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Review Article

FAECAL TRANSPLANT TECHNOLOGY IN THERAPEUTICS OF ALZHEIMER'S

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Abstract: In the mid-1900s, at the time when medicine became science and found treatments for many diseases, nevertheless many are not under control, especially brain disorders. A nerve injury can affect the brain's ability to communicate with muscles and organs. Early diagnosis and treatment may prevent complications and permanent damage. Faecal Transplant Technology (FMT), a newly developed and effective therapeutic method for many diseases also showed promise to manage some of the brain disorders. Here the progress report of the application of FMT in the management and possible treatment of Alzheimer's disease is discussed.

Keywords: Alzheimer's, FMT, Gut microbiota

INTRODUCTION

Reason for the onset of Alzheimer's Disease (AD), is a complex series of degenerative brain changes that may occur over decades. According to the Alzheimer's Association, 2022 (WHO), it has become the seventh leading cause of death worldwide [1]. It is believed that AD is caused by the build-up of amyloid and tau proteins plaques and tangles which result in the death of the brain cells. A combination of genetic, environmental, and lifestyle factors are anticipated as contributory factors in the prognosis of the disease [2,3].

During the preclinical stage, the disease is asymptomatic and continues for years or even decades. Recently developed sensitive imaging tests can detect deposits of amyloid protein in the brain that interferes with the communication system. The prognosis of AD is the progressive decline in memory, thinking, and organizing skills over time. Due to this, basic daily activities become very difficult for the patient. During the advanced stage, symptoms such as disorientation, confusion, behaviour changes, speaking, trouble remembering names, events, or conversations, problems concentrating, personality changes, like not caring about things used to, mistrust

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Dedication: I am associated with Dr. P.D. Gupta for more than two decades on various projects. We togather developed a "blind women model" to describe light as an epigenetic model for breast cancer. I have honour to present this article on the occasion of 85th birthday. of Dr. Gupta.

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of others, or aggression, mood changes, depression, impaired judgments or decision making, swallowing, and walking become hard.

Neuroscientists have identified risk factors responsible for the disease such as Age (increasing age is the leading risk factor), genetics, traumatic head injury, depression, diabetes, smoking, obesity, traumatic brain injury, and air pollution. Cardiovascular diseases such as high blood pressure, and high cholesterol may also be responsible, Staying mentally, physically, and socially active and by monitoring the diet are suggested to decrease the risk of developing AD [3,4]. Some people develop AD before age 65 - typically in their 40s or 50s. This is called early-onset AD, the incidence and prevalence of Alzheimer's disease and other dementias increased by 147.95 and 160.84%, respectively [4]. About 60% to 80% of people who have dementia suffer from AD, providing a strong clue for t the close relationship between them though they are not the same.

Relation between AD and Dementia: Dementia is designated as the decline in mental function from a previously higher level, severe enough to interfere with daily living implying that it is a state of a person's mental function and not a specific disease. Specific impairments such as memory loss, difficulty in reasoning, handling of complex tasks and language, understanding visual form, space relationship, display of behavior, and personality maintenance are known. Other common causes of dementia include vascular dementia, dementia with Lewy bodies, frontotemporal dementia, and dementia due to Parkinson's disease [3].

Alzheimer's disease will progress through stages at different speeds. Moreover, all changes considered to be characteristics of the disease will not occur in each and every patient. Lack of uniform expression of the disease poses difficulty for clinicians to place a person with AD in a specific stage as stages may overlap. Normally the stage of development is classified as Mild, Moderate and Severe/or Early, Middle, Late.

Gender differences in the susceptibility to the disease: In-depth studies suggest that the prevalence of AD is more in women than in men may be due to reproductive capacity, hormone levels, genetic susceptibility, mental status, and inherently more prone to Alzheimer's disease. It has been acknowledged that women are more likely to develop structural and functional disorders of the nervous system and twice likely to suffer from psychological problems, such as depression than men. All these conditions are risk factors for Alzheimer's disease. The disease burden in men is increasing at a faster rate than in women due to higher rates of smoking and drinking in men [1].

