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THE GUT-BRAIN AXIS AND ISCHEMIC STROKE

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ABSTRACT

The gut-brain axis initiates the complex interaction between the gut and the brain, and ischemic stroke is one of the primary causes of impairment. This review initially looks at the epidemiological burden, historical context, and intricate pathophysiology of ischemic stroke before delving into the relationship between the gut and brain axis. We provide an overview of the current understanding of how gut dysbiosis in stroke, characterized by alterations in the gut microbiota, exacerbates ischemia-reperfusion (IR) deficit. We examine the unique effects of gut microbiota organisms on inflammation and neuronal damage following a stroke. We also discuss promising approaches for the future, including the possibility for fecal microbiota transplantation (FMT), specific supplements, and fermented foods to reduce stroke-related neurological deficits. This study attempts to lay the groundwork for creating innovative gut-targeted therapies to enhance stroke outcomes by thoroughly examining the role of the gut-brain axis in ischemic stroke.

KEYWORDS: Ischemic stroke, Gut-brain axis, Gut microbiome, Ischemia Reperfusion injury, Faecal microbiota transplantation.

INTRODUCTION

Stroke is the second leading cause of mortality globally, with 60–85% of cases being ischaemic in nature. Thrombectomy and rt-PA thrombolysis are among the few available therapy alternatives, hence the majority of patients remain untreated. The gut microbiota is an important modulator of metabolism, vascular function, and immunity that influences brain health through the gut-brain axis. Synapse changes, behavioural deficits, and blood-brain barrier damage can all be caused by imbalances.[1] Post-stroke gastrointestinal issues can lead to increasing neurological impairments, delayed outcomes, and higher mortality, all of which

can negatively impact the patient's treatment plan. Poor gut flora has also been linked to an increased risk of stroke and a worse prognosis following a stroke, per a number of recent research. The gut microbiota is also a major player in the pathophysiology of several cerebrovascular diseases, according to current research. Tens of trillions of bacteria reside in the human gut, with about 1000 different varieties and three million genes, 150 times more than the human genome.[2] In this overview of the gut microbiota's participation in ischemic stroke, we discuss our current understanding of how the gut microbiota influences illness outcome and the potential mechanisms behind these interactions.

HISTORY

The history of stroke, a disorder marked by abrupt neurological impairments, extends back to ancient Egypt. One of the oldest surviving surgical records that details head traumas and associated neurological effects, such as paralysis and sensory loss, is the Edwin Smith Surgical Papyrus, which was written circa 3500 BC.[3] By witnessing and recording a variety of neurological illnesses, such as paralysis and convulsions, and frequently connecting them to particular brain traumas, the Greek physician Hippocrates (460–370 BC) contributed to our understanding of neurological disorders.[4] The basis for comprehending the intricate connection between brain structure and function was established by his findings. Because of the dramatic and frequently disastrous nature of stroke, he created the term "apoplexy" to describe abrupt neurological occurrences. But the fundamental causes were still mostly unknown, and ancient Greek and Roman doctors frequently blamed these occurrences on fluid imbalances in the body rather than particular vascular or neurological disorders.[5] The contributions of ancient Egyptian and Greek physicians are highlighted in this section, which offers a thorough summary of the early detection of stroke-like symptoms.[6]

STROKE EPIDEMIOLOGY

Globally, stroke ranks as the second most common cause of death. Every year, it kills over 5.5 million people and impacts over 13.7 million. The prevalence of ischemic infarctions, which account for around 87% of strokes, increased significantly between 1990 and 2016 as a result of better treatment choices and lower death rates. Over the same time span, the incidence of stroke decreased 42% in high-income countries while doubling in low- and middle-income ones.[7] In 2019, there were 6·55 million (6·00-7·02) stroke-related deaths, 143 million (133-153) DALYs, 101 million (93·2-111) prevalent cases, and 12·2 million (95% UI 11·0-13·6) incident cases.[8] Men aged 70 years have a baseline stroke risk of 8% if

