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REVIEW ARTICLE

Influence of Gut Microbiota on Risk and Prognosis of Hemorrhagic Stroke

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ABSTRACT: Hemorrhagic stroke is a highly fatal yet understudied cerebrovascular disorder. While genetic and proteomic factors have been widely studied as contributors to hemorrhagic stroke, recent research emphasizes the human gut microbiota as an important factor in the causation and progression of the disease. This literature review was conducted to highlight evidence surrounding microbiome composition's influence on hemorrhagic stroke risk and outcomes, addressing the knowledge gap on this topic. This review finds that Mendelian randomization, DNA sequencing, and case-control studies are the most frequently utilized methods in hemorrhagic stroke studies with a focus on the gut microbiome. These methods are used in collecting and interpreting the genomic and metabolomic data from various gut flora. In addition, these studies consistently revealed that specific pro-inflammatory bacteria taxa, such as Proteobacteria and Escherichia-Shigella, were elevated in stroke patients and influenced stroke outcome, as well as how metabolites such as trimethylamine N-oxide (TMAO) are linked to increased platelet reactivity, promoting vascular stress. The influence of gut microbiota on the risk and prognosis of hemorrhagic stroke suggests that certain gut bacteria may trigger inflammation and produce metabolites like TMAO that can stress blood vessels and increase the risk of clotting. Collectively, these findings suggest that the gut-brain connection may influence both the occurrence and prognosis of hemorrhagic stroke through metabolic and vascular pathways.

KEYWORDS: Medical and Health Sciences, Biology, Microbiome, Hemorrhagic Stroke, Gut-Brain Connection.

Introduction

With regard to finding relationships between the microbiome and cerebrovascular disease, there is a lack of unification among the various findings and concepts illustrated by current research. Additionally, given that hemorrhagic stroke is a comparatively rare condition, research tends to focus on the more common ischemic stroke variety. This review aims to unify the findings of current research surrounding the microbiome's effects on hemorrhagic stroke and increase awareness of this condition in general.

Not to be conflated with ischemic stroke, hemorrhagic stroke is a medical emergency identified by a ruptured blood vessel in the brain. Within the category of hemorrhagic stroke, there are intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH), which differ based on the locality of the bleeding site.[1] By comparison to its ischemic counterpart, hemorrhagic stroke typically entails a higher mortality rate and a more adverse prognosis, while simultaneously constituting a smaller percentage of the total worldwide documented cases of stroke. Indeed, in 2021, ICH constituted 28.8% (28.3 to 28.8) of incident strokes globally, and SAH constituted 5.8% (5.7 to 6.0) of incident strokes globally.[2] The mortality rate for ICH is 42 (38 to 46) per 100,000 cases per year, and the mortality rate for SAH is 4 (4 to 5) per 100,000 cases per year.2 On account of its high mortality rate and comparative rarity, research on not only its effects but also its causality must be explored. Among contemporary research surrounding the causality of ICH and SAH, there is a primary focus on proteomic and genetic biomarkers, namely glial fibrillary acid protein (GFAP), anti-N-methyl-D-aspartate (anti-NMDA) neuroreceptor antibodies, D-dimers, and RNA expression, to name a few.[3] Conversely, there is a relative paucity of research honing in on the specific impact on ICH and SAH of an unlikely source that all humans share: the gut microbiota.

While seemingly extraneous to ruptured blood vessels within the skull, the bacteria present in the human gut may play a role in vascular inflammation and blood pressure, as well as possess a connection to the central nervous system through the microbiota-gut-brain axis. This literature review highlights and discusses the methods used in collecting and analyzing the data, as well as contextualizes and provides an overview of the literature related to the effect of human gut microbiota on the brain. These findings could help illustrate the factors that contribute to rare hemorrhagic strokes as well as provide commentary on how to conduct further research based on analysis of the most effective methods.