Role of microbiota in the development of AD: Microbiota is the lifeline of human beings, found in all most all organs in the human body and body fluids. This group of microorganisms is a conglomeration of bacteria, fungi, protozoans, and viruses. However, if the balance in interspecies of microbiota is a causal factor for serious diseases but can be fatal also [5].

Studies have shown that victims of severe SARS-CoV-2 infection exhibit cognitive decline and may eventually be prone to develop AD. It has been anticipated that long-term accumulation of pro-inflammatory cytokines, which induces or accelerates the neurodegenerative process and direct viral involvement of the central nervous system. The virus finds its entry in to brainstem through the olfactory nerve and results in respiratory failure. Once infected, patients with dementia are at increased risk of intracranial inflammation and increased mortality [6-9]. To substantiate the role of the virus in the development of AD is from a recent epidemiological survey on the disease burden and shingles vaccine Zostavax. Shingles are most common in older adults and can cause severe pain and rashes. This recent work has suggested that people infected with Shingles are caused by the reawakening of inactive *varicella zoster* virus (VZV), the herpes virus viruses that affect the brain have higher rates of neurodegenerative diseases. Research has also suggested that those vaccinated against certain viral diseases are less likely to develop dementia. Maria Glymour, an epidemiologist at the University of California, San Francisco, who studies AD points out that most of the difference in dementia rates was recorded in the first four years after vaccination, but AD develops over decades. Clinical trials are still wanting to confirm the efficacy of vaccines in reducing the burden of dementia caused by AD [10].

Treatment and management of Alzheimer's: Neither Alzheimer's nor dementia have a cure though certain medications and therapies can help to manage

the symptoms temporarily keeping the disease from getting worse but would not stop or reverse AD. The present scenario on treatment is highly personalized because AD affects everyone differently [3]. The available medications overlap therapeutically for the 2 diseases. cholinesterase inhibitors, glutamate inhibitors, sleep medications, antidepressants, and antipsychotic medications, may help with behaviour changes. The FDA has given accelerated approval for aducanumab (Aduhelm™), the first disease-modifying therapy for Alzheimer's disease to reduce amyloid deposits in the brain. Cholinesterase inhibitors which work by blocking the action of acetylcholinesterase, the enzyme responsible for destroying acetylcholine, are used as drugs to increase the titre of acetylcholine, one of the chemicals that help nerve cells communicate with each other. NMDA antagonists such as Memantine (Namenda®) are FDA-approved for treating moderate to severe AD. It helps to keep certain brain cells healthier. Many steps are suggested by healthcare providers to manage behavioural changes in AD patients to keep them comfortable in their own environment.

Antidepressants, anti-anxiety drugs, anticonvulsant drugs, and antipsychotics (neuroleptics) cause unpleasant or potentially dangerous side effects (like dizziness, which could lead to falls). The drugs are prescribed only when behavioural problems are severe and that too for a short period and only after safer initial trials of non-drug therapies [2,3].

Gut-brain axis and therapeutic efficacy of FMT: Taking antibiotics too often or for the wrong reasons can alter the infectious microenvironment and may reduce the ability of immune cells to kill bacteria therefore scientists were looking for alternatives to antibiotics. Faecal microbiota transplantation (FMT) is one of those. FMT is a procedure that delivers healthy human donor stool to a patient via colonoscopy, enema, nasogastric (NG) tube, or in a capsule. FMT has emerged as a highly effective, safe, and cost-effective treatment option for recurrent clostridioides difficile infection (CDI) with a success rate of around 90% [11]. In addition to CDI infection, this technique is also effective in diseases such as carbapenem-resistant *Enterobacteriaceae* (CRE), Alzheimer's, arthritis, diabetes mellitus, inflammatory bowel disease, autism, and obesity, polycystic ovary [12] and endometriosis [13].

