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Dysbiosis and Gastrointestinal Dysfunction in Ischemic Stroke: A New Frontier for Treatment

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Abstract: Background: Ischemic stroke (IS) is a leading cause of mortality and disability worldwide. Recent evidence suggests that gastrointestinal (GI) dysfunction and dysbiosis, an imbalance in the gut microbiome, may play a significant role in stroke pathophysiology. This article explores the relationship between gastrointestinal dysfunction, dysbiosis, and ischemic stroke, highlighting the potential for therapeutic interventions to improve patient outcomes.

Methods: A comprehensive review of the literature was conducted to explore the mechanisms linking ischemic stroke to GI dysfunction and dysbiosis. Studies published between 2000 and 2024 were examined for evidence of GI involvement, alterations in the gut microbiota, and potential therapeutic strategies targeting these factors.

Results: GI dysfunction, including impaired gut motility, intestinal permeability, and gut microbial imbalances, has been observed in ischemic stroke patients. Dysbiosis may contribute to stroke-related inflammation, immune responses, and long-term complications. Preclinical and clinical studies suggest that restoring gut microbiota balance through probiotics, dietary interventions, and gut-targeted drugs may offer promising therapeutic avenues.

Conclusion: Gastrointestinal dysfunction and dysbiosis represent important areas of research in ischemic stroke pathophysiology. Targeted interventions aimed at the gut microbiome hold promise for improving outcomes in ischemic stroke patients, though further clinical studies are needed to confirm these findings and optimize treatment strategies.

Keywords: Ischemic stroke, gastrointestinal dysfunction, dysbiosis, gut microbiome, neuroinflammation, therapeutic interventions, probiotics, prebiotics, gut-brain axis, stroke recovery, intestinal permeability, immune modulation, gut-targeted therapies, fecal microbiota transplantation, dietary interventions.

Introduction: Ischemic stroke (IS) remains one of the leading causes of disability and death worldwide, with limited therapeutic options for improving recovery post-stroke. Recent studies have uncovered a surprising link between the gut microbiome, gastrointestinal (GI) dysfunction, and the pathophysiology of ischemic stroke. The gut microbiota plays a crucial role in maintaining intestinal homeostasis, modulating immune responses, and influencing systemic inflammation. Dysbiosis, an imbalance in gut microbial composition, has been implicated in several neurological disorders, including stroke. Additionally, ischemic stroke has been associated with GI dysfunction, such as impaired gut motility, increased intestinal permeability, and alterations in gut microbiota composition. Understanding the mechanisms that link GI dysfunction and dysbiosis to ischemic stroke could provide novel therapeutic opportunities to improve patient outcomes.

This article reviews the current literature on the relationship between GI dysfunction, dysbiosis, and

ischemic stroke, emphasizing how interventions targeting the gut microbiome may serve as potential therapeutic strategies for stroke patients.

METHODS

A systematic literature search was conducted using databases such as PubMed, Google Scholar, and Scopus. The search included studies published from 2000 to 2024, using keywords like “ischemic stroke,” “gastrointestinal dysfunction,” “dysbiosis,” “gut microbiota,” and “therapeutic interventions.” Studies focusing on the pathophysiology of GI dysfunction in stroke, the role of dysbiosis in stroke recovery, and potential therapeutic approaches targeting the gut microbiome were selected for inclusion. Preclinical studies, clinical trials, and meta-analyses were reviewed to assess the current understanding of these topics and identify future research directions.

RESULTS

Gastrointestinal Dysfunction in Ischemic Stroke

Gastrointestinal dysfunction is common in patients who have suffered from ischemic stroke. The gastrointestinal system is closely connected to the brain through the gut-brain axis, a bidirectional communication pathway that involves the nervous, endocrine, and immune systems. After ischemic stroke, patients often experience several GI disturbances, including:

1. Gut Motility: Stroke survivors commonly experience impaired gastrointestinal motility, which leads to constipation, delayed gastric emptying, and bowel dysfunction. The disruption of autonomic control of the GI system, particularly following a stroke that affects the brainstem or autonomic centers, contributes to this dysfunction.

