miR-155, miR-146a, miR-126	[20,21]
Lewy body dementia	- α-synuclein aggregation exacerbated by gut inflammation - Autonomic nervous system dysregulation - Altered gut microbiota	TNF-α, IL-6, IL-10	miR-21, miR-7, miR-155	[22,23]
Frontotemporal dementia	- Pro-inflammatory cytokine imbalance - Microglial activation - Genetic overlap in immune regulation	IL-6, IL-1β, IFN-γ	miR-124, miR-223, miR-146a	[24,25]
Parkinson's disease dementia	- Gut-originated α-synuclein pathology - Gut-brain axis dysfunction - Peripheral and central nervous system inflammation	TNF-α, IL-6, IL-8	miR-155, miR-7, miR-21, miR-124	[26,27]

IBD: Inflammatory bowel disease, TNF-α: Tumor necrosis factor alpha, IL: Interleukin

POTENTIAL MECHANISM OF IBD ASSOCIATED DEMENTIA

Microbiota and metabolites mediated pathogenesis

GI inflammations are typically associated with intestinal microbes and their metabolites. Numerous studies have indicated that neurotoxins and pro-inflammatory biopolymers, such as lipopolysaccharides, are produced by gut bacteria. These substances can generate amyloids, which are often found in the brains of dementia patients.[30] These biopolymers from gut microbiota infiltrate the tissue of the brain by compromising the paracellular barrier of the gut. Over time, this barrier becomes more permeable, allowing neurotoxins and biopolymers to enter systemic circulation and penetrate the brain–blood barrier (BBB) into the brain.[31,32] In IBD, the altered microbiota and its metabolites not only disrupt the intestine but can also impact gut-brain communication, potentially leading to central nervous system (CNS) disorders.[33] We discuss the potential relationships between IBD associated dementia and effects of microbiota and their metabolites on different regions of brain [Figure 1].

Gut microenvironment

The gut microbiota exerts a pivotal influence on the immune system and maintaining homeostasis. Disruptions in this microbial environment can lead to both intestinal and extra-intestinal disease. Factors such as intestinal infections, poor diet, lack of hygiene, and genetic predispositions are primary contributors to dysbiosis in this microenvironment of intestine.[34] This imbalance can progressively result in IBD and other inflammatory conditions, including neurodegenerative diseases. Significant differences in the microenvironment were evident in blood and fecal samples from healthy individuals compared to those with dementia and IBD. Clinical data revealed that the microbiota composition of individuals with IBD and dementia was similar, with a marked reduction in microbiome diversity. In addition, beneficial bacteria (*Roseburia, Akkermansia muciniphila,* and *Bifidobacterium)* were notably decreased in both conditions[35,36] [Table 2].

Bacterial metabolites

Short-chain fatty acids (SCFAs) are produced via the microbial fermentation of dietary fibers by gut bacteria, predominantly in the colon, involving the bacterial phyla *Bacteroidetes* and *Firmicutes*.[43] Some SCFAs, including butyric acid, exhibit anti-inflammatory effect. It stimulates antioxidant enzymes and decreases oxidative stress.[44] SCFAs influence cellular processes through two primary mechanisms by regulating gene expression via histone deacetylase (HDAC) inhibition and G protein-coupled receptors (GPR41 and GPR43) activation. These receptors are critical in modulating inflammatory responses and represent promising therapeutic targets for the management of immune-related disorders.[45] Specifically, SCFAs inhibit HDAC, leading to