their systolic blood pressure is 160 mm Hg. Other factors, including diabetes, smoking, atrial fibrillation, cardiovascular illness, hypertension medication, and ECG-detected left ventricular hypertrophy, increase the risk for women. Stroke risk rises to 90% for women and 85% for men when all variables are present.[9] An estimated 11.6 million incident ischemic strokes (IS) and 5.3 million HS occurred worldwide in 2010, with low- and middle-income nations accounting for 63% of IS and 80% of HS, respectively. 2,3 The incidence new stroke rate rose to 13.7 million in 2016 (95% CI 12.7–14.7; Figure (1). Strokes caused 5.5 million fatalities globally in that year, with IS and HS accounting for 2.7 million and 2.8 million of those deaths, respectively. The methodologic difficulties of constructing a geographic distribution of the burden of stroke include the lack of information for many and the variation in research methodologies for reporting the incidence of stroke in various nations (Table 1).[10]

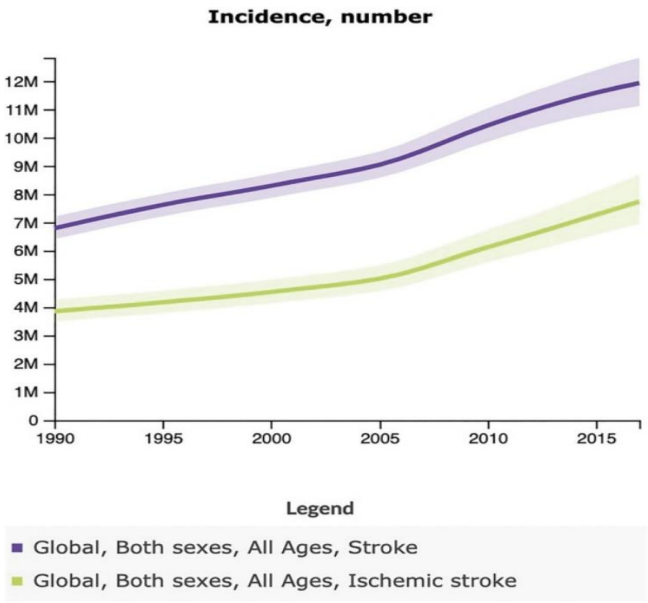

Figure 1: Global incidence stroke and ischemic stroke for all ages and both sexes, from 1990 to 2017.

Table 1 Age-Adjusted Incidence, Outcomes, and Utilization of Acute Interventions for Stroke Across the Globe.

Table 1 Age-Adjusted Incidence, Outcomes, and Utilization of Acute Interventions for Stroke Across the Globe[1,4,6,10,51-60]