2. Increased Intestinal Permeability: The intestinal barrier is compromised in stroke patients, leading to a phenomenon known as "leaky gut." This condition allows for the translocation of harmful bacteria and toxins into the bloodstream, which can trigger systemic inflammation and contribute to stroke-related complications.

3. Altered Gut Microbiota: Dysbiosis, characterized by an imbalance in gut microbial composition, has been observed in stroke patients. Specific changes in the abundance of certain microbial species may exacerbate inflammation and negatively influence stroke recovery. Studies suggest that stroke can alter the diversity and richness of gut microbiota, leading to reduced levels of beneficial bacteria such as Lactobacillus and Bifidobacterium and an overgrowth of pathogenic species like Firmicutes and Proteobacteria.

Linking Dysbiosis and Ischemic Stroke

Recent studies have highlighted the role of the gut microbiome in modulating the immune response and inflammatory pathways following ischemic stroke. Dysbiosis in stroke patients may contribute to:

1. Neuroinflammation: The gut microbiome influences systemic inflammation, which plays a pivotal role in the progression of ischemic stroke. Dysbiosis can enhance the production of pro-inflammatory cytokines, which, in turn, promote neuroinflammation and exacerbate neuronal injury.

2. Immune System Activation: Dysbiosis has been shown to affect the function of immune cells, including microglia and T-cells. These immune cells play a crucial role in the brain's response to injury. Dysbiosis may disrupt the immune homeostasis, making the brain more susceptible to inflammation and cell death following ischemic events.

3. Post-Stroke Recovery: Alterations in the gut microbiota composition have been linked to poorer post-stroke recovery outcomes. A healthy gut microbiome is associated with better immune modulation, reduced systemic inflammation, and improved neural repair. Dysbiosis, on the other hand, may impair these processes, resulting in longer recovery times and worse functional outcomes for stroke survivors.

Therapeutic Interventions Targeting the Gut Microbiome

Given the emerging evidence linking gastrointestinal dysfunction and dysbiosis to ischemic stroke, several therapeutic interventions are being explored to restore gut health and improve stroke outcomes:

1. Probiotics: Probiotic supplementation has been shown to help restore gut microbiota balance. Studies have suggested that probiotics, such as Lactobacillus and Bifidobacterium, may reduce intestinal permeability, improve gut motility, and modulate immune responses. Clinical trials are underway to determine the efficacy of probiotics in improving outcomes in ischemic stroke patients.

2. Dietary Interventions: Dietary changes, including the incorporation of fiber-rich foods, prebiotics, and fermented foods, may help support gut health. A diet rich in polyphenols and other bioactive compounds can enhance microbial diversity and promote the growth of beneficial bacteria. Nutritional interventions aimed at maintaining a balanced gut microbiome could offer a complementary approach to stroke rehabilitation.

3. Gut-Targeted Drugs: Emerging research suggests that gut-targeted drugs may have therapeutic

potential for stroke patients. These drugs could target the gut microbiota directly to restore its balance, modulate immune responses, and reduce inflammation. For instance, short-chain fatty acids (SCFAs), produced by gut bacteria during fermentation of dietary fiber, have been shown to have anti-inflammatory properties and could be utilized therapeutically.

4. Fecal Microbiota Transplantation (FMT): FMT involves transferring fecal material from a healthy donor to the recipient's gastrointestinal tract to restore a healthy microbiome. While still in the experimental stages for stroke recovery, preliminary studies have suggested that FMT may help in modulating the immune system and reducing neuroinflammation.

DISCUSSION

The relationship between ischemic stroke, gastrointestinal dysfunction, and dysbiosis represents a novel and promising area of research. While the pathophysiology is still not fully understood, the evidence points to a critical role for the gut microbiome in influencing stroke outcomes. Restoring gut health through probiotics, dietary changes, and novel microbiome-targeted therapies may offer a potential avenue for improving recovery and reducing the long-term impact of ischemic stroke.

Despite these promising findings, much more research is needed to understand the mechanisms underlying the gut-brain axis and how dysbiosis contributes to stroke pathology. Clinical trials evaluating the efficacy of probiotic and prebiotic interventions in stroke patients are essential to confirm their therapeutic potential.