All the initial dose of microbes is of maternal origin that multiplies and the grown-up human body contain in a range of 30 to 40 trillion in numbers. These microbes produce many chemicals some are beneficial to the host and others are harmful. Once the gut-brain axis is established the microbial products in the gut start influencing the brain. Hundreds of neuro-chemicals produced by the gut microbes regulate basic physiological processes as well as mental processes such as learning, memory, and mood. Dysbiosis and inflammation of the gut are responsible for anxiety and depression which are prevalent in society today [14]. The nervous system that regulates the gut is often called the body's "second brain," capable of taking part in neurochemistry but not in wisdom as the brain is involved. This efficient and vigilante's extensive network uses the same machinery (same chemicals and cells) as the brain to help in digestion and also send messages to alert the brain when something is wrong [15]. Bacteria present in the gut stimulate directly neurons of the enteric nervous system (ENS) which send signals via the vagus nerve to the brain. Microbes are capable of producing hormones and neurotransmitters identical to that are produced by the neuroendocrine system. By leveraging animal models, several different pathways of communication have been identified along the "gut-brain-axis" including those driven by the immune system, the vagus nerve, or by modulation of neuroactive compounds of microbiota origin. Of the latter, bacteria have been shown to produce and/or consume a wide range of mammalian neurotransmitters, including dopamine, norepinephrine, serotonin, or gamma-aminobutyric acid (GABA) that regulates both mood and gastro intestinal tract (GI) activity [16].

The initial stage of the involvement of gut microbiota in the pathogenesis of AD may be due to the dysfunction of the blood-brain barrier (BBB). The mechanism of action of the secreted products of gut microbiota origin, when gets access into the blood circulation, disturbs the BBB integrity, easily cross the disrupted BBB and enter the brain to promote pathological changes in AD. Though the close link between the imbalance of gut microbiota and AD is still an enigma, evidence from many animal models and 2 clinical trials, these have been suggested that dysbiosis can lead to the increased secretion of lipopolysaccharides and amyloid, which may impair the permeability of the intestine and BBB [17,18].

In turn, bacteria possess receptors for these hormones

which influence their own growth as well as virulence. Short-chain fatty acids of bacterial origin which are identified to have beneficial effects may exert neurotoxicity. Bacterial components such as lipopolysaccharides act as a low-grade tonic to stimulate the innate immune system [11]. In particular, Gut microbiota (GM) can influence the neural network controlling gut function through the intrinsic and extrinsic nervous systems, such as the autonomic nervous system, enteric nervous system, and neuroendocrine and immune systems. As a consequence, GM has been implicated in the regulation of neural development, neurotransmission, and the maintenance of brain homeostasis [19]. All this evidence demonstrate the regulation of brain homeostasis through bidirectional communication between the gut and the brain. GM disturbance has been also been discovered to be related to various neurological disorders, including Alzheimer's disease [20].

In terms of human studies, two case studies are showing promising results [21-23]. Hazan [2] demonstrated an improvement in AD symptoms (including cognitive function, memory and mood) in a man aged 82 after FMT from the recipient's wife [22]. In a second case study, a woman aged 90 with AD and severe *C. difficile* infection who underwent FMT from a healthy young donor showed improvements in cognitive function, GM composition, and SCFA production [22]. Interestingly, FMT also improved GM dysbiosis and cognitive deficits in the mouse model of HD [23]. Nandwana et al. (2021) have given a strong support for the efficacy of FMT to treat AD [18].

These studies demonstrate that FMT can rapidly and effectively restore GM dysbiosis and brain dysfunction in patients, suggesting that restoration of GM homeostasis by FMT may have beneficial effects on AD treatment also. However, several limitations remain for its wide application, such as standardization of the procedures, time point, and treatment period, as well as inclusion criteria of donor and recipient. Therefore, more human trials will be conducted in the future to provide evidence for the efficacy of FMT and optimize the intervention [19].

CONCLUSIONS

Nutrition, medications, lifestyle, geographical location, stress, and dietary habits are responsible for maintaining healthy gut microbiota. The dysbiosis of the intestinal bacteria has a profound influence on the onset and progression of AD due to the "gut-brain axis". This, imply that modulation of gut microbiota using FMT represents a forward-looking approach for AD to avoid drugs, and that too for a prolonged period. Currently, the rationale for the clinical application of FMT is based on a small number of case reports and animal models. The technical advancement to form a capsule containing desirable bacteria is a more comfortable option for patients and may replace FMT in the future. Detail understanding of the pros and cons of FMT could be achieved only from large-scale, randomized, double-blind human trials. Emerging evidences suggests that (FMT) might represent a potential therapeutic option for AD.

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