	Incidence of stroke per 100,000 (95% CI)	Incidence of ischemic stroke per 100,000 (95% CI)	DALYs per 100,000 (95% CI)	Case-fatality 28 or 30 days, % (95% CI)	Mortality per 100,000 (95% CI)	Access to stroke unit, %	IVT use, % (year)	MT use, n (year)
Global	156.2 (145.5–167.9)	101.3 (91–113.6)	1,728.3 (1,655.6–1,797.7)	NA	80.7 (79.1–82.8)	NA	<5	<100,000
High income[b]								
Australia	76 (59–94; Adelaide 2009–2010); 67 (56–79; Perth 2000–2001)	55.1 (48.7–62.9) (2017)[c]	428 (386–470)	18 (14–24; Adelaide 2009–2010)	18.3/19.7 (F/M, 2015)	49.5	10 (2019)	1,907 (2019)
Barbados[g]	88 (79–98) (2001)	NA	1,080 (990–1,164)	29.9 (24.9–34.8) (2001)	45.1/59.5 (F/M, 2013)	NA	NA	NA
Canada	100.5 (92.5–110.2) (2017)[c]	66.8 (59.2–76.6) (2017)[c]	492 (438–547)		15/16.7 (F/M, 2015)	23	NA	NA
Estonia[d]	200 (181–218) (2016)		856 (733–1,036)	28 (Tartu 2001–2003)	37.1 (31.7–48.8) (2017)[c]	61	NA	NA
France	86.6 (83.9–89.3; Dijon, 1987–2012)	70.9 (68.5–73.4; Dijon, 1987–2012)	420 (380–461)	NA	13.9/18.8 (F/M, 2015)	33	NA	6,880 (2018)
Germany	85 (76–95; Erlangen 1995–1996)	73.9 (65.6–83.4) (2017)[c]	543 (486–599)	NA	19.6/25 (F/M, 2015)	70	NA	NA
Israel	97.5 (89.5–106.7) (2017)[c]	64.3 (56.9–74.1) (2017)[c]	443 (400–482)	NA	16.4/20.5 (F/M, 2015)	5	NA	NA
Italy	80.2 (73–87; Valley d'Aosta 2004–2008)	79.7% (Valley d'Aosta 2004–2008)	458 (422–498)	16.1 (Valley d'Aosta 2004–2008)	24.2/30.6 (F/M, 2015)	33	NA	NA
Japan	90.4 (77.4–107.7; Shiga 2011); 140 (130–163; Iwate state)	55.7 (46.5–68.4; Shiga 2011)	684 (620–747)	13.3–14.5 (Takashima 2001–2005)	17/31.5 (F/M, 2015)	Present (NA)	16.8 (Shiga 2011)	2.1 (Shiga 2011)
Saudi Arabia[f]	29.8–50.9	58.5%–87%	1,315 (1,169–1,470)	NA	20.6/25.4 (F/M, 2012)	Present (NA)	NA	NA
Spain	95.9 (88.3–104.5) (2017)	60.7 (53.4–69.5) (2017)[c]	464 (420–507)	NA	16.1/22.3 (F/M, 2016)	23	NA	NA
Sweden	126 (111–140; Orebro 1999–2000)	65.8 (58–75) (2017)[c]	518 (469–567)	19 (Orebro 1999–2000)	17.7/23.4 (F/M, 2016)	87.5	NA	NA
United Kingdom	73 (64–83; Oxfordshire 2002–2004)	56.8 (50.2–64.5) (2017)[c]	549 (511-5,840	15.9 (Scottish borders 1998–2000)	20.1/22.6 (F/M, 2016)	83	NA	NA
United States[a]	184.1 (170.6–199.8) (2016)[c]; 113 (102–126; Greater Cincinnati/Northern Kentucky 1999)	78.9 (70.6–89.3) (2017)[c]	692 (625–759)	NA	20.2/22.8 (F/M, 2016)	Present (NA)	10–15	11,469 (2016)
Upper middle income[b]								