Methodology

This literature review aims to highlight the comparatively under-researched microbiotic aspect of hemorrhagic stroke using related peer-reviewed papers and honing in on the fundamental results that stem from them. The studies being reviewed in this paper were sourced through online databases PubMed and Google Scholar. Searches were conducted using the following Boolean keyword combinations: "gut microbiota" or "intestinal flora" or "microbiome," and "hemorrhagic stroke" or "intracerebral hemorrhage" or "subarachnoid hemorrhage" or "cerebrovascular rupture." Search filters were applied to include

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studies published between 2020 and 2025, and to ensure comprehensiveness, manual searching through reference lists was conducted in order to manually identify eligible publications not included in the database searches. Studies were evaluated according to predefined inclusion and exclusion criteria. Empirical research and reviews examining the gut microbiome's role in cerebrovascular conditions, studies addressing microbial metabolites, and peer-reviewed articles published between 2020 and 2025 were all eligible for review. Non-peer-reviewed literature, studies focusing exclusively on stroke or unrelated neurological issues, papers not available in English, and studies published before 2020 were not eligible for this review. In total, 105 studies were initially retrieved. After duplicate removal and screening, 30 studies were found suitable (24 empirical) for inclusion in the final review. All of these sources are secondary in nature to this review. From these sources, the data collected includes methods of data analysis, methods of data collection, various studies' findings on microbiome composition, trimethylamine-N-oxide production, and trimethylamine-N-oxide effects. This study relied on previously published literature, and no new data were collected, no ethical approval was required. All reviewed studies followed the ethical research guidelines as stated in their original publications.

Discussion

Frequency of Data Collection Methods among the Studies:

The 24 empirical studies, despite focusing on a similar topic, used a diverse array of statistical analyses and data collection methods. The following table (Table 1) covers the collection and analysis methods explicitly stated by the papers and states the number of occurrences for each. The table is ranked from the highest frequency at the top to the lowest frequency descending, and Mendelian randomization, DNA sequencing, and case-control studies were the most frequently used (5, 4, and 3 uses, respectively).

Table 1: Frequency of Methods.

Collection and Analysis Methods (As Explicitly Stated)	Frequency among 24 Empirical Papers
Mendelian randomization (MR)	5
DNA sequencing (DNA-S)	4
Case-control study (CCS)	3
Metabolomics (MBO)	2
Bioinformatic analysis (BIA)	1
RNA sequencing (RNA-S)	1
Metagenomics (MGN)	1
Meta-analysis (ME-A)	1
Alpha-diversity analysis (AD-A)	1
Beta-diversity analysis (BD-A)	1
Random forest (RF)	1
Receiver operating character analysis (ROC-A)	1
Inverse variance weighting (IVW)	1
Statistical Analysis (ST-A)	1

Among the studies in Table 1, the MR approach proved to be the most prevalent data analysis method. MR is reliant on the principle of random allocation, or how, at birth, people are given genetic variants that affect their physical and behavioral traits.[4] MR is a tool for inferring causal relationships between risk factors and illnesses, helping bridge the gap between observational epidemiology and randomized controlled trials (RCTs). MR relies on three factors: relevance, or how a genetic variant affects a potential cause (exposure); independence, or how the variant is independent from confounders; and an exclusion restriction, or how the variant influences an outcome solely through the exposure, and not through other pathways.[4] This approach is extremely useful for inferring causation between gut microbiota composition and the risk for hemorrhagic stroke due to a central scientific dogma: correlation does not equal causation. Lots of evidence comes from observational studies, comparing gut flora composition in stroke-risk patients vs. controls. But, observational studies cannot tell whether gut flora composition causes stroke, stroke alters the gut microbiota (reverse causation), or even if both are affected by a third factor (diet, medicine, other conditions, etc.). Because so many confounding variables, such as diet, medications, or living conditions, exist, it is difficult to know whether changes in gut bacteria lead to stroke risk or just occur alongside it. This is where MR offers a workaround. In this case, it would use genetic variants that influence gut microbiota composition or microbial metabolites, and because these variants are randomly assigned at birth, they are not altered by lifestyle or environment.[4] If people who genetically have higher levels of a certain metabolite, for example, also show higher rates of hemorrhagic stroke, that suggests a causal relationship. Additionally, given the rarity and high mortality of hemorrhagic stroke, conducting large-scale RCTs could be impractical or even unethical, making MR a much more feasible method.

