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Journal of Cancer Research and Cellular Therapeutics
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Short Communication

Alternate Approach in Therapeutics for Amyotrophic Lateral Sclerosis

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Received Date: July 07, 2023; **Accepted Date:** July 24, 2023; **Published Date:** August 05, 2023

Citation: K Pushkala and P D Gupta, (2024), Alternate Approach in Therapeutics for Amyotrophic Lateral Sclerosis, *J. Cancer Research and Cellular Therapeutics*, 8(5); **DOI:10.31579/2640-1053/201**

Abstract

Motor neurons present in the brain and spinal cord control voluntary muscle movement and breathing. On a set of Amyotrophic lateral sclerosis (ALS) motor neurons stop sending messages to the muscles, which causes the muscles to weaken, start fasciculations, and atrophy. The exact cause of the disease ALS is still not known therefore it remained incurable. This disease starts with muscle twitching and weakness in an arm or leg, trouble swallowing or slurred speech due to loss of control of the muscles needed to move, speak, eat, and breathe. Since Faecal microbiota transplantation (FMT) has shown promise for treating various neurodegenerative, a pilot study with FMT as a potential intervention to modify the immunological response to ALS was also tried and all the evidence from the study conveyed towards dysfunction of the adaptive immune response for this disease too.

Keywords: neurodegenerative diseases; faecal microbiota transplantation (fmt); loss of speech; hearing; jaw movements and breathing

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a neurological disorder in which motor neurons present in the brain and spinal cord degenerate and die. These neurons control voluntary muscle movement and breathing; they stop sending messages to the muscles, which causes the muscles to weaken, start to fasciculations, and be atrophied. Eventually, in people with ALS, the brain loses its ability to initiate and control voluntary movements such as walking, talking, chewing, and other functions, as well as breathing. ALS is a progressive disease that can strike at any age but commonly develops between the ages of 55 and 75. Although not as common, people with ALS also may experience problems with language or decision-making. Some also develop a form of dementia known as FTD-ALS. Most people with ALS die from being unable to breathe on their own (known as respiratory failure,) usually within three to five years from when the symptoms first appear. However, about 10% survive for a decade or more [1].

Nearly all cases of ALS are considered sporadic, with no associated risk factors and no family history of the disease [2]. Although family members of people with ALS are at an increased risk for the disease, the overall risk is very low, and most will not develop ALS. So far researchers could not decide from where ALS begins, however, about 25-40% of all familial cases (and a small percentage of sporadic cases) are caused by a defect in the C9orf72 gene. C9orf72 is a protein found in motor neurons and nerve cells in the brain [3]. Though it is very rare, the childhood form is linked to the gene SPTLC1 which is part of the body's fat production system and may be caused by changes in the way the body metabolizes fatty materials (lipids) [4].

Causes Symptoms and management

Neurodegeneration in ALS is caused by incorrect protein folding, compromised axonal transport, and activated glial cells though, the exact cause of the disease is still not known. ALS is incurable, and treatment focuses on symptom management and addressing family and caregiver stress. This disease starts with muscle twitching and weakness in an arm or leg, trouble swallowing or slurred speech due to loss of control of the muscles needed to move, speak, eat, and breathe. There is no cure for this fatal disease [5].

Symptoms of ALS vary from person to person depending on which nerve cells are affected. Symptoms might include Trouble in walking or doing usual daily activities, tripping and falling, weakness in the legs, feet, or ankles, hand weakness or clumsiness, slurred speech or trouble swallowing, weakness associated with muscle cramps and twitching in the arms, shoulders, and tongue, untimely crying, laughing or yawning, thinking or behavioural changes [6]. This disease often starts in the hands, feet, arms, or legs followed by spreading to other parts of the body. When more nerve cells die muscles get weaker resulting in chewing, swallowing, speaking, and breathing.

Upper as well as lower motor neurons gradually deteriorate and then die affecting muscle function since messages are not sent to the muscles. Established risk factors for ALS include: Genetics, age, sex, smoking, environmental toxin exposure, and military service [7].