Brazil[a,e]	137 (112–166.4; Matao 2003–2004)	91.9 (71.5–116.3; Matao 2003–2004)	2,342 (2,218–2,470)	18.5 (10.7–28.7; Matao 2003–2004)	41.8/60.4 (F/M, 2016)	Present (NA)	NA	NA
China[a]	354 (331–378) (2016); 297.4 (Tianjin 2014)	238.8 (Tianjin 2014)	3,136 (2,969–3,308)	NA	122.4 (118.6–126.7) (2017)[c]	Present (NA)	NA	NA
Iran[f]	203 (175–231; Mashhad 2006–2007)	167 (142–193; Mashhad 2006–2007)	1,141 (1,071–1,211)	NA	61.3 (59.2–65.1) (2017)[c]	NA	1.1 (2008)	NA
Mexico[a]	93 (86.2–100.1) (2017)[c]	53.8 (47.8–61) (2017)[c]	683 (656–713)	NA	29 (27.9–29.8) (2017)[c]	NA	NA	NA
Russia[a]	190.9 (176.8–206) (2017)[c]	139.7 (126–155.6) (2017)[c]	2,511 (2,397–2,625)	22.7 (17.7–27.7; Novosibirsk 1992)	105.4/154.6 (F/M, 2013)	13	NA	NA
Lower middle income[b]								
Bangladesh[a]	135.7 (126.2–146.5) (2017)[c]	78.7 (70.2–88.7) (2017)[c]	2,870 (2,603–3,155)	NA	153 (138.8–168.2) (2017)[c]	NA	NA	NA
El Salvador[e]	89.3 (82.6–96.6) (2017)[c]	50.8 (44.8–58) (2017)[c]	683 (589–782)		15.6/18.8 (F/M, 2014)			
India[a]	130 (123–137; Ludhiana 2010–2013); 145.3 (120–175; Kolkata 2003–2005)	74.8 (66.3–83.2; Trivandrum, 2005)	1,592 (1,509–1,665)	22 (Ludhiana 2010–2013); 41.1 (Kolkata 2003–2005)	77.4 (72.7–81.1) (2017)[c]	Present (NA)	NA	NA
Indonesia[a]	171.5 (159.7–184.8) (2017)[c]	98.5 (87.3–110.9) (2017)[c]	3,481 (3,285–3,685)	NA	178.3 (167.6–189.7) (2017)[c]	NA	NA	NA
Pakistan[a]	131.6 (121.7–142.6) (2017)[c]	80.5 (71.6–90.5) (2017)[c]	2,534 (2,118–2,948)	NA	133.7 (112.7–155.7) (2017)[c]	Present (NA)	<2 (2,005–2,007)	NA
Nigeria[a,h]	60.7 (Ondo state, 2,010–2,011); 54.1 (Lagos state, 2007)	NA	1,252 (951–1,666)	16.2 (Lagos state, 2007)	NA	Present (NA)	NA	NA
Lower income[b]								
Afghanistan	223.9 (207.4–241.4) (2017)[c]	141 (125.2–157.2) (2017)[c]	3,665 (3,206–4,186)	NA	165.8 (144.3–188.2) (2017)[c]	NA	NA	NA
Madagascar[h]	148.8 (138.9–160.6) (2017)[c]	75.4 (66.4–85.1) (2017)[c]	2,661 (2,481–2,851)	NA	181.9 (153.4–213.6) (2017)[c]	NA	NA	NA
Rwanda[h]	96 (88.2–104.5) (2017)[c]	56.3 (49.3–63.8) (2017)[c]	1,390 (1,098–1,670)	NA	76 (58.2–93.7) (2017)[c]	NA	NA	NA
Somalia[h]	129 (119.2–139.3) (2017)[c]	71.2 (62.9–80.8) (2017)[c]	2,783 (2,139–3,511)	NA	136.2 (104.5–168.4) (2017)[c]	NA	NA	NA
Uganda[h]	102.4 (94.9–110.8) (2017)[c]	57.9 (50.9–65.5) (2017)[c]	1,476 (1,248–1,712)	NA	77.8 (64.8–91.3) (2017)[c]	NA	NA	NA