The second most utilized technique in contemporary research is DNA sequencing. In the most current method of DNA sequencing, Next-Generation Sequencing (NGS), DNA fragments are mapped in parallel, allowing for faster and more efficient analysis.[5] This technique is more efficacious than previous methods, including Sanger sequencing, where analysis is restricted to only substitutions, insertions, and deletions.[5] Another advantage of NGS is that, unlike other methods of sequencing, it does not require prior knowledge about the genes in question and therefore can identify novel genetic mutations. NGS can identify genetic mutations occurring post-fertilization as well, which highlights its sensitivity in identifying even the most uncommon mutations.[5] The main drawback to this approach, however, is accessibility, as it requires specialized hardware and personnel expertise. The cost itself does not factor into these disadvantages, though, as a top-of-the-line NGS system can produce around 150,000,000 reads for approximately £1000 (about $1332 U.S.).[5] Despite this disadvantage, NGS remains a widespread DNA sequencing method among state-of-the-art institutions and is one of the most effective methods in use.

The CCS approach was the third most prevalent statistical method for collecting and analyzing data. Case control studies determine whether an exposure is associated with an outcome, beginning with individuals who already have the outcome (cases) and comparing them to those who do not (controls), looking retrospectively to identify possible exposures.[6] An

advantage of this approach is its efficiency in producing results. Using the gut-stroke relationship as an example, unlike an approach that utilizes a pool of healthy people and waits to see who develops stroke, CCS would start with a pool of stroke patients and then look back in time to obtain exposure data. This leads to rapid results that are relatively inexpensive to obtain. Though some may say that this approach is much more susceptible to confounding factors due to its temporal relationship, they can be mitigated through matching the cases with their controls.[6] The temporal relationship CCS has, however, does posit an alternate issue. Unlike MR, which looks at set genetic factors that strongly suggest causation, the retrospective nature of CCS may support an association but not prove causation.[6] Once again, an example using the gut-stroke relationship helps illustrate this idea. In a CCS intended to support a relationship between gut flora and ICH, one may come to the conclusion that a change in microbiome composition could result in the occurrence of a stroke. On the other hand, it may also be the case that the occurrence of a stroke leads to a change in microbiome composition; using CCS is not a viable method to identify an exactly ordered cause-and-effect relationship.

While not as prevalent as some of the other methods, metabolomics plays an integral role in understanding how metabolites produced by gut bacteria can have an effect on the brain. Metabolomics is the systematic approach to identifying and quantifying an organism's metabolites (molecules or substances produced as a result of metabolic processes) using statistical methods for data extraction, interpretation, and pattern recognition.[7] As metabolites are a direct result of an organism's metabolism, an analysis of these substances would generate a "snapshot" of that organism's internal state, which is very important when it comes to identifying how an organism affects its environment. Within metabolomics, there are a few techniques used to achieve different results. For example, an approach called target analysis quantifies only a small set of specific compounds of interest, while the technique of metabolic profiling analyzes a larger set of compounds, both known and unknown, to quantify a larger number of metabolites.[7] Metabolomics, used in congruence with DNA and RNA sequencing, can generate a comprehensive picture of biological processes within specific organisms that have the potential to affect their environment, including metabolites of the gut microbiome affecting the human body.