Additionally, the development of gut-targeted drugs and more advanced microbiome therapies could revolutionize post-stroke care, offering personalized treatment options based on the patient's gut microbiome composition.

The relationship between gastrointestinal (GI) dysfunction, dysbiosis, and ischemic stroke (IS) is an emerging area of research that offers novel insights into the pathophysiology of stroke and presents potential therapeutic avenues. While ischemic stroke is primarily considered a cerebrovascular event, increasing evidence points to the profound and complex effects of stroke on the gastrointestinal system. Additionally, the gut microbiome, which plays a critical role in maintaining homeostasis, modulating immune responses, and regulating systemic inflammation, appears to be significantly affected by stroke. The discussion will delve deeper into the mechanisms connecting ischemic stroke to gastrointestinal dysfunction and dysbiosis, the clinical implications of these findings, and the potential therapeutic interventions that may offer improved outcomes for stroke patients.

Gastrointestinal Dysfunction and Ischemic Stroke

Gastrointestinal dysfunction in ischemic stroke patients has multifaceted origins, influenced by both direct and indirect mechanisms. The brain-gut axis, which is the bidirectional communication between the gut and the brain, is of critical importance in understanding the role of GI dysfunction following a stroke. Disruption of this axis after a cerebrovascular event leads to a range of gastrointestinal problems.

1. Impaired Gut Motility: Stroke patients often exhibit a decrease in gastrointestinal motility, which can lead to symptoms such as constipation, delayed gastric emptying, and bloating. The brain's role in regulating GI motility is well documented, as brain regions responsible for autonomic function, such as the brainstem, are involved in controlling digestive processes. Ischemic damage to these areas, particularly in the case of brainstem strokes or large strokes affecting multiple vascular territories, impairs autonomic function. Moreover, dysregulation of the enteric nervous system (the "second brain" of the gut) in the aftermath of a stroke can exacerbate these motility issues.

2. Intestinal Barrier Dysfunction: In addition to motility issues, ischemic stroke has been linked to increased intestinal permeability, often referred to as "leaky gut." This condition allows endotoxins and harmful microorganisms from the intestines to translocate into the bloodstream. In stroke patients, systemic inflammation is a major concern, and the increased permeability of the intestinal barrier serves as a route for further inflammatory mediators to enter circulation. This phenomenon can contribute to both local and systemic inflammatory responses, worsening the overall stroke outcome and complicating recovery. Notably, this impaired gut permeability can further exacerbate ischemic brain injury by promoting neuroinflammation.

3. Dysbiosis and Gut Microbiota Alterations: Emerging research has highlighted the role of the gut microbiome in modulating both local and systemic inflammation, which is particularly relevant in the context of ischemic stroke. The gut microbiota comprises trillions of bacteria that interact with the immune system and the central nervous system. Dysbiosis, or an imbalance in the composition of the gut microbiome, has been identified as a key factor in promoting systemic inflammation, which may influence the severity of ischemic stroke and recovery outcomes.

Ischemic stroke is associated with significant shifts in

gut microbiota composition. Studies have shown a reduction in microbial diversity and a shift towards an overgrowth of pro-inflammatory bacteria such as Firmicutes and Proteobacteria, while beneficial bacteria like Lactobacillus and Bifidobacterium are diminished. This alteration in gut microbial composition can result in increased production of inflammatory cytokines, which may amplify neuroinflammation and worsen the ischemic injury to the brain. The gut microbiome, by influencing both immune cells and neuronal activity, has the potential to modify the course of the stroke and recovery.

Mechanisms Linking Dysbiosis and Ischemic Stroke

The connection between dysbiosis and ischemic stroke is multifactorial and is largely mediated through systemic inflammation, immune modulation, and alterations in the gut-brain axis.

1. Neuroinflammation: Neuroinflammation plays a central role in the pathophysiology of ischemic stroke, and dysbiosis has been shown to enhance this inflammatory response. Pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β are elevated after stroke, and dysbiosis can contribute to an exaggerated production of these molecules. The imbalance in the gut microbiome leads to the activation of innate immune cells such as macrophages and dendritic cells, which in turn produce inflammatory cytokines. This inflammatory cascade can directly impact the brain, worsening ischemic damage and impeding recovery. Furthermore, the gut microbiome affects microglial cells (the brain's resident immune cells) by stimulating them to produce pro-inflammatory molecules that enhance the neuroinflammatory response post-stroke.