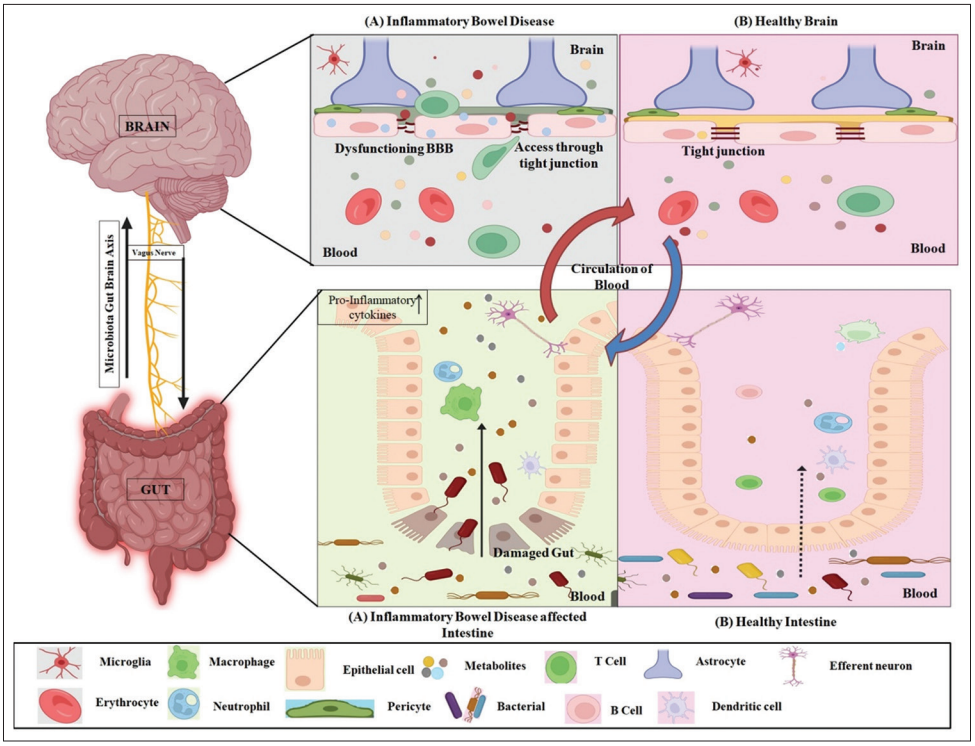

Figure 1: Impact of intestinal dysbiosis on barrier integrity (a) Disruption of the intestinal barrier in inflammatory bowel disease compromises the blood-brain barrier, contributing to dementia-like conditions. (b) In contrast, a healthy gut maintains the integrity of both the intestinal and blood–brain barriers

Table 2: Change composition of microbiota in condition IBD and dementia at the family and genus level

Condition	Changes in gut microbiota	Sequencing method	Sample	References
IBD	Proteobacteria↑ Fusobacteria↑ Enterobacteriaceae↑ Fusobacteriaceae ↑	16S rRNA sequencing Metagenomic sequencing	Blood and fecal	[37-39]
	Firmicutes↓ *Bacteroidetes*↓ Lachnospiraceae↓ Ruminococcaceae ↓	Metagenomic sequencing Shotgun sequencing	Blood and fecal	
	Increased *Bacteroides fragilis*	16S rRNA sequencing	Blood	
	Reduced microbial diversity	16S rRNA sequencing	Fecal	
Dementia	Proteobacteria↑ *Verrucomicrobia*↑ Prevotellaceae↑ Enterobacteriace ↑	16S rRNA sequencing Metagenomic sequencing	Blood and fecal	[40-42]
	Firmicutes↓ *Bacteroidetes*↓ Lactobacillacea↓ Bifidobacteriaceae ↓	16S rRNA sequencing	Blood and fecal	
	Reduced microbial diversity	16S rRNA sequencing	Fecal	

IBD: Inflammatory bowel disease, rRNA: Ribosomal ribonucleic acid

increased acetylation of histone. This process affects gene expression related to inflammation, immune regulation of the gut and supports intestinal homeostasis. SCFAs that cross from the bloodstream to brain tissue contribute to reducing microglial activation, preserving the integrity of BBB, and supporting neurogenesis and angiogenesis. They also reduce glial activity, either alone or in combination with other treatments.[46,47] For example, Butyric acid suppresses the expression of cyclooxygenase-2 and CD11b in Aβ-induced microglia and attenuates NF–κB p65 signaling, exerting anti-inflammatory effects in AD.[48] Furthermore, SCFAs modulate cognitive processes or emotional regulation by increasing the release of neuropeptides like glucagon-like peptide-1 and tyrosine.[49]