Something that all of these methods have in common is their reliance on statistics, more specifically statistical data, and despite only being mentioned by name once among the reviewed studies, inverse variance weighting (IVW) is necessary for all of these approaches to function. IVW analyzes effect sizes (the significance of a phenomenon/relationship between variables) by calculating the weighted mean of the effect sizes using the inverse variance of the individual studies as weights.[8] Inverse variance in this approach means assigning more importance (weight) to data points with less uncertainty (smaller variance) when combining them, resulting in giving more precise data points more importance in the weighted average. The model for IVW can be shown as:

$$\overline{X} = \frac{\Sigma W_i X_i}{\Sigma W_i}$$

where W_i represents the weight where i = 1,2,… and X_i is the observed effect.[8] The observed effect X_i can be written as:

$$X_i = \mu + e_i$$

where μ is the true effect size, and e_i (the deviation of X_i from μ) is the observation error.[8] Advantages of IVW include maximizing precision due to the inverse variance weight and being widely applicable, as shown through its use in Mendelian randomization, DNA sequencing, and more. However, it is sensitive to incorrect variance estimates, assumes independence of estimates, and is primarily optimized for normally distributed error.

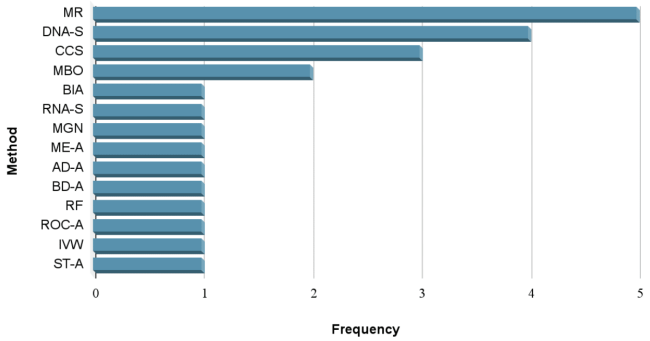

Figure 1: Frequency of Collection/Analysis Methods. This horizontal bar plot, created with Google Sheets, visually displays the relative frequencies of the methods used in the reviewed studies. MR, DNA-S, and CCS are shown to be the most frequent.

In Figure 1, MR is shown as the most used, which aligns with its importance in statistics and data analysis. Despite this, the other methods ranking lower are not a measure of their unimportance, but rather how often they are utilized by themselves. These methods are quite interdependent and frequently used together, so it would be unfair to categorize one as being the best.

Microbiome Composition of Stroke Patients:

Despite utilizing a wide net of data collection and analysis methods, many of the studies agree upon specific bacterial families, genera, species, and phyla that possess a link to stroke patients, with only a few differences here and there. According to one CCS study that consisted of a hemorrhagic transformation (HT) group, a non-HT group, and a healthy control (HC) group, the largest phyla among all three groups were *Firmicutes*, *Proteobacteria*, and *Bacteroidetes*, and the most abundant families were *Pseudomonadaceae*, *Lachnospiraceae*, and *Enterobacteriaceae*.[9] A further analysis in the study showed that the species *Proteobacteria*, *Enterobacteriaceae*, and *Escherichia-Shigella* were relatively more prevalent in the HT group than the non-HT and HC groups.[9] The study also notes that among the HT group was a relative decrease in the abundances of the phyla *Bacteroidota* (P = 0.021) and *Actinobacteriota* (P = 0.024). In the HC group, the subjects had higher levels of anti-inflammatory microbiome taxa than the HT group, including *Ruminococcaceae*, *Acidobacteriota*, *Faecal-*

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ibacterium, and *Clostridiales*.[9] Another study comprised of an ischemic stroke (IS) group, a hemorrhagic stroke (HS) group, and an HC group, using a comparative analysis, found that the dominant phyla among all three groups were *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, *Fusobacteria*, *Actinobacteria*, and *Tenericutes*, comprising 58.53%, 25.60%, 8.77%, 5.99%, 0.33%, and 0.58%, respectively in the IS group.[10] In the HS group, the percentages were 58.37%, 24.95%, 7.88%, 8.24%, 0.24%, and 0.12%, and the HC group consisted of 64.63%, 26.73%, 5.33%, 3.02%, 0.17%, and 0.03%, respectively. The HS group possessed significantly higher levels of *Atopobium*, *Hungatella*, *Eisenbergiella*, *Butyricimonas*, *Odoribacter*, *Lachnoclostridium*, *Alistipes*, *Parabacteroides*, and *Fusobacterium* in comparison to the HC group.[10] Conversely, *Ruminococcus* and *Coprococcus* were found to be more prevalent in the HC group vs. the HS group.[10] All of the studies honing in on microbiome composition echo these papers' findings, with only minor discrepancies which can be attributed to natural diversity.