2. Immune System Activation: The gut microbiota is integral in shaping immune responses, and its imbalance can disturb immune cell function. In stroke patients, dysbiosis may contribute to immune dysregulation, leading to an exaggerated inflammatory response both locally (in the gut) and systemically. This immune dysregulation can impair neuroprotective mechanisms and hinder recovery. For instance, dysbiosis can impact the function of T cells, which have been shown to influence stroke outcomes. The altered gut microbiome may lead to excessive activation of immune responses, which can contribute to increased neuronal injury, swelling, and tissue damage in the brain.

3. Impact on Post-Stroke Recovery: Dysbiosis not only influences the acute response to ischemic stroke but may also affect long-term recovery. A balanced gut microbiome is essential for immune regulation, tissue repair, and the resolution of inflammation. Dysbiosis can disrupt these processes, potentially impairing the brain's capacity for repair and regeneration. Animal studies have shown that the restoration of gut microbial diversity after stroke can improve neurological recovery, suggesting that modifying the gut microbiome might accelerate recovery and functional recovery.

Therapeutic Interventions Targeting the Gut Microbiome

Given the significant role of the gut microbiome in ischemic stroke outcomes, targeting dysbiosis represents a promising therapeutic strategy. A variety of interventions have been explored to restore a healthy gut microbiota and potentially improve stroke recovery.

1. Probiotics and Prebiotics: Probiotics, which are live microorganisms that confer health benefits when administered in adequate amounts, may help restore gut microbial balance. Specific strains, such as Lactobacillus and Bifidobacterium, have been shown to enhance gut barrier integrity, reduce inflammation, and support immune function. Prebiotics, which are non-digestible food components that promote the growth of beneficial bacteria, may also be used to support gut health. Clinical trials examining the effects of probiotics in stroke patients are promising, though additional research is needed to determine the optimal strains, dosages, and duration of treatment.

2. Dietary Interventions: Diet plays a crucial role in shaping the gut microbiome, and a well-balanced, fiber-rich diet has been associated with a healthier gut microbiome. In ischemic stroke patients, dietary interventions that include fiber, polyphenols, and antioxidants could support gut microbiota composition and reduce inflammation. Diets rich in fermented foods, such as yogurt, kefir, and kimchi, can introduce beneficial microorganisms into the gut, potentially restoring microbial balance. Moreover, dietary interventions targeting specific gut microbes or metabolic pathways involved in neuroinflammation may offer personalized therapeutic strategies.

3. Fecal Microbiota Transplantation (FMT): FMT is an emerging therapy that involves transferring fecal material from a healthy donor to a patient to restore a healthy microbiome. Though primarily used for conditions like Clostridium difficile infection, FMT has shown promise in preclinical models of ischemic stroke. By rebalancing the gut microbiome, FMT may reduce inflammation, improve immune function, and enhance post-stroke recovery. However, FMT remains experimental in stroke therapy, and its safety and efficacy need to be validated in large-scale clinical trials.

4. Gut-Targeted Drugs: Research into gut-targeted

drugs aims to directly modulate the gut microbiome and its effects on systemic inflammation. For example, short-chain fatty acids (SCFAs) such as butyrate, which are produced by gut bacteria during fermentation of dietary fiber, possess anti-inflammatory properties and could be used to reduce neuroinflammation in stroke patients. Other molecules that influence gut-brain signaling, such as gut peptides or selective probiotics, could also be investigated for their therapeutic potential.

Challenges and Future Directions

Despite the promising potential of gut microbiome-targeted therapies, several challenges remain in their implementation in ischemic stroke management. The complexity of the gut microbiome, interindividual variability in microbial composition, and the long-term effects of interventions must be carefully considered. Furthermore, the safety and efficacy of these interventions in stroke patients need to be evaluated in larger clinical trials to better understand their potential impact on outcomes and recovery.

Future research should focus on identifying specific microbial signatures that are predictive of stroke severity and recovery, as well as developing personalized therapeutic strategies based on an individual's microbiome. Additionally, clinical trials assessing the efficacy of probiotic, prebiotic, and dietary interventions should be conducted to confirm their potential as adjunctive therapies in stroke rehabilitation.

