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Journal of Women Health Care and Issues
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Review Article

Treatment of Sepsis Associated Encephalopathy by FMT

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Received date: August 07, 2024; Accepted date: August 15, 2024; Published date: August 27, 2024

Citation: K Pushkala and P D Gupta, (2024), Treatment of Sepsis Associated Encephalopathy by FMT, J. *Women Health Care and Issues, 7*(6); **DOI:10.31579/2642-9756/220**

Abstract

Sepsis associated encephalopathy (SAE) is a poorly understood neurological complication that occurs secondary to infection generally encountered in critically ill patients results in critical neuromyopathy. Mortality is almost certain due to multiorgan failure. Lately, Faecal Microbiota Transplantation (FMT) showed some promising results, FMT effectively improved the spatial memory and EEG abnormalities. FMT was likely mediated through the vagus nerve. Several cases of bacteremia, multiple drug resistance bacterial infection, respiratory failure, and multiple organ dysfunction showed significant improvement from FMT. Further research into the pathophysiology, management and prevention of SAE is needed.

Key words: neurological complication; multiple organ dysfunction; Faecal Microbiota Transplantation; bacteremia; electroencephalography

Introduction

Sepsis associated encephalopathy (SAE) is a neurological complication expressed by diffuse brain dysfunction secondary to infection elsewhere in the body without overt CNS infection. Acute systemic infection caused by various pathogenic bacteria that invade the bloodstream and rapidly proliferate and produce life-threatening toxins. Recent studies have however reported that SAE is a relatively common cause of altered mental status with diffuse disturbance in cerebral function without any lateralizing signs is characteristic of SAE [1]. SAE can develop early in the course of a sepsis or later in the course of illness as part of the multiorgan dysfunction (MODS) seen in the setting of refractory septic shock. MODS may be due to major trauma, severe illness and widespread infection. Treatment focuses on treating the initial insult and working to prevent severe injury to other organ systems. It can be scary to hear that your organs or a loved one's organs aren't working [2].

Pathophysiology of SAE

SAE is a poorly understood, common, complex and multifactorial including a number of intertwined mechanisms such as vascular damage, endothelial activation, breakdown of the blood brain barrier, altered brain signalling, brain inflammation, and apoptosis. The prevalence rate ranges from 8 to 70% depending on the inclusion and exclusion criteria in critically ill patients admitted in the ICU. The term “septic encephalopathy” might be used to define a septic state, that is, a systemic inflammatory state summoned by an infectious process of the brain or CNS instead of Sepsis associated encephalopathy [3]. The prognosis ranges from mild symptoms such as malaise and concentration deficits to deep coma. Lack of any specific investigations or biomarkers and the common use of sedation in critically ill patients pose a problem of evaluation for cognitive dysfunction.

Abnormalities in electroencephalography (EEG) and somatosensory-evoked potentials (SSEP),[4] increase in biomarkers such as neuron- specific enolase, S-100 β protein and some abnormalities on neuroimaging which are not specific could be suspected for SAE but remains a diagnosis of exclusion and can only be confirmed after other infectious, metabolic, and toxic causes have been ruled out by appropriate investigations. The activated glial cells acquire neurotoxic properties, notably by releasing nitric oxide, cytokines, reactive oxygen species, and glutamate inducing apoptosis within vulnerable areas of the brain leading to this brain signalling mechanism which is actually meant to serve as a protective and anti-inflammatory mechanism becomes the culprit in the pathogenesis of SAE [5].

The pathophysiology of SAE has not been established, though several likely mechanisms have been proposed [6], such as direct cerebral localisation of microorganisms with formation of micro abscesses in human SAE, endothelial and blood brain barrier dysfunction, cerebral microcirculation, alterations in neurotransmission, oxidative Stress, mitochondrial dysfunction, apoptosis and the alteration of calcium homeostasis impairs learning memory and cognitive function [7]. Inflammatory cytokines and complement system are the final common pathway in the pathophysiology of brain dysfunction in SAE. Presence of extracranial infection and impaired mental state are the two essential prerequisites for making a diagnosis of SAE. The primary clinical feature of SAE thus is a change in mental status especially that of awareness/consciousness and cognition is the normal clinical presentation.

Limited evidence is now available for the use of prebiotics, probiotics, fecal microbiota transplantation, and vagus nerve stimulation for the successful treatment and prevention of SAE. Management of SAE is limited in spite of

high mortality rate, available drugs to treat the underlying infection and symptomatic treatment for delirium and seizures. Early detection of delirium which proves to be the first manifestation of sepsis by determination of the underlying infection and organism, accurate and prompt treatment of the infection, and providing supportive care is indispensable. Subsequent intravenous antibiotic therapy should be initiated immediately after obtaining appropriate cultures, since; early initiation of antibiotic therapy is associated with lower mortality [8].

Impact of Sepsis Treatment on the Gut Microbiota

Therapies employed for sepsis and septic shock management also pathologically alter the constitution of the gut microbiota. Antibiotics indirectly affect the gut microbiota through alteration of the host innate immune system. Antibiotic-associated depletion of gram-negative organisms reduces expression of toll-like receptors, signalling proteins and antimicrobial peptides (e.g., Reg3g) responsible for killing gram-positive organisms. Other medications commonly used in the critically ill septic patient such as corticosteroids, vasopressors, opioids, and proton pump inhibitors also promote gut dysbiosis. Antibiotics indirectly affect the gut microbiota through alteration of the host innate immune systemic responsible for depletion of gram-negative organisms that in turn reduces expression of toll-like receptors, signaling proteins and Reg3g responsible for killing gram-positive organisms. Corticosteroids though their anti-inflammatory and immunomodulatory effects are well-known, elevation in glucocorticoid concentrations may also reduce gut microbiota diversity [9].