Immune system-mediated pathogenesis

IBD and dementia are immune-mediated disorders involving systemic and neuroinflammation. Systemic inflammation can exacerbate the CNS inflammation, leading to activation of microglia and astrocytes. Chronic inflammatory conditions like atherosclerosis, obesity and arthritis generate pro-inflammatory cytokines that can induce dementia. Research indicates that during middle age, inflammation acts as an early driver of systemic inflammatory processes, precipitating cognitive impairment in the years preceding older adulthood.[6,50] Zhang *et al*. reported that the administration of non-steroidal anti-inflammatory drugs might be associated with the prevention of dementia, which highlights the potential of these drugs in preventing dementia.[51] PRRs of the immune system encompassing TLRs and NLRs, which sense signals from the gut microbiota and start triggering innate immune responses. These interactions play a significant role in the pathogenesis of IBD and dementia. PRRs activate the innate immune system, which triggers the NLRP3 inflammasome. This activation promotes the secretion of chemokines and cytokines. As a result, the balance of interstitial mucosal immunity is disturbed and exacerbates IBD. The synthesis of aggregated Aβ in combination with TLR4 activates the microglial pathways, leading to the release of cytokines and ROS. These molecules damage neuronal processes and cause cell death.[52,53]

GBA-mediated pathogenesis

The GBA theory suggests a connection between the intestinal microenvironment and the brain, facilitated by neurohormones and inflammatory mediators. This axis links the CNS with enteric nervous system (ENS) and autonomic nervous system, coordinating with the endocrine and neuroimmune systems. The intestinal microenvironment is crucial for homeostasis in the human body. Dysbiosis of gut microbiota and disruption of its barrier by pathogens can affect the CNS and peripheral nervous system, triggering inflammatory immune responses.[54] Nerves present in intestinal tract are part of ENS, forms a connection with CNS via vagus nerve. Intrinsic neurons of ENS are located in the GIT wall and regulate intestinal functions. The vagus nerve forms a connecting link between ENS of GIT and CNS of brain, and facilitating signal exchange between the brain and gut. During inflammation, the intrinsic immune system gets activated and releases the neuropeptides such as gonadotropin-releasing hormone, somatostatins and neuropeptides Y. These neuropeptides bind to receptors on