Abbreviations: CI = confidence interval; DALY = disability-adjusted life-years; IVT = IV thrombolysis; MT = mechanical thrombectomy; NA = not available.
[a] Top 10 most populous countries in the world (census.gov/popclock/world; updated on July 1, 2019).
[b] Countries are classified on income level according to the World Bank.
[c] Standardized by country as standardization by world population is not available; the rest are standardized by WHO world population.
[d] Countries based on region: Eastern Europe.
[e] Countries based on region: Latin America.
[f] Countries based on region: Middle East.
[g] Countries based on region: Caribbean.
[h] Countries based on region: Africa.

[11,12,13,14]

PATHOGENESIS OF STROKE

When the blood flow to the brain is interrupted, the brain's cells are deprived of oxygen and nourishment, which results in an ischemic stroke. Numerous processes could be at blame for this disturbance. The most frequent cause is thrombosis, which is a blood clot that forms inside a brain artery.[15] Atherosclerosis, a disorder where plaque accumulates inside artery walls, is frequently the cause of this. When a clot or other debris, such as fat or air, travels from one area of the body to another and becomes lodged in a brain artery, embolic events take place., limiting blood flow. In conditions like atrial fibrillation and deep vein thrombosis, the heart is often the cause of emboli. Damage to small penetrating arteries, which is frequently caused by diabetes, hypertension, smoking, and aging, is the main cause of lacunar infarcts, which are tiny strokes that affect deep brain regions.[16] When cerebral arteries are blocked and blood flow is restricted, cerebral ischemia occurs, causing brain dysfunction with symptoms that linger for at least 24 hours. Neuronal metabolism is stopped within seconds of oxygen and energy deprivation during an ischemic stroke, and within minutes, structural damage is caused. When energy-dependent systems malfunction, ionic gradients are upset, which causes cellular imbalance and, eventually, necrotic cell death and apoptosis.[17] The ischemic center of the brain sustains severe, permanent damage, while the penumbra around it has metabolically active but recoverable cells, making it a prime target for therapeutic approaches. Each area of the brain experiences ischemic injury differently. However, the penumbra triggers a number of detrimental processes, including oxidative stress, excitotoxicity, inflammation, and apoptosis, which result in neuronal death and play a significant role in the development of ischemic stroke.[18]

GUT-BRAIN AXIS

GBA is the reciprocal link between the GI tract and the central nervous system (CNS). According to recent research in the fields of neuroscience and neuroimmunology, a number of intricate pathways mediate the functional crosstalk between the gut microbiota and brain via GBA signal.[19] While the stomach sends signals to the brain from the bottom to the top that affect cognitive and neurobehavioral functioning, the brain-to-gut routes affect the GI tract's sensory, motor, and secretory modalities.[20] The specific pathways involved in the GBA are currently unknown. However, recent research has demonstrated that the GBA encompasses both neuronal and non-neuronal impacts of gut microbiota on brain activity and vice versa.[21] The gut wall is influenced by the brain in a top-down fashion through direct and indirect routes. Examples of direct channels (i) include the extrinsic parasympathetic and

sympathetic branches of the autonomic nervous system, as well as the endocrine system, which alters the signals of the brain-gut HPA axis, especially in reaction to various stressful events. The HPA axis is also triggered by afferent fiber activation, and this triggers the brain's hypothalamic neurons that control pituitary secretions and the nucleus tractus solitarii, which has downstream projections. (ii) Indirect pathways include the intrinsic branches of the enteric nervous system, which is a highly developed neuronal network found in the gut wall's submucosa and myenteric plexus. Astrocytes and microglia, which are contained in the central nervous system, make up the immune system.[22] Numerous neurotransmitters or neuropeptides, such as dopamine, serotonin (5-HT), norepinephrine, and epinephrine, as well as stress hormones (release of cortisol, CRH, and ACTH) and resident immune cell activation through the release of different cytokines and chemokines, are all regulated by these neural pathways.[23]

GUT MICROBIOME AND ISCHEMIA REPERFUSION INJURY

There are two main stages to the complex process of intestinal ischemia-reperfusion (I/R) injury: ischemia and reperfusion. Ischemia results in tissue hypoxia and cell damage due to reduced blood flow. Despite being necessary for cell survival, reperfusion exacerbates damage by triggering an inflammatory response and oxidative stress.[24] During this inflammatory response, a number of pro-inflammatory cytokines and chemokines are generated, such as TNF-α, IL-1, IL-6, and others. The influx of inflammatory cells is made possible by enhanced vascular permeability, which exacerbates the inflammatory response. I/R damage has a critical effect of rupturing the intestinal mucosal barrier, which leads to bacterial translocation. Bacteria that break the mucosa and travel to other organs can cause systemic inflammation and sepsis.[25] Targeting bacterial translocation may be a promising therapeutic approach, given the significant role that bacteria play in the pathogenesis of I/R injury, as evidenced by recent studies. There is mounting evidence that gut flora and intestinal ischemia-reperfusion (I/R) injuries are reciprocally associated.[26] I/R injury can be prevented by a healthy gut microbiota through immune response modulation, inflammation reduction, and intestinal barrier integrity preservation. However, an imbalance in the gut flora, known as dysbiosis, may make I/R injury worse. Several studies have shown that the loss of gut commensals can lead to increased susceptibility to I/R harm. To prevent I/R damage, however, probiotics such as Bifidobacteria and Lactobacillus species have been shown to reduce inflammation, improve intestinal barrier integrity, and control the immune response.[27]