Bacterial Metabolites:

While some studies focused on identifying the relative percentage makeup of subjects' gut flora, others examined the effects of certain metabolites produced by the microbiome, the most well-known of which is trimethylamine N-oxide (TMAO), a compound released from the digestion of choline, lecithin, and L-carnitine, among others, and commonly found in dairy, eggs, fish, and meat.[11] According to a study discussing the proposed role of TMAO in stroke patients, once foods rich in choline, lecithin, and L-carnitine are absorbed by the gut, various enzymes, including choline trimethylamine-lyase (CutC/D), YeaW/X, and carnitine oxygenase (CntA/B), catalyze the compounds into trimethylamine (TMA).[11] Once in the liver, TMA is converted into TMAO by the liver's flavin-containing monooxygenase 3 enzyme (FMO).[11] TMAO is associated with increased platelet response to agonists, contributing to increased stroke risk and vascular stress.[12] A study that isolated platelet-rich plasma from healthy volunteers found an association between TMAO and platelet hyperresponsiveness through how TMAO releases Ca2+ from intracellular stores.[12] When dormant, platelets keep a steady level of cytosolic calcium when passing through undamaged vessels. However, mobilization of the calcium occurs when a stimulus is present, such as a site of vessel injury.[12] This mobilization is a precursor to thrombus formation. To establish an association, they used a calcium-sensitive dye to monitor Ca2+ levels before and after platelet activation, and found that physiological levels of TMAO significantly increased stimulus-dependent calcium release within 10 minutes of exposure when exposed to thrombin and adenosine diphosphate (ADP).[12]

In sum, for the methodologies used in the studies, Mendelian randomization, DNA sequencing, and case-control studies were the most commonly utilized, with Mendelian randomization being the most common method due to its independence from confounding factors. In terms of microbiome composition and bacterial metabolites, elevated levels of *Escherichia*, *Enterobacteriaceae*, *Proteobacteria*, and *Lachnospiraceae* are present in experimental groups with hemorrhagic transformation. These bacteria are associated with inflammation, and some produce the TMAO metabolite, which influences platelet hyperreactivity.

■ Conclusion

The current body of research surrounding the link between the gut microbiome and occurrence of hemorrhagic stroke rely on a few methods of data analysis, with the most prevalent being mendelian randomization, an approach involving random genetic variants assigned at birth that can suggest causation, and case-control studies, which are relatively quick and inexpensive methods of collecting data, but lack the ability to support causation. Additionally, the research underscores the influence of the gut microbiome on cerebrovascular health, with evidence increasingly pointing to specific bacterial phyla and species such as *Escherichia*, *Enterobacteriaceae*, *Proteobacteria*, and *Lachnospiraceae* as pro-inflammatory factors. Metabolites of these bacteria may be at fault, with research suggesting that gut-derived metabolites such as TMAO may cause platelet hyperreactivity to stimuli, leading to increased vascular stress and thrombosis. With all this in mind, future studies should prioritize strengthening the knowledge surrounding the gut-brain axis, as certain pathways used by gut bacteria affecting the brain are not completely understood. Clinically, this research could provide a promising preventative measure for stroke through diet modification, probiotics, or enzyme inhibition (ie, TMAO synthesis reduction). Ultimately, understanding and manipulating the gut-brain axis may offer novel therapeutic strategies to mitigate the incidence and severity of hemorrhagic stroke.

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