International Journal on Science and Technology (IJSAT)
E-ISSN: 2229-7677 ● Website: www.ijsat.org ● Email: editor@ijsat.org

Faecal Transplantation in Epilepsy Patients

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Abstract

Faecal microbiota transplantation [FMT] is a process of collecting faeces from a healthy individual and transplanting it to a patient with gut dysbiosis. FMT has been used for Clostridium difficile infections for years now. Gut microbial flora is a very crucial part of our physiology as gut dysbiosis directly affects the organs. Connection or relationship between gut and nervous system is known as the gut - brain axis, which is partly indicated by epileptic seizures. It is roughly estimated that 30% of patients who have epilepsy, their seizure can't be controlled by anti-epileptic drugs [1]. Hence when we perform FMT , it helps resolve the imbalance of the gut flora, as a result the seizure threshold also increases , which means that the stimulus needed for the seizure to occur decreases, in turn reducing the count of seizures as a whole. Ketogenic diet is recommended along with FMT for better results, as indirect effects and metabolites of this diet have a positive and a needed effect on epileptic patients. According to various faecal analysis, there is variation in the type of microbes in each disease; hence when we perform a FMT we need to prioritise which microbe is more important and more beneficial for that particular disease.

Keywords: Faecal microbiota transplantation; epilepsy; gut - brain axis; ketogenic diet; gut microbes

1. Introduction

This research reviews the use of faeces in the treatment of epilepsy, one of the most common neurological disorders in the world.

1.1 FMT (Faecal Microbiota Transplantation) : Faecal microbiota transplantation is a procedure of introducing the gut flora obtained from a donor into the recipient's gastrointestinal tract. Approximately 1,700 years ago, a medical researcher named Ge Hong used the faeces for the first time for curing severe diarrhoea and food poisoning [2]. Many diseases are associated with gut dysbiosis, as an imbalance in gut bacteria may also affect our body's immune system.

Analytically, when the faecal microbiota of epileptic patients was compared to healthy individuals, the p value was less than 5% indicating that the number of microbes in the healthy individuals was statistically significant [3]. FM Tis being clinically used for C Difficile infection; but nowadays with emerging studies on FMT, researchers are trying to incorporate this method for osteoporosis, cancer, metabolic syndromes, neurological disorders [such as parkinson's , alzheimer's, epilepsy] , psychiatric disorders [such as anxiety, depression, bipolar disorder].

The FMT could also have some ill effects, there could be bloating; if the air gets trapped inside the colon while performing this procedure, it may lead to abdominal cramps; constipation, pneumonia, infections; tear which in turn may cause perforations; bleeding [4].

1.2 Epilepsy : A chronic neurological disease that occurs when the signalling from the neurons gets irregular, which leads to loss of brain function for a short amount of time [5]. According to WHO [6], Around 50 million people worldwide have epilepsy and epilepsy is considered as one of the most common among all the neurological problems[7]. When there is imbalance of these cerebral neuronal signals, some symptoms and signs can be seen externally, these are termed as seizures [8]. WHO also states that 70% of people can be seizure free if they are properly diagnosed and treated. It is also observed that the patients who have had inflammatory bowel disease tend to have more likely to develop epilepsy [1].

1.3 Microbiota gut- brain axis : This axis contains 3 components: the gut microbiota, the enteric nervous system and the central nervous system.

The human gut and the brain are connected by 2 pathways, an ascending pathway and a descending pathway; these are supported by a direct neural pathway, immunological pathway and also the neuroendocrine system [9]. But, out of these three, the neuroimmune and the neuroendocrine pathway are crucial.This communication involves the vagus nerve , which uses direct neural signalling,the enterochromaffin cells (which are a subtype of intestinal enteroendocrine cells) [10]. The gut brain axis is extremely affected when there is some kind of inflammatory reaction taking place; a damage to the gut barrier, if the cytokines are excessively released or if the neural portion of the gut is affected , it may affect the axis [5].