Treatments can't reverse the damage of ALS, but they can slow the progression of symptoms. The treatment of ALS is multidisciplinary and involves physical, occupational, and speech therapists, home ventilation therapy, nutrition support, psychotherapy, training for caregivers, cognitive screening, and end-of-life care. Riluzole, Edaravone, and sodium phenylbutyrate are the only approved medications to treat ALS but provide limited survival benefits [8]. However, recently applied treatment with faecal microbiota transplantation (FMT) showed much improvement in disease management [9].

Efficacy of Fecal microbiota transplantation (FMT)

FMT has shown promise for treating various neurodegenerative and neurological diseases [10-13]. However, clinical data on its efficacy in ALS are limited. Mandrioli J and his colleagues in 2019 performed a pilot study with FMT as a potential intervention to modify immunological response to ALS and disease progression at an early stage. All the evidence from their study conveyed a dysfunction of the adaptive immune response during ALS. With this as a clue they focussed on modulating neuroimmune system by gut microbiota (GM) through the gut-brain axis. Earlier reports were available for the dysbiosis of the GM composition in ALS [14].

Moreover, alterations in GM composition in ALS have been reported in previous studies. Fang et al. (4) found a significantly increased population of harmful microorganisms (genus *Dorea*) with a reduced population of beneficial microorganisms (genus *Oscillibacter*, *Anaerostipes*, *Lachnospiraceae*) in ALS patients. The authors suggested that the imbalance in intestinal microflora constitution may cause a pro-inflammatory dysbiosis that may alter the intestinal epithelial barrier, promoting immune/inflammatory responses with a major role in ALS pathogenesis. Another study detected a higher amount of *E. coli* and *Enterobacteria* and a low presence of total yeast in the GM composition of ALS patients concerning healthy controls [4].

Mechanism of action of gut microbiota

The mechanism by which the FMT acts against ALS progression probably is by the regulation of the mutual signaling between gut microbiota and CNS and employing bidirectional communication (via neuronal, hormonal, immunologic, and toxic signaling). In addition to direct communication through the vagus nerve, changes in tryptophan and norepinephrine metabolism, production and absorption of neuroactive metabolites, immune activation through molecular mimicry, and the direct production of neurotoxins all of which carry a therapeutic value in the management of ALS disease [14].

Lu and his group (7) gave evidence from one female case with ALS, who benefited from washed microbiota transplantation (WMT), an improved faecal microbiota transplantation (FMT), through a transendoscopic enteral tube [7]. In 2020 this methodology involving an automatic purification system and washing process was standardized. This course of the rescue WMT successfully stopped the progression of the disease again with a quick improvement in the patient she could get out of her wheelchair and walk with the help of others, and her muscle tone was also alleviated [2].

Microbial analysis indicated that the composition of the gut microbiota from the patient after WMT treatment was closer to those of healthy donors indicating successful colonization of donor gut microbiota (Table 1). Similarly, a changing trend of potentially harmful bacteria, such as the *Proteobacteria* phylum, changed after WMTs.Some bacteria from the donors colonized successfully after WMTs, such as the *Firmicutes* and *Verrucomicrobia* phylum, *Prevotella* spp., and *Ruminococcus* spp. Similarly, the changing trend of the potentially harmful bacteria, such as the *Proteobacteria* phylum, changed after WMTs. These rebiosis could have contributed to the positive treatment results of ALS. No adverse events were observed within both short-term and long-term follow-up after WMTs.

Table1. Microbiol (types of bacterial species) contents in Healthy, Amyotrophic **Lateral Sclerosis** Patients and Patient after FMT