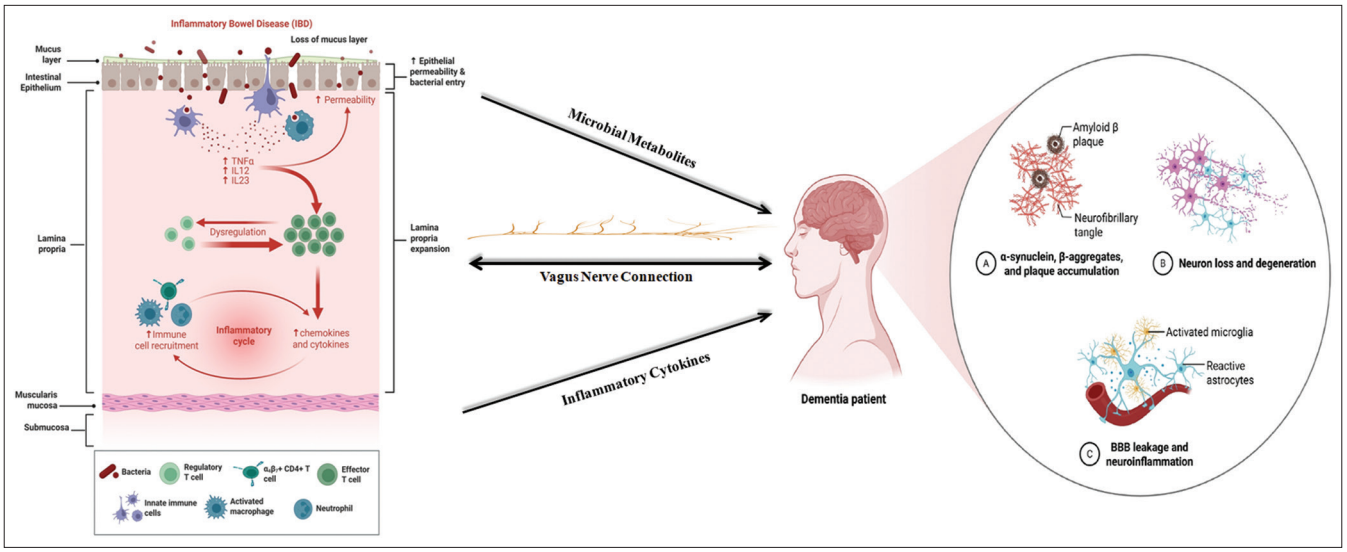

Figure 2: Mechanistic link between inflammatory bowel disease and dementia through gut–brain axis

T lymphocytes and enhance their function. In addition, they act as messengers for the GBA.[55,56] The GBA is pivotal in regulating the intestinal microenvironment. Dysregulation of this axis is implicated in numerous inflammatory conditions like IBD and is associated with the progression of neurodegenerative disorders. Recent studies indicate that GIT inflammation can precipitate significant neuroinflammatory conditions such as dementia and AD through GBA. This process may lead to the buildup of inflammatory Aβ in the intestine, which subsequently disseminates to the brain through the vagus nerve.[57,58] A study by Sun *et al*. revealed that injecting $A\beta_{1-42}$ exogenously in the intestine of ICR mice for 1 year led to the deposition of Aβ in vagus nerve and brain, which clearly mimics the pathological feature of dementia.[59] Another preclinical study has shown that the removal of vagus nerve through a surgical procedure reduces the τ lesion and Aβ plaques caused by gut inflammation and restores the cognitive ability of animals.[29] The overall finding showed us that intestinal inflammation associates dementia via GBA[60] [Figure 2].

CONCLUSION

IBD-associated dementia represents a multifaceted pathological process, primarily driven by chronic intestinal inflammation, microbial dysbiosis, and systemic metabolic disturbances. Epidemiological and preclinical evidence suggests a significant association between IBD and an increased risk of cognitive decline, with neuroinflammation emerging as a key mediator. The GBA plays a central role in this interaction, where alterations in microbial metabolites such as SCFAs can disrupt BBB integrity and exacerbate neuroinflammatory responses. Although the intestinal microenvironment is increasingly recognized as a contributor to neurodegeneration, the precise mechanisms linking gut pathology to brain dysfunction remain insufficiently understood. Elucidating the interplay between genetic susceptibility, immune dysregulation, and microbial signaling is crucial for uncovering the pathogenesis of IBD-related cognitive disorders. Importantly, current IBD therapies do not address the neurological consequences of the disease, underscoring a critical gap in clinical care.

Future research should prioritize the identification of predictive biomarkers and therapeutic strategies that target both intestinal and neuroinflammation. Approaches such as microbiota modulation, gut barrier restoration, and anti-inflammatory interventions may hold promise in mitigating dementia risk. While not all individuals with IBD develop dementia, recognizing intestinal inflammation as a modifiable risk factor introduces a novel avenue for early intervention and disease prevention. A comprehensive understanding of the gut–brain crosstalk in IBD may ultimately lead to more effective, holistic management strategies for reducing the burden of dementia.

AUTHOR CONTRIBUTIONS

Jeetendra Kumar Gupta (JKG) designed the structure and framework of the manuscript. Yati Sharma (YS) refined the language and enhanced the editorial quality of manuscript. Aniruddh Pratap Singh (APS) wrote the whole draft and compiled the tables and figures in the manuscript. JKG, YS, and APS collaboratively conducted the final review and refined the manuscript for publication.

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