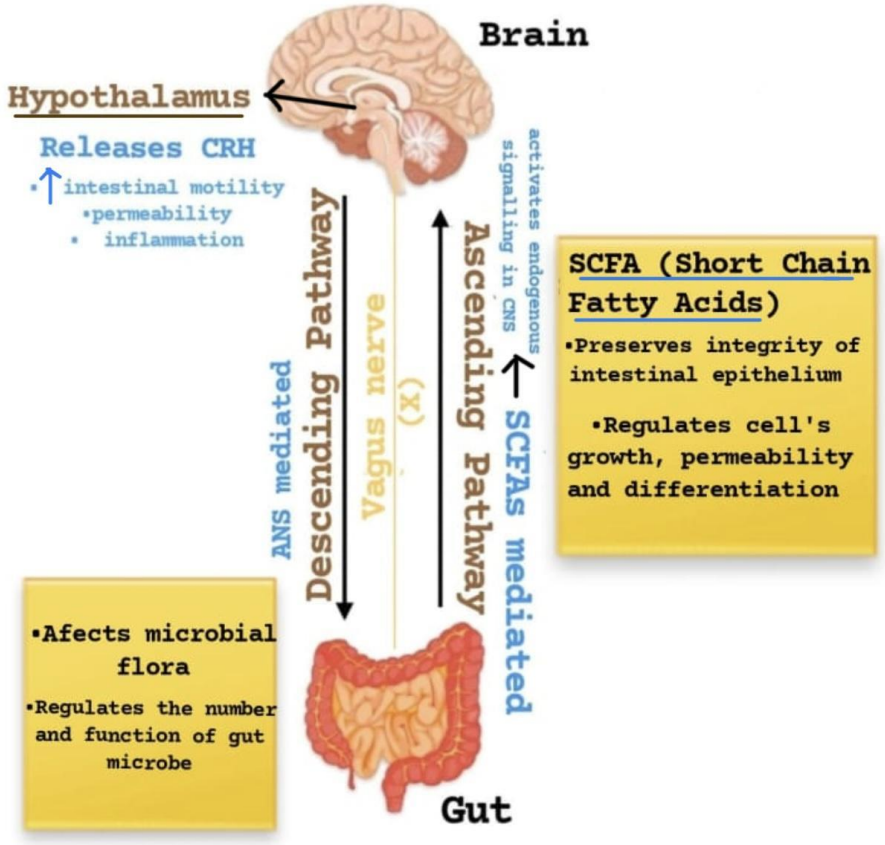

Fig.1 Gut-brain axis [The data has been obtained from [10]]]

1.4 Microbial composition : There are approximately 100 trillions microbes in our gut. The microorganisms that were found to be increased in number in the epileptic patients when the gut microbiota analysis was done are the following ones : Firmicutes, Proteobacteria, Verrucomicrobia, and Fusobacteria with a decline the quantity of Bacteroidetes and Actinobacteria [11]. According to a study by Charles A L Reed [12], “Bacillus Epilepticus” a probable intestinal origin microbe was found in epileptic patients, which could have been involved in the trigger for a seizure and its continuity. This microbe was tested on rabbits and it did induce seizures in them, but according to a few studies this microbe was never observed again and this experiment by reed was hypothesised. When there is alteration in the number of organisms in the gut , it leads to a phenomenon called gut dysbiosis. As we know that the gut and brain are firmly associated with one another, the gut dysbiosis may cause some problems in the neurons as well. Gut dysbiosis may cause increased oxidative stress, mitochondria may stop functioning properly,there could be programmed cell death i.e. apoptosis, a decline in the synaptic transmission which may bargain the neuronal development and neuroprotection.

The vast majority of gut microbial flora have positive as well as negative effects on epilepsy. There are microbes that produce metabolites that have a negative effect on epilepsy, I.e. epilepsy promotes metabolites, these metabolites alter the GABA/ glutamate ratio which in turn promotes the disease. But, some release / produce metabolites that inhibit the occurrence of epilepsy, they are SCFA and serotonin [1].

2. **Methods**

The data sources included in this are pubmed, google scholar, John Hopkins medicine, World health organisation site, Davidson's principle and practice of medicine, eBioMedicine,etc.

According to John Hopkins Medicine [4], a criteria exists for the faecal transplant donor. The donor should fit in the criteria of being a healthy adult and should also clear the screening by a physician.

Firstly, the criteria of a donor as a healthy adult is that he shouldn't be immunocompromised, no antibiotic exposure in the past six months,has no risk of infectious disease, and shouldn't have any chronic GI diseases [13].

Furthermore, the criteria of a donor to pass a physician's screening test, is that he shouldn't have the following diseases- hepatitis A, B or C , HIV, syphilis, intestinal parasites, C difficile.

2.1 Preparation of the faecal microbiota solution for transplantation [14]

It is estimated that approximately 30-100g of the faecal matter should be collected from the donor. The viability of the fresh faeces is not long enough, hence the preparation that is needed should be formed within 6-8 hours. For this, we need to dilate it first so that it can be easily transplanted. Various solvents are used for this, namely normal saline; water could also be used but it should be sterile; some research also shows that 4% milk is also used. After mixing them, a suspension is formed which should be smothered out before inculcating. Once this process is done it could either be used directly by pouring into an administration container or if needed for later use, we could put in 10% glycerol which would convert it to a frozen sample.