Name of the disese	Gut biome before FMT	Gut biome of the patient	After FMT	REF
Amyotrophic Lateral Sclerosis	Differences in both alpha and beta diversity of the gut microbiota compared to that of the donor. *Bacteroides uniformis* *B.stercoris*, *Collinsella aerofaciens*, *Enterococcus faecalis*, *Firmicutes*, *Klebsiella pneumoniae*, *Prevotella* spp. *Ruminococcus* spp., *Verrucomicrobia* ,	**Increase** *Actinobacteria* . *Cyanobacteria (Harmful).* *Dorea*, *Firmicutes*, *Proteobacteria*, **Decrease** *Anaerostipes*, *Butyrivibrio ibrisolvens* *Escherichia coli*, *Firmicutes*, *Lachnospira*, *Oscillibacter*, *Peptostreptococcus*, *Prevotella* spp. *Ruminococcus* spp. *Roseburia intestinalis* and *Eubacterium rectal* (butyrate-producing) . *Anaerostipes*, *Lachnospiraceae* *Bacteroidales*, *Oscillibacter*,	**Increased** Alpha diversity *Bacteroidetes*/*Firmicutes*. *Bacteroidetes* (coenzyme A biosynthesis super pathway(energy metabolism) , glycolysis energy metabolism), L-aspartate, L-asparagine, and L-Histidine metabolism). **Increased** Beneficial Bacterial species *Alistipes finegoldii*, *Bacteroides fragilis*, *B. intestinalis*, *B. longum*, *B. stercoris*, *B. thetaiotaomicron* *B. uniformis*, *B. vulgatus*(glycolysis),, *Bacteroides. adolescentis*, *Bifidobacterium dentium*, *Bifidobacterium pseudocatenulatum*, *Escherichia coli*.	Hao M.X. et al., (2021) Lu et al.,(2022). Zhai et al. (2019)

		(Imbalance). Beneficial Bacterial species *Bacteroides vulgatus* , *Faecalibacterium prausnitzii.*	*Faecalibacterium prausnitzii (*glycolysis), *Firmicutes*, *Fusobacterium plautii*, *Klebsiella pneumonia*, *Parabacteroides merdae*, *Prevotella* spp. *Ruminococcus gnavus*, *R. torques*, *Verrucomicrobia* ,	

Subsequently, Yan, J *et al*., (14) reported the results of (FMT) in two patients with late-onset classic ALS who required tracheostomy and mechanical ventilation. In both patients, following two rounds of FMT significant improvements in respiratory function were noticed, leading to weaning off mechanical ventilation was a positive observation in treatment. In addition, muscle strength improved, allowing for assisted standing and mobility, improved swallowing function, and reduced muscle fasciculations [14]. Metagenomic and metabolomic analysis revealed an increase in beneficial Bacteroides species (Table) as well as elevated levels of metabolites involved in arginine biosynthesis and decreased levels of metabolites involved in branched-chain amino acid biosynthesis. These findings offer a potential rescue therapy for ALS with respiratory failure and provide new insights into ALS in general.

Recent studies have indicated disparities in the gut microbiota between patients with ALS and healthy individuals which include a diminished abundance of butyrate-producing bacteria, an increase in potentially harmful bacteria (*Cyanobacteria*), and an imbalance in potentially protective microbes. The patient's microbiota was dominated by *Firmicutes* and *Actinobacteria.* After the second FMT, alpha diversity increased, narrowing the gap between the microbiota profiles of the patient and donor. Beta diversity tended to align more closely with the donor's. A noticeable shift occurred at the phylum level, resulting in an elevated *Bacteroidetes*/*Firmicutes* (*B/F*) ratio. Predominant top five abundant species before first FMT and after FMT, as well as bacteria high in abundance, including B. stercoris, R., *torques*, *Bacteroides vulgatus*, *Faecalibacterium prausnitzii*, *B. uniformis*, and *Bifidobacterium pseudocatenulatum*, after second FMTis tabulated (Table 1). Five out of which were within the top 10 most abundance in the donor was also observed an observation for the positive treatment modality.

Glycolysis and coenzyme A biosynthesis are essential pathways for energy metabolism and defects in energy metabolism are potential pathogenic mechanisms in ALS. Glycolysis upregulation as provided by a high sugar diet improves the locomotor and lifespan defects in motor neurons or glia. And thus high sugar diet appears to be beneficial in ALS.

Further, consistent with the predicted functional pathway, non-targeted metabolomics revealed increased levels of specific amino acids and their metabolic products in patients with ALS after FMT. For example, L-Arginine can delay skeletal muscle atrophy, promote muscle growth, maintain muscle function, and protect cells from oxidative damage [14].

Conclusion:

The positive results of these individual case reports of ALS patients advocate the benefits of FMT. This research field is therefore highly innovative and is gathering increasing interest from the international scientific community.

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DOI:10.31579/2640-1053/201