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Dysbiosis of Gut Microbiome in Neurocritically Ill Patients in Intensive Care: Systematic Review

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ABSTRACT

Background: The human microbiome is a community of microorganisms that live in symbiosis with humans. This relationship between humans and the microbiome affects the physiology of health and disease, but not many studies have evaluated the condition of the digestive microbiome in neurology critical condition patients and its changes. This study aims to describe the microbiome characteristics of neurological patients in the intensive care unit.

Methods: We conducted a systematic literature review of the relationship between the microbiome and neurology patients admitted to the intensive care unit by searching MEDLINE/PubMed, the Cochrane Database for Systematic Reviews, and Google Scholar for articles in English published through 13 June 2022.

Results: There is a change in the normal flora pattern in neurological patients who are treated in the intensive care unit. The decrease in the number of colonies occurred in commensal flora bacteria and an increase in pathogenic bacteria such as Enterobacteriaceae.

Discussion: The overgrowth of opportunistic pathogens suggests dysbiosis in patients with neurocritical conditions. This is thought to be correlated with the gut-brain axis relationship. This dysbiosis evaluation can be used to provide targeted microbiome therapy and to assess the risk of clinical deterioration and death in neurologic patients in intensive care.

Conclusion: This study reported a significant difference between the composition of the gut microbiota in neurology patients in intensive care and the healthy population. The magnitude of this dysbiosis increases during hospitalization in the intensive care unit and has an impact on patient outcomes. Intestinal microbiota analysis is expected to provide an overview of targeted microbial therapy and predict future patient outcomes.

Keywords: Neurocritical patients, intensive care, microbiome

INTRODUCTION

The human microbiota is a community of microorganisms that live in symbiosis with humans. This relationship between humans and the microbiome influences physiology in both health and disease. However, not much is known about the microbiome in adults, especially those with critical neurological conditions. Recently, several reports have revealed that changes in the gut microbiota are associated with myasthenia gravis, Parkinson's disease, and critical illness[1],[2],[3]. Significant changes in the gut have been hypothesized to trigger multiple organ dysfunction syndromes as a result of commensal bacterial disorders and will affect the risk of death in patients[4],[5].

Neurological intensive care has undergone considerable development in the last decade, but there is not much data regarding the pattern of changes in the microbiota during critical illness and whether the pattern of the gut microbiome is associated with outcomes and predictions of mortality in patients in

intensive care. Several efforts have been made to restore the health of the gut microbiome, such as the use of prebiotics and probiotics, but the composition and pattern of microbial structure in patients in critical condition are not widely known. Knowledge of the characteristics of the gut microbiota in neurological patients in critical condition is needed to better understand microbial pattern disorders and their relationship to patient outcomes so that targeted microbiota therapy can be carried out to improve patient outcomes[6],[7].

This study is a systematic review to describe the pattern of changes in the gut microbiome in neurology patients in intensive care in several published studies.

MATERIALS & METHODS

Literature search

This systematic review identified articles that are original clinical studies of any design study the human microbiome in neurology patients in intensive care. Review articles and editorials are manually checked for any additional relevant information. We searched systematically for published articles on MEDLINE/PubMed, the Cochrane Database for Systematic Reviews, and Google Scholar published through June 2022. The search terms used were as follows: (("neurology") OR ("neurologic) OR ("neurology patient")) AND (("intensive care") OR ("intensive care unit") OR ("neurointensive care")) AND (("microbiota) OR ("microbiome")). Two raters (IAA and IWW) independently reviewed all search results and came to a consensus about the inclusion/exclusion of each article.

RESULT

There are 396 articles in our search engine. All articles collected were selected according to their suitability with the topic and type of article. A total of 22 articles were evaluated and there were 6 articles which were original and research articles, 4 articles that did not discuss the treatment of neurology patients in the intensive room were excluded and 3 articles were selected to be included in this study (see **Figure 1**). The studies' characteristics were shown in **Table 1**.