Opioid analgesics therapy for pain management in critically ill patients with sepsis and septic shock is being recently implicated with direct mucosal injury, compromising the protective gut barrier and increasing the risk of bacterial translocation. Chronic opioid use has also been shown to alter the composition of gut microbiota and confer increased risk of infection [10]. Proton pumps inhibitors (PPI), used for stress ulcer prophylaxis in ICU patients, is found to substantially alter gut microbiota diversity and consequently increase pathogenic bacteria expression. Imhann et al., [11] examined stool sample of 211 patients with chronic PPI use demonstrated an abundance of oral microbiota but reduced healthy gut microbiota, and with an increased growth of pathogenic bacteria including Enterococcus, Streptococcus, Staphylococcus and Escherichia coli, compared to non-PPI users [11].

Faecal microbiota transplantation (FMT) as Therapeutic tool

FMT provides a new therapeutic tool to replace the entire intestinal ecosystem. FMT takes a complete intestinal ecosystem along with the necessary substrates and metabolites responsible for immunomodulation (e.g., short chain fatty acids, D-lactate) and transfers these microbes into the diseased recipient to restore the gut microbiota in its entirety [12]. Gut microbiota have been proved to induce the clonal expansion of specific B cell populations and increase production of antibodies. Toxins and other harmful antigens secreted by pathogenic bacteria or viruses can be neutralized by these antibodies and prevent the spread of infection [13]. Li et al. (14) found that FMT effectively improved the spatial memory and EEG abnormalities in an LPS-induced rat model of sepsis combined with cervical vagotomy, and the therapeutic effect of FMT was likely mediated through the vagus nerve [14]. In addition, several case reports indicate that non-Clostridium difficile infection in sepsis patients with prolonged ICU stay and complications including bacteremia, multiple drug resistance bacterial infection, respiratory failure, and organ dysfunction significantly benefitted from FMT. A total of 5 patients received FMT, of which 4 showed clinical improvement and 1 died from non-FMT-related causes [15].

Gut dysbiosis in Sepsis patients results in outgrowth of pathogenic gut-resident organisms over healthy commensal organisms. In severe cases reduced Bifidobacterium and Lactobacillus but increased colonization of pathogenic Staphylococcus and Pseudomonas spp [16]. Due to Sepsis, intestinal wall permeability is induced allowing bacterial antigens to interact with gut-resident immune cells and influence systemic immunity intensifying the progression and severity of sepsis. Endotoxin released from gut bacteria intensifies the systemic inflammation and promote organ damage in addition to promoting the development of SAE [17]. Endogenous gut microbiota such as Bifidobacterium and Lactobacillus produce gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the CNS, which can pathologically alter neural signalling. Li et al., (13) hypothesized that reconstitution of microbial diversity with increased presence of commensal, beneficial bacterial species such as Bifidobacterium, Lactobacillus, and Faecalibacterium and reduction in noxious bacteria contributed to the neuroprotective benefits of FMT therapy [18]. Qin H., et al., [19] endorsed the successful management of severe scrub typhus with pneumonia, sepsis, and MOD in a pregnant woman. The patient responded very well to FMT and oral faecal microbiota capsule therapy successful management of severe scrub typhus with pneumonia, sepsis, and MOD in a pregnant woman. Despite initial challenges, the patient responded favourably to FMT and oral fecal microbiota capsule therapy [19]. Cummulative effect of the changes of this endogenous microflora observed in sepsis lead to the substantial impacts on CNS function. The reduction in SCFA production from gut microflora during sepsis increases inflammatory markers, endotoxins due to the inability to downregulate inflammation [20].

FMT offers the broader scope to correct the dysbiosis in addition to restoring the dynamic balance of bacterial species and their essential metabolites that exhibit anti-inflammatory effects to reduce the harmful neuroinflammatory mediators that contribute to SAE [21].

Rare inflammatory, infectious and procedural complications, gram-negative bacteremia and subsequent death secondary to aspiration during the procedure or due to bacterial translocation have been reported with FMT Septic Patients with underlying immunocompromised conditions or those with an acute immunocompromising illness are at a elevated risk of developing bacteremia and septic complications [12]. Besides FMT has inherent risks to critically patients. Thorough understandings of the mechanism by which an FMT can shape the host immune response is essential. Future microbiota directed therapies may focus on the restoration of bacterial metabolites such as butyrate or the delivery of specific bacterial communities capable of restoring specific microbiota functions necessary in restoring the host immune response and potential therapeutic strategies to modulate the gut microbiota to mitigate sepsis-induced brain injury.

Name of the disease	Gut biome of the patient	After FMT	REF
Sepsis-associated encephalopathy	Associated: absence of anaerobes, including *Staphylococcus species* and *Escherichia coli*, with *Clostridium difficileinfection*, high relative abundance of pathogenic gram negatives, and *Enterococci* [15]. **Increase** *Staphylococcus and Pseudomonas* spp (pathogenic bacteria) [16] **Decrease** *Bifidobacterium* and *Lactobacillus [16]*		[15]. Hao M.X. et al., (2021) [16]. Shimizu K. *et al.,* (2006).

Table. Microbiol (types of bacterial species) contents in Healthy, Sepsis-associated encephalopathy Patient and after FMT

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DOI:10.31579/2642-9756/221