2.2 Approaching the gastrointestinal tract

Primarily, before reaching the GI we should collect the suitable faeces sample from the donor I.e. close relatives, family members or any healthy unrelated individuals. The faeces sample could be fresh faeces solution or could be in a frozen state. The frozen sample is easy to inculcate into the GIT whereas the fresh sample is more efficient.

This sample could be delivered in the GI tract via a capsule or directly by nasogastric tube, nasoduodenal tube or by colonoscopy.

Faecal transplantation is done by a gastroenterologist. Most preferred route of a FMT is colonoscopy. The patient should lie in a lateral decubitus position while undergoing the colonoscopy procedure. A colonoscope is inserted via the anal canal into the intestine and the solution containing faeces is put through it. The faeces sample is completely liquid as it is mixed with saline priorly. The faeces microbiota sample is sprayed at the wall of the intestines.The GIT could also be approached using a nasogastric tube. The patient should be sitting upright with slight flexion of the neck, but the NG tube has a higher risk of occurrence of side effects and also doesn't require a bowel prep. After the completion of this procedure, the doctor would prescribe the patient with anti-diarrhea drugs so that transplant to stay in its place and doesn't rush out of the body [13].

2.3Mechanism of signalling between GIT and Brain [10]

- The communication mechanisms that take place between the gut and the brain occur essentially by the neuroimmune- neuroendocrine pathways.This is carried out with the tenth cranial nerve with the enteroendocrine system,the enterochromaffin cells (a subtype of enteroendocrine cells), and a direct neural signalling.
- There are two pathways connecting the GIT and the brain, they are : ascending and descending pathways.
- The upward communication pathway is through short chain fatty acids whereas the descending pathway is through the autonomic nervous system.
- It is analysed that the gut microbiota also helps in making GABA, adrenaline and noradrenaline and as well as serotonin.
- According to the study by Cleophas MCP [15], if the small chain fatty acids production is reduced , as a result it hinders the upward communication of GIT and brain.

2.4 Ketogenic diet

- Studies have shown that when an epileptic patient is on a diet or in a fasting state, this gives a sedative effect to their body [16].
- "Ketogenic diet" is a preferred diet along with FMT in the epileptic patients or in general with neurological disorder patients. According to Y. Fan [17], this diet contains the correct amount of proteins, it's a high fat diet and is low carb and due to the diet being low carb, gradually there is almost complete elimination of carbohydrates which causes near dependency on ketone bodies, which then becomes the main source of energy. Ketone body's derivatives i.e. acetoacetate and β-hydroxybutyrate, help in decreasing the epileptic effects especially the acetoacetate does this job [18]. In the ketogenic diet, the acetone level noticeably increases which gives anticonvulsant action and also gives antagonistic effects to various kinds of seizures [1].
- Many researchers have studied the effect of ketogenic diet on our body and have also compared KD to other controls (Table 1).

3. **Literature review**

FMT has been used since ages and was discovered roughly 1,700 years ago. But the development in utilisation of FMT in neurological disorders and especially in epilepsy has been a very recent discovery. There are just 2 clinical trials till date that have taken place as registered online.

3.1 Case 1 : This was performed by Zhi He et al. [19]

A 17 year old girl with epilepsy and Crohn's disease was given the treatment of FMT.She had her first seizure since the age of 6She used to have around 120 seizures every year and then got diagnosed using EEG.Started taking anti- epileptic drugs and the seizures reduced from 120 per year to 2-3 only if she forgot to take the medicines.But due to these drugs she faced side effects like growth retardation, mild malnutrition, and menarche was at 17 with menstrual cycle disorders. She was given 200mL of fresh faecal microbiota suspension. Simultaneously, she was prescribed 3gm mesalamine per day when the follow- up was done. This patient who initially took the FMT for Crohn's disease, and luckily showed results for epilepsy as well.With a 20 month follow up, she has been seizure free for more than 20 months and till date.

3.2 Case 2 : This was performed by Citraro R et al. [20]

WAG/Rij rats were used, they were developed as animal model of human absence epilepsy. This trial was conducted for absence epilepsy. It was a comparative study on rats; interventional group being the one with disturbed gut microbiota as well as altered intestinal histology given FMT treatment and the control group being non epileptic rats. It was studied at an interval of 1, 4, 8 months. After the completion of FMT, EEG and histopathological examinations were conducted which showed improvement in both intestinal morphology and gut microbial flora which lead to the conclusion that FMT is helpful in seizure management.