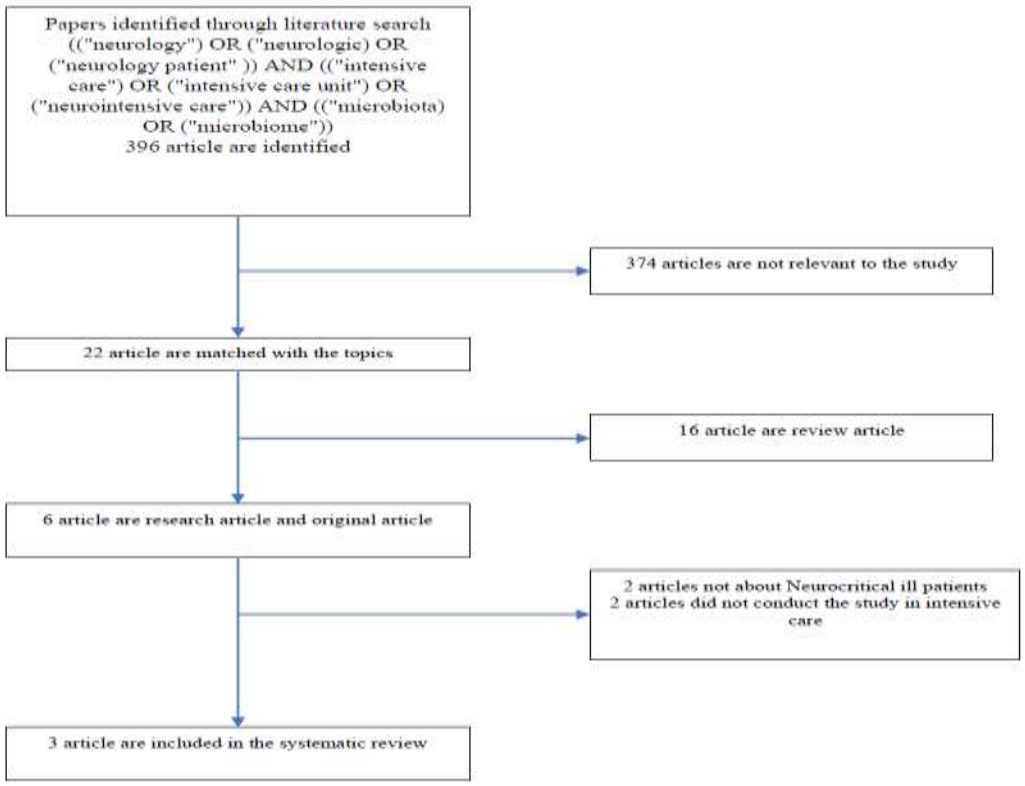

Figure 1. Flowchart of literature search for articles studying the human microbiome in neurology patients in intensive care.

Table 1. Characteristics of Study Included in Systematic Review

Study	Population and Characteristic	Control	Sample	Time Sampling	Microbiome characterization method	Changes in microbiota	Outcome
XU, et al (7)	98 neurological patients in critical condition 61 male: 37 female Median GCS 7.5 Median SOFA score of 5 Diagnosis: 38 ischemic stroke patients 20 hemorrhagic stroke patients 5 seizure patients 13 patients with intracranial infection 5 patients with hypoxic encephalopathy 17 other patients	84 samples with healthy condition	Fecal samples	first 72 hours (before antibiotic therapy), taken serially every week.	Analysis of 165 rRNA gene sequences	-There was a significant change in the composition of the gut microbiota during the treatment period. - colony enhancement *Christensenellaceae* and *Erysipelotrichaceae* - an increased colony of *Enterobacteriales* and *Enterobacteriaceae*	- *Christensenellaceae* and *Erysipelotrichaceae* associated with risk of death (aHR) = 1.545; 95% confidence interval (CI) 1.163–2.053, p = 0.003) and (aHR = 1.493; 95% CI, 1.094–2.038, p = 0.012) -Increased colonies of *Enterobacteriales* and *Enterobacteriaceae* in the first week were associated with an increased risk of death at 180 days by 92% in the multivariate analysis (aHR=1,920; 95% CI,1,016-3,628, P=0.044)
Tan, et al (8)	140 patients with acute ischemic stroke 95 male: 48 female Median age 59 years	92 samples with healthy condition	Fecal samples	Within 48 hours of stroke onset. Stored in temperature 80ºC	Analysis of 165 rRNA gene sequences and Gas chromatography	There is a decrease in bacterial colonies that produce SCFA such as *Roseburia*, *Bacteroides*, *Lachnospiraceae*, *Faecalibacterium*, *Blautia*, and *Anaerostipes* There was an increase in bacterial colonies of *Lactobacillaceae*, *Akkermansia*, *Enterobacteriaceae*, Dan *Porphyromonadaceae*	A decrease in SCFA-producing bacteria colonies was associated with an increased risk of adverse outcomes at 90 days. (OR=2.37; 95% CI, 1.32-4.25, P = 0.004)
XU, et al (9)	28 encephalitis patients. Median age 46 years 23 male; 5 female Median GCS 6.5 Median SOFA score 6.5	28 samples with healthy condition	Fecal and serum samples	At the time of hospital admission	Analysis of 165 rRNA gene sequences	There was an increase in SCFA in the feces of encephalitis patients and a decrease in the colony of producing bacteria including the family *Lachnospiraceae*, genus *Ruminococcus*, and genus *Faecalibacterium*. There is increased intestinal permeability in patients with encephalitis There was an increase in the bacteria phylum *Proteobacteria*, classes *Bacilli* and *Gammaproteobacteria*, and families *Porphyromonadaceae*, *Enterobacteriaceae*, and *Rikenellaceae*.	Study Correlation analysis showed that the severity of the disease had a positive correlation with an increase in *Proteobacteria* and *Akkermansia* colonies but a negative correlation with an increase in colonies of *Firmicutes*, *Clostridia*, and *Ruminococcaceae*. (r = 0.387, p = 0.042; r = 0.383, p = 0.044; r = 0.384, p = 0.044)