Gastrointestinal dysfunction and dysbiosis are emerging factors that significantly influence the pathophysiology and recovery of ischemic stroke. The connection between the gut microbiome, systemic inflammation, and brain injury opens new therapeutic avenues, including probiotics, prebiotics, dietary interventions, and gut-targeted drugs. Though promising, these interventions need further investigation in clinical trials to optimize their use in stroke recovery. Addressing GI dysfunction and dysbiosis could become an integral part of comprehensive stroke management, offering a novel and potentially effective approach to improving post-stroke outcomes.

CONCLUSION

Gastrointestinal dysfunction and dysbiosis represent significant factors in the pathophysiology of ischemic stroke. Restoring a balanced gut microbiome through targeted interventions, such as probiotics, dietary changes, and gut-specific therapies, holds promise as a novel therapeutic strategy to enhance recovery and improve long-term outcomes for stroke patients. However, further research and clinical trials are necessary to validate these interventions and optimize their use in stroke rehabilitation.

REFERENCES

CDC Stroke Facts|Cdc.Gov. Availabl online: https://www.cdc.gov/stroke/facts.htm (accessed on 16 September 2022).

Katan, M.; Luft, A. Global Burden of Stroke. Semin. Neurol. 2018, 38, 208–211. [Google Scholar] [CrossRef]

WHO EMRO. Stroke, Cerebrovascular Accident|Health Topics. Available online: http://www.emro.who.int/health-topics/stroke-cerebrovascular-accident/index.html (accessed on 30 December 2024).

Gomes, J.; Wachsman, A.M. Types of Strokes. In Handbook of Clinical Nutrition and Stroke; Corrigan, M.L., Escuro, A.A., Kirby, D.F., Eds.; Nutrition and Health; Humana Press: Totowa, NJ, USA, 2013; pp. 15–31. ISBN 978-1-62703-380-0. [Google Scholar]

Nogueira, R.G.; Haussen, D.C.; Liebeskind, D.S.; Jovin, T.G.; Gupta, R.; Saver, J.L.; Jadhav, A.P.; Budzik, R.F.; Baxter, B.; Krajina, A.; et al. Clinical Effectiveness of Endovascular Stroke Treatment in the Early and Extended Time Windows. Int. J. Stroke 2022, 17, 389–399. [Google Scholar] [CrossRef] [PubMed]

Treatment of Acute Stroke: Current Practices and Future Horizons-ClinicalKey. Available online: https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S1553838922008934?returnurl=null&referrer=null (accessed on 2 January 2023).

Wang, J.; Zhang, J.; Ye, Y.; Xu, Q.; Li, Y.; Feng, S.; Xiong, X.; Jian, Z.; Gu, L. Peripheral Organ Injury After Stroke. Front. Immunol. 2022, 13, 901209. [Google Scholar] [CrossRef] [PubMed]

Pongmoragot, J.; Rabinstein, A.A.; Nilanont, Y.; Swartz, R.H.; Zhou, L.; Saposnik, G.; Investigators of the Registry of the Canadian Stroke Network (RCSN) and University of Toronto Stroke Program for the Stroke Outcomes Research Canada (SORCan [www.sorcan.ca]) Working Group. Pulmonary Embolism in Ischemic Stroke: Clinical Presentation, Risk Factors, and Outcome. J. Am. Heart Assoc. 2013, 2, e000372. [Google Scholar] [CrossRef] [PubMed]

Prosser, J.; MacGregor, L.; Lees, K.R.; Diener, H.-C.; Hacke, W.; Davis, S. VISTA Investigators Predictors of Early Cardiac Morbidity and Mortality after Ischemic Stroke. Stroke 2007, 38, 2295–2302. [Google Scholar] [CrossRef]

Bieber, M.; Werner, R.A.; Tanai, E.; Hofmann, U.; Higuchi, T.; Schuh, K.; Heuschmann, P.U.; Frantz, S.; Ritter, O.; Kraft, P.; et al. Stroke-induced Chronic