3.3

1. Apart from these two studies, some ongoing studies related to FMT use in epilepsy is being conducted by National Institute of Health in China as mentioned in clinical trials site [21], under the NCT ID : **NCT02889627.** It is being conducted and sponsored by The Second Hospital Of Nanjing Medical University. The last time the record of this trial was updated and verified was on 31st of August 2023. This study was initially started in June 2016.
2. This study measures the rates of patients who have equal to or more than 50% less frequency of seizures after the FMT has been given.
3. It has a time frame of 3 months.

A link between the ketogenic diet and neurological disorders have also been studied. Ketogenic diet has a very positive effect on the epileptic patients or in general in the neurological patients, and due to this diet our brain gets dependent on the ketone bodies rather than on the glucose. Some studies showing the effect of KD have been listed below in Table 1.

Study	**Details**	**Intervention**	**Control**	**Primary Outcome**	**Statistical Significance**
Lambrechts 2017[22]	1-18 years, 57 candidates 9 dropped out	KD (N=13)	CAU (N=4)	p=0.024 i. KD: 56% (95% CI 36-76%) ii. CAU: 99% (95% CI 65-133%)	Lower/decreased
Neal 2008[23]	2-16 years, 103 candidates	KD (N=54)	CAU (N=49)	p<0.0001 i. KD 62% (95% CI 42.4-107.4%) ii. CAU 136.9%	Lower/decreased
Freeman 1998[24]	1-16 years, 150 children	KD	None	In 3 months, 34% had >90% decrease in seizure	Lower/decreased

Schoeler 2023[25]	1-24 months	KD (N=61)	ASM (N=47)	IRR 1.3, (95% CI 0.84-2.11%)	Null hypothesis proved Not statistically significant
KD = ketogenic diet; CAU = control as usual ; ASM = anti- seizure medication ; CI = confidence interval ; IRR = incidence rate ratio; Ref. = reference; here primary outcome is decrease mean seizure frequency					
Statistical significance here compares seizure frequency in intervention vs control					

Table 1: Studies comparing ketogenic diet to controls.

3. **Results**:

From the above reviewed data, we obtain the results that FMT is better done with colonoscopy and is much more efficient with fresh faeces. This microbial flora produces metabolites that direct the neural signalling and helps recover the communication between gut and the brain that had been hindered due to gut dysbiosis. Studies mentioned in this review indicate that maximum patients showed at least a 50% reduction in their seizure frequency and a significant increase in the seizure threshold. 3 of 4 studies from Table 1 have rejected the null hypothesis and have shown statistical significance.

4. **Discussion** :

We discussed 2 studies performed by the researchers that proves the Faecal microbiota transplantation experiment does work in epileptic patients[19,20]. In the above text we have discussed some side effects that take place after the transplantation, some explanations for those side effects are :

1) Constipation : Occurs as the patients have been prescribed with anti- diarrheal drugs so that the transplant remains in place[4].
2) Infections : There are some tests conducted to determine if the donor is suitable and healthy for transplant, but if these tests have not been performed accurately then the bacterial or viral species present in the donor's faeces may get into the patient causing infections [4].
3) Pneumonia: One of the procedures to access the GIT for transplantation is a nasogastric tube which may lead to this inflammatory disease [4].

When the urine analysis was performed, Selenium urine levels show a statistical difference in epileptic patients and hence selenium supplementation also contributes to improvement of the disease [26]. Hence performing the urine analysis, is also an impactful method in searching the aetiology and also contributes in determining which supplements would be helpful in curing the diseases.

5. **Conclusion** :

After reviewing the various studies and articles regarding FMT we understand how important gut flora is. The quantity and quality of microbes have so much impact on our body. FMT is going to be a very crucial and useful method for further discoveries of treatments of so many diseases. Ketogenic diet has also shown strong impact on the patients with epilepsy. It has shown better results than the population who were on CAU.

To summarise the process of FMT:
Examine the donor to be a healthy adult ⇒ Then collect the faeces sample ⇒ Turn it into a smoothened/ filtered solution ⇒ Either use it immediately or store it in a frozen state. ⇒ Introduce the sample into the GIT with either one of the following : NG tube, colonoscopy, enema, capsules; keeping in mind the feasibility, viability and the complications ⇒ Prescribe the antidiarrheal drugs ⇒ Put the patient on ketogenic diet ⇒ Decide the follow up time ⇒ Study the results in each ⇒ Continue accordingly.

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