*Abbreviation: GCS: Glasglow Coma Scale; SOFA: Sequential Organ Failure Assessment; aHR: adjusted hazard ratio; CI: Confidence Interval; SCFA: Short-Chain Fatty Acids; OR: Odd Ratio

Dysbiosis of Gut Microbiome in Intensive Care Patients

All three studies demonstrated differences between microorganisms in neurology patients in intensive care and healthy samples[7],[8],[9]. The group of bacteria that increased in patients during intensive care was mainly in the families *Enterobacteriaceae*, *Porphyromonadaceae*, *Enterococcaceae*, *Verrucomicrobiaceae*, *Rikenellaceae,* and *Lactobacillaceae*. In a study of patients with neurocritical ill conditions, an increase in the colony of the *Enterobacteriaceae* family was significantly correlated with the length of hospital stay (r = 0.153, p = 0.059). Meanwhile, the analysis conducted on patients who survived and was discharged from the hospital showed an increase in the microbiota of *Proteobacteria* (r = 0.254, p = 0.012), *Gamma-proteobacteria* (r = 0.203, p = 0.045) and *Enterobacteriaceae* (r = 0.240, p = 0.017) families. This is in line with the increase in the modified Ranking Score (mRS) in patients when they leave the hospital[7].

Two other studies not only evaluated the pattern of the microbiota but also assessed the metabolites of short-chain fatty acids (SCFAs). It has been reported that gut microbiota derived from short-chain fatty acids (SCFAs) influence central nervous system diseases modulate brain function directly or indirectly via immune endocrine, vagal, and other humoral pathways, and regulate gut permeability and blood-brain barrier[10],[11],[12].

In the study by Tan, et al. There was a decrease in the colonies of bacteria that produce SCFA such as the *Roseburia*, *Bacteroides*, *Lachnospiraceae*, *Faecali-bacterium*, *Blautia*, and *Anaerostipes* family groups, and an increase in the colonies of *Lactobacillaceae*, *Akkermansia*, *Enterobacteriaceae*, and *Porphyro-monadaceae*, this indicates dysbiosis in patients with acute ischemic stroke. In addition, acute ischemic stroke patients with higher stroke severity appeared to have lower SCFA-producing bacteria and higher bacterial counts in the *Lactobacillaceae*, *Akkermansia*, *Entero-bacteriaceae*, and *Porphyromonadaceae* families[8]. This study is also similar to a study evaluating encephalitis patients who were admitted to the intensive care unit. The patient group appeared to have an increase in bacteria from the phylum *Proteobacteria*, classes *Bacilli* and *Gammaproteobacteria*, and families *Porphyromonadaceae*, *Enterobacteriaceae*, and *Rikenellaceae* compared to the healthy group[9].

The relationship between dysbiosis of the gut microbiome and patient outcomes

Xu et al. who evaluated microbiome patterns in neurologic patients in intensive care reported the results of a univariate study showing *Christensenellaceae* and *Erysipelotrichaceae* were associated with 180-day mortality and independently associated with 180-day mortality in age-adjusted multivariate Cox regression analysis, APACHE (Acute Physiology and Chronic Health Evaluation), white blood cell count and serum creatinine (adjusted hazard ratio (aHR) = 1.545; 95% confidence interval (CI) 1.163–2.053, p = 0.003; and aHR = 1.493; 95% CI, 1.094–2.038, p = 0.012)[7]. Increases in *Enterobacteriales* and *Enterobacteriaceae* were also found to be independently associated with mortality within 180 days by a multivariate Cox regression study, with adjusted APACHE, respiratory distress, intracranial hypertension, and serum lactate. An increase in these bacteria in the first week of intensive care was associated with a 92% increase in the risk of death within 180 days (aHR = 1,920; 95% CI, 1.016-3,628, P = 0.044)[7].

