

Management of Huntington's Disease by Faecal Microbiota Transplant (FMT) Technology

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ABSTRACT

Huntington's disease (HD) is an inherited autosomal dominant neurodegenerative disorder in which nerve cells in the brain break down over the time. Huntington's disease results in a decline in thinking and reasoning skills, including memory, concentration, judgment, and ability to plan and organize. Brain changes in this disease lead to alterations in mood, especially depression, anxiety, uncharacteristic anger and irritability. Unfortunately, no cure exists, but drugs, physiotherapy and talk therapy can help to manage some symptoms. Bidirectional communication between the gut microbiome and central nervous system via gut-brain axis gives a clue that dysbiosis of the gut microbiota in HD is the causal factor for the prognosis of the disease.

Promising results were obtained from Faecal Microbiota Transplant (FMT) treatment in human trials and animal models are discussed here. The intensity of the symptoms could be reduced by FMT.

Keywords: Huntington's Disease, Gut-Brain Axis, Bidirectional Communication, Dysbiosis, Faecal Transplant Technology

Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative inherited disorder that causes damage in nerve cells (neurons) in the parts of the brain to gradually break down and die. This disease attacks areas of the brain that help to control voluntary (intentional) movement, as well as other areas. Each child of an affected parent has a 50% chance of developing the disease. The child inherits a mutation (a change) in a particular gene from chromosome 4p from the parent. Occasionally HD occurs sporadically without a family history also. The mutation in the gene for a protein called Huntington is the causal factor for the defect in the building blocks of DNA called cytosine, adenine, and guanine (CAG) to repeat many more times than they normally do.

Most people have fewer than 27 CAG repeats in their HD gene, so they are not at risk for the disease. People who have CAG repeats in the middle range (27 to 35) are not likely to develop the disease, but they could still pass it on to future generations. People with HD may have 36 or more CAG repeats.

Most people develop Huntington's disease between 30-54 years old but it can manifest as early as 4 years old and as late as 80 years. The worldwide prevalence of HD is approximately 2.7 per 100,000.

Gut microbiota proves to be the centre of a bidirectional communication between intestine and brain via gut-brain axis.

This axis is responsible for a signalling pathway between the gastrointestinal (GI) tract and CNS (central nervous system), that permits a bidirectional communication between the two systems. The primary function is to monitor and integrate intestinal functions as well as to link, through immune and neuro-endocrine mediators, the emotional and cognitive centres of the brain with peripheral intestinal mechanisms such as immune activation, intestinal permeability, enteric reflex, and entero-endocrine signalling.

To accomplish its role successfully different routes of communication between the gut microbiota and the brain have been predicted such as involving vagus nerve, generation of metabolites and bioactive peptides (such as short-chain fatty acids) as well as the modulation of transmitters (e.g., serotonin and acetylcholine) by microbiota and through the secretion of cortisol by the hypothalamus-pituitary-adrenal axis (HPA) in case of stress that can affect intestinal motility, integrity and mucus production, leading to changes in gut microbiota composition. These alterations, in turn, may affect the CNS through the modulation of stress hormones. In addition, pro-inflammatory cytokines and chemokines [1] toll-like receptors (TLRs) and peptidoglycans (PGNs) mediating the immune response towards microbes, low-grade immune activation of local microenvironment is also involved [2].

Reconstruction of the healthy gut microbiota is a promising new strategy for treating cerebral diseases. This review is focussing on the altered gut microbiota in humans with Huntington's

disease highlighting the importance of understanding how the gut microbiota fits into the progression of the disease. This review lastly tantalizing proposition of whether the gut may be a potential target for future therapeutic intervention to improve outcomes in Huntington's disease and other neurodegenerative diseases.

Diagnosis and Treatment of the HD

In general, clinicians use a combination of tests and other information to see if a person has HD. These include medical history, neurological and lab tests, brain imaging, and genetic testing. Completely wiping out or reverse HD is a remote chance but some of the symptoms can be treated. For chorea associated symptoms, the drugs tetrabenazine and deuterenazine is used. Antipsychotic drugs may ease chorea and to control hallucinations, delusions, and violent outbursts. Depression and anxiety relieving drugs are available. Side effects of drugs used to treat the symptoms of HD may include fatigue, sedation, decreased concentration, restlessness, or hyper excitability. Drugs are prescribed when HD symptoms create problems for the person living with HD [3].