GUT MICROBIOME AND STROKE OUTCOME PREDICTION

A key factor in stroke recovery is the gut microbiome. The SDI, a novel index for assessing gut microbial dysbiosis in stroke patients, is presented in this work. A greater SDI is associated with worse results and more extensive brain damage.[28] Beneficial bacteria like Clostridiaceae and Lachnospira are less prevalent in patients with higher SDI, whereas dangerous bacteria like Enterobacteriaceae are more prevalent. These alterations may worsen brain damage by causing a decrease in the immune system and an increase in inflammation. The study also demonstrates a causal link between gut microbiota dysbiosis and stroke outcome by transplanting mice's fecal microbiota. Mice that received microbiota from patients with high SDI had poorer stroke outcomes than mice who got microbiota from individuals with low SDI. The study suggests that treating gut microbial dysbiosis could be a promising therapeutic approach for stroke patients. Altering the gut microbiota with probiotics, prebiotics, or fecal microbiota transplantation may improve the prognosis of stroke patients.[29] However, more investigation is required to completely comprehend the mechanisms underlying the association between gut microbiota and stroke as well as to create safe and efficient therapeutic interventions.[30]

ORGANISM

Table 2: Types of organism and its bacteria.

ORGANISM	BACTERIA
Obligate Anaerobes	C. coccoides group C. leptum subgroup B. fragilis group Bifidobacterium Atopobium cluster Prevotella C. difficile C. perfringens
Facultative Anaerobes	Lactobacillus Enterobacteriaceae Enterococcus Streptococcus Staphylococcus
Aerobes	Pseudomonas

[31,32]

FUTURE DIRECTIONS

As the relationship between the gut microbiota and stroke outcomes becomes more clear, probiotics and prebiotics become increasingly important. Live beneficial bacteria, or

probiotics, are frequently found in fermented foods and supplements and can aid in reestablishing a balanced gut flora.[33] On the other hand, prebiotics are fibers that serve as food for these bacteria, promoting their growth and function. Through modifications to the gut microbiota, these therapies may reduce inflammation and improve the internal environment, perhaps aiding stroke victims' recuperation and improving their overall health.[34] Fecal microbiota transplantation (FMT) is another potential approach that involves introducing fecal material from a healthy donor into the recipient's stomach. Although Clostridium difficile and other serious gastrointestinal illnesses are already treated with this medication, its promise goes beyond the stomach. FMT may have a beneficial impact on stroke recovery by reducing inflammation and mending gut-brain communication networks. Even though this research area is very young, the preliminary results are encouraging. In this context, the concept of personalized medicine is very appealing. Health care professionals could create individualized interventions to maximize gut health by knowing each person's particular gut microbiota composition. These could consist of FMT, specialized probiotic or prebiotic supplements, or even dietary guidelines.[35]

CONCLUSION

Inflammation, oxidative stress, and bacterial translocation are some of the pathogenic pathways involved in the intricate process of intestinal ischemia-reperfusion (I/R) injury. Gut microbiota plays a significant role in the degree of I/R damage and stroke prognosis. A disruption in the gut microbiota known as dysbiosis worsens results by lowering immunological response and raising inflammation. Addressing gut microbiota dysbiosis may be a promising treatment approach for stroke and I/R damage, per the study's findings. Through fecal microbiota transplantation, the gut microbiota can be altered. Prebiotics, often known as probiotics, may enhance patient outcomes. All things considered, the pathophysiology of I/R damage is significantly influenced by the gut microbiota. The negative effects of I/R injury might be lessened by altering the gut microbiota through dietary changes, probiotics, or fecal microbiota transplantation. However, further study is required to completely comprehend the underlying mechanisms and create viable treatment alternatives.

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