Tan et al. reported that low SCFA levels predict poor outcomes in acute ischemic stroke patients. Samples with a poor 90-day outcome had significantly lower SCFA levels after adjusting for age, sex, history of hypertension, diabetes, atrial fibrillation, coronary heart disease, and stroke (OR, 2.37; 95% CI, 1.32–4.25; P = 0.004). This is thought to be related to an imbalance of gut

flora in patients with acute ischemic stroke[8].

Xu et al. reported a positive correlation between the family *Ruminococcaceae* and the level of consciousness on the Glasglow Coma Scale (GCS) of patients (r = 0.384, p = 0.044). Phylum *Firmicutes* and order *Clostridiales* were also reported to be positively correlated with length of stay in the intensive care unit (r = 0.387, p = 0.042 and r = 0.383, p = 0.044), while the genus *Akkermansia* was reported to be negatively correlated with length of stay in the intensive care unit (r = 0.404, p = 0.033). This study also reported that there was a disintegration of the intestinal mucosa in encephalitis patients compared with healthy samples, this was significant during the presence of cerebral inflammation[9].

DISCUSSION

This systematic review accumulated reports of the microbiome pattern in neurology patients admitted to intensive care unit. All studies included in the review were observational studies, one study evaluated all neurology patients in intensive care, one study evaluated ischemic stroke patients and another study evaluated encephalitis patients. These three studies took fecal samples to evaluate the microbiome pattern, and SCFA levels and conducted a correlation study with clinical parameters of outcome and patient mortality.

The general gut microbiome comprises four domains, including Firmicutes (i.e., *Clostridium*, *Bacillus*, and *Lactobacillus*), Bacteroides, Actinobacteria (i.e., *Bifidobacterium*), and *Proteobacteria*. In the studies reviewed, both changes in variability and large interindividual variability in these patients were reported relative to characteristics in healthy controls. It was also reported that the composition of the bacterial community in the gut on discharge was significantly different from that observed on admission. The overgrowth of opportunistic pathogens defines dysbiosis in patients with neurocritical disease. Intestinal flora dysbiosis is currently considered to be associated with the host immune response[7],[13]. Studies evaluating patients with acute ischemic stroke reported an imbalance of the gut microbiome described by low levels of SCFA in patients, especially with severe disease. This is also associated with an increased risk of poor functional outcomes at 90 days[8]. Another study also reported changes in microbiome patterns during treatment to be an important risk factor for death at 180 days[7].

Several studies have demonstrated complex interactions between the gut microbiota and the central nervous system (CNS). This bidirectional relationship forms the gut-brain axis (GBA) of the microbiota (see **Figure 2**)[14]. Increased gut permeability allows microbes or microbial metabolites to enter the bloodstream. Gut microbes produce neuromodulatory metabolites (e.g., short-chain fatty acids (SCFA)), and induce the production of host-derived vitamin B12, neurotransmitters (e.g., serotonin), and hormones (peptide YY) that can affect host health and nervous system. Bidirectional interactions can occur directly through the innervation of the vagus nerve, providing a direct line of communication between the enteric and central nervous systems. In addition, gut-brain interactions may occur via immune-mediated inflammatory pathways, such as (a) microbial-driven systemic inflammation associated with the development of neurodegenerative diseases, and (b) stressors that may alter the gut via inflammatory pathways. Finally, gut microbes can metabolize xenobiotics and affect neurological function[14].