In the recent past studies increasingly show that dysbacteriosis in non-neurological problems such as Obesity Polycystic ovary endometriosis etc. Many successful cases of FMT in the treatment of neurological diseases/psychiatric diseases often have obvious GI symptoms, and the improvement of neurological symptoms/mental symptoms is also related to the GI symptoms [4-7].

Gamma-Amino Butyric Acid (GABA) in Huntington's

The role of gut microbiota and GMBA in HD is of utmost importance since, volumes of evidence support the theory that the composition of the gut bacteria affects dramatically any age-related neurological disorder, such as HD, and mood disorders. In addition, extrinsic factors including diet, lifestyle, pro-inflammatory insults, along with intrinsic components including genetic polymorphism, immunity, metabolites, and hormones, profoundly affect the composition of the gut microbiota. The alteration in turn produces signalling molecules such as short chain fatty acids (SCFAs), tryptophan, choline, and hormones (such as ghrelin, leptin) in the GI tract to regulate CNS functions. Aging has a strong influence on gut microbiota composition favouring the development of pro-inflammatory bacteria (such as *Bacillus fragilis*, *Faecalibacterium prausnitzii*, *Eubacterium rectale*, *Eubacterium hallii*, and *Bacteroides fragilis*) to the detriment of anti-inflammatory bacteria, a condition that induces local systemic inflammation then leading to enhanced permeability of the gastrointestinal tract, an impairment in the blood-brain barrier (BBB), finally promoting neuroinflammation [2]. Indeed, Cattaneo et al. observed such pro-inflammatory bacteria in amyloid-positive patients compared to healthy subjects [8].

Efficacy of FMT to Ease HD

Faecal microbiota transplantation (FMT) is one of those procedure that delivers healthy human donor stool to a patient via colonoscopy, enema, nasogastric (NG) tube, or in capsule. FMT has emerged as highly effective, safe, and cost-effective treatment [7]. Many successful cases of FMT in the treatment of neurological diseases/psychiatric diseases often have obvious GI symptoms, and the improvement of neurological symptoms/mental symptoms is also related to the GI symptoms.

FMT can significantly replenish the richness of gut microbiota simultaneously restoring the proportion of anti-inflammatory bacteria. Reconstructed healthy gut microecology is observed to improve the clinical symptoms as well. FMT has also been shown to improve neurological and psychological symptoms by modulating the gut-brain axis. Based on the many studies addressing gut microbiota dysregulation in HD, we review the potentiality of microbiota transplantation as complementary therapeutic options for this devastating and progressive disease.

Gubert et al., reported, for the first time in mice, a significant gut dysfunction in the late stage of the HD phenotype [9]. Sexual dimorphism was also observed for this trait, males being more affected. However, in females, the FMT intervention was able to fully rescue the cognitive deficits observed in HD mice. Altogether, these results reflect the sexually dimorphic FMT engraftment observed in HD mice and support the hypothesis that interventions that ameliorate gut microbiome dysbiosis could in turn be therapeutic for this disease.

Indeed, transplanting healthy faecal microbiota from wild-type mice to mouse models of Alzheimer's documented a decrease in cognitive impairment, and circulating levels of pro-inflammatory markers and improved cognition [2].

The efficacy of FMT depends on the types of antibiotics, microbial composition, intervention procedure, and donors. The exact influence of these factors and the potential adverse effects of FMT are currently an enigma due to lack of long-term follow-up and appropriate controls [10].

Conclusion

Successfully, researchers have confirmed unequivocally that interventions aimed at manipulating gut microbiota influence brain disorders. FMT can reconstruct the healthy gut microecology and improve clinical symptoms. Apart from its direct therapeutic effect in GI diseases, FMT has also been shown to improve neurological and psychological symptoms by modulating the gut-brain axis by maintaining homeostasis of the gut microbiome.

Thus, some of the clinical manifestations or brain changes evident in HD may be related to gut-driven modulation of brain inflammatory pathways, via link between gut, endocrine, immune and neural pathways.

Though FMT represents a forward-looking approach for various neurological disorders the current rationale for the clinical application of FMT is based on a small number of case reports and animal models. For a complete understanding of the role of FMT in neurological diseases, however, still large-scale, randomized human trials are needed.

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