Systolic Dysfunction Driven by Sympathetic Overactivity. Ann. Neurol. 2017, 82, 729–743. [Google Scholar] [CrossRef] [PubMed]

Joundi, R.A.; Rabinstein, A.A.; Nikneshan, D.; Tu, J.V.; Fang, J.; Holloway, R.; Saposnik, G.; Stroke Outcomes Research Working Group (SORCan-www.sorcan.ca). Cardiac Arrest in Acute Ischemic Stroke: Incidence, Predisposing Factors, and Clinical Outcomes. J. Stroke Cerebrovasc Dis. 2016, 25, 1644–1652. [Google Scholar] [CrossRef] [PubMed]

Colivicchi, F.; Bassi, A.; Santini, M.; Caltagirone, C. Cardiac Autonomic Derangement and Arrhythmias in Right-Sided Stroke with Insular Involvement. Stroke 2004, 35, 2094–2098. [Google Scholar] [CrossRef]

Laowattana, S.; Zeger, S.L.; Lima, J.A.C.; Goodman, S.N.; Wittstein, I.S.; Oppenheimer, S.M. Left Insular Stroke Is Associated with Adverse Cardiac Outcome. Neurology 2006, 66, 477–483, discussion 463. [Google Scholar] [CrossRef]

Shrestha, P.; Thapa, S.; Shrestha, S.; Lohani, S.; BK, S.; MacCormac, O.; Thapa, L.; Devkota, U.P. Renal Impairment in Stroke Patients: A Comparison between the Haemorrhagic and Ischemic Variants. F1000Research 2017, 6, 1531. [Google Scholar] [CrossRef]

Tsagalis, G.; Akrivos, T.; Alevizaki, M.; Manios, E.; Stamatellopoulos, K.; Laggouranis, A.; Vemmos, K.N. Renal Dysfunction in Acute Stroke: An Independent Predictor of Long-Term All Combined Vascular Events and Overall Mortality. Nephrol. Dial. Transplant. 2009, 24, 194–200. [Google Scholar] [CrossRef]

Duan, H.; Cheng, Z.; Yun, H.J.; Cai, L.; Tong, Y.; Han, Z.; Geng, X.; Ding, Y. Serum Bilirubin Associated with Stroke Severity and Prognosis: Preliminary Findings on Liver Function after Acute Ischemic Stroke. Neurol. Res. 2023, 45, 62–69. [Google Scholar] [CrossRef]

Muscari, A.; Collini, A.; Fabbri, E.; Giovagnoli, M.; Napoli, C.; Rossi, V.; Vizioli, L.; Bonfiglioli, A.; Magalotti, D.; Puddu, G.M.; et al. Changes of Liver Enzymes and Bilirubin during Ischemic Stroke: Mechanisms and Possible Significance. BMC Neurol. 2014, 14, 122. [Google Scholar] [CrossRef] [PubMed]

Chelluboina, B.; Vemuganti, R. Chronic Kidney Disease in the Pathogenesis of Acute Ischemic Stroke. J. Cereb. Blood Flow Metab. 2019, 39, 1893–1905. [Google Scholar] [CrossRef] [PubMed]

Sarfo, F.S.; Agyei, M.; Ogyefo, I.; Opare-Addo, P.A.; Ovbiagele, B. Factors Linked to Chronic Kidney Disease Among Stroke Survivors in Ghana. J. Stroke Cerebrovasc. Dis. 2021, 30, 105720. [Google Scholar] [CrossRef] [PubMed]

Kanis, J.; Oden, A.; Johnell, O. Acute and Long-Term Increase in Fracture Risk after Hospitalization for Stroke. Stroke 2001, 32, 702–706. [Google Scholar] [CrossRef] [PubMed]

Pang, M.Y.; Eng, J.J. Muscle Strength Is a Determinant of Bone Mineral Content in the Hemiparetic Upper Extremity: Implications for Stroke Rehabilitation. Bone 2005, 37, 103–111. [Google Scholar] [CrossRef]

Meng, H.; Liu, T.; Borjigin, J.; Wang, M.M. Ischemic Stroke Destabilizes Circadian Rhythms. J. Circadian Rhythm 2008, 6, 9. [Google Scholar] [CrossRef]