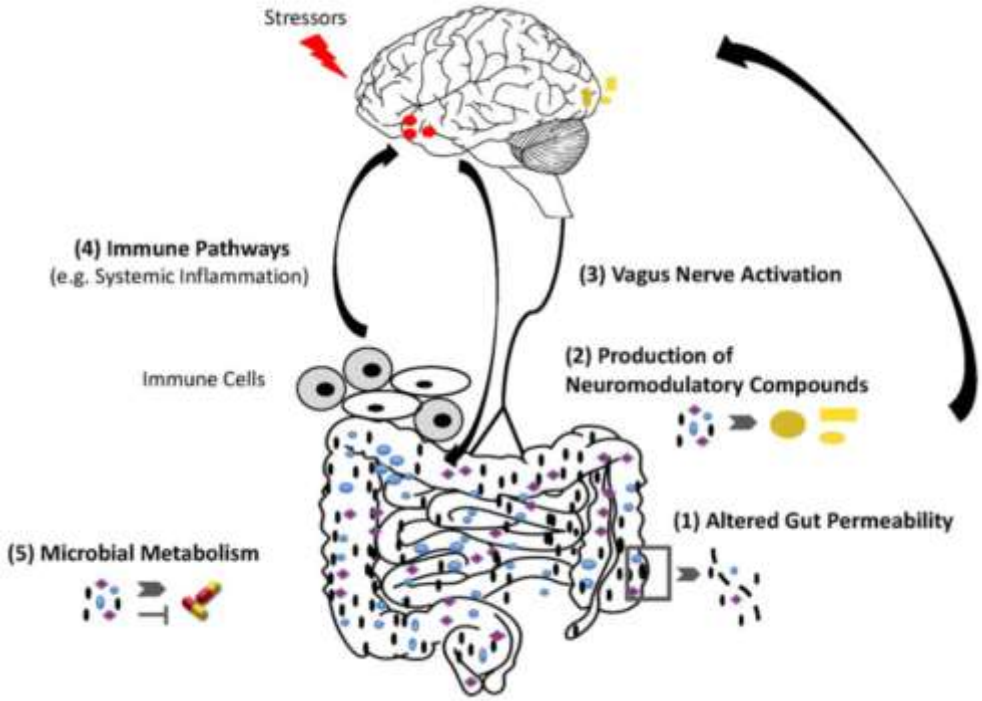

Figure 2. The Gut-Brain Axis Interaction. The Gut-Brain Axis is thought to be a two-way interaction model and is an outgrowth of the host, brain, and microbiome interactions[14].

Gut microbiome dysbiosis has been indicated to be a driving force for the development and progression of neurological diseases including stroke. In addition, it has been confirmed that remodeling of the gut microbiota offers an effective therapy for cerebral ischemic stroke. One study analyzed the gut microbiota of acute ischemic stroke patients with different stroke severity and identified a lack of SCFA-producing bacteria and an overgrowth of opportunistic pathogens (*Enterobacteriaceae* and *Porphyromonadaceae*) as well as *Lactobacillaceae* and *Akkermansia*[8]. Yamashiro et al also reported that intestinal dysbiosis occurs in patients with ischemic stroke and correlates with host metabolism and inflammation[15].

Enterobacteriaceae are a dangerous group of symbiotic human microbial communities that produce enteropathy and impair gut mucosal immunity as well as microbes in a healthy gut. *Enterobacteriaceae* are also one of the most detrimental pathogens to patients in the intensive care unit[16]. *Lactobacillus* and *Akkermansia* are largely recognized as probiotics and beneficial microbes. However, an increase in *Lactobacillaceae* and *Akkermansia* bacteria was reported among patients with acute ischemic stroke in the study by Tan et al[8]. This difference might be explained by strain and/or species specificity as some strains/species of Lactobacillus are opportunistic pathogens. The increase in Lactobacillaceae and Akkermansia may represent a compensatory response to the loss of other butyrate-producing bacteria. Additional studies are needed to determine the precise role of Lactobacillaceae and Akkermansia in patients with acute ischemic stroke[8].

This study reported changes in the gut microbiome in patients and presents a possible relationship between the gut and brain (Gut-Brain Axis). Previous studies have shown that commensal maintenance of "healthy microbes" or modulation of SCFA may exert beneficial effects through several pathways, including immune system modulation of cell proliferation, suppression of microbial pathogens with antimicrobial factors, and protective effects of the intestinal epithelial barrier[17]. Patients with sepsis can have a positive impact with symbiotic therapy and have a significantly

lower incidence of infectious complications compared to patients without symbiotic therapy[18].

CONCLUSION

This study shows that there is a significant difference between the composition of the gut microbiome in neurological patients treated in intensive care and a healthy population. The magnitude of this dysbiosis increases during hospitalization in the intensive care unit and has an impact on patient outcomes. Gut microbiome analysis is expected to provide an overview of the microbiome pattern for targeted microbiota therapy and predict future patient outcomes.

Declaration by Authors

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