

Fecal Microbiota Transplantation for Fibromyalgia: A Case Report and Review of the Literature

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Abstract

A 58-year-old patient diagnosed with fibromyalgia, irritable bowel syndrome (IBS) and chronic fatigue syndrome (CFS), non-responsive to variety of treatments over the years, suffered from significant social and occupational disabilities. The patient was interested in fecal microbiota transplantation (FMT), but given that FMT is not approved for these indications, he used an online protocol for FMT screening and preparation and self-instilled the filtrate using an enema 6 times. FMT resulted in a gradual improvement of symptoms and 9 months after the last treatment, the patient reported full recovery of symptoms, going back to work at full time employment. Improvement of symptoms was associated with major alterations of the enteric microbiota, according to next generation sequencing analysis performed before the first FMT and after the last FMT. Most prominent alterations at the genus level included a decrease in fecal *Streptococcus* proportion from 26.39% to 0.15% and an increase in *Bifidobacterium* from 0% to 5.23%. This case is added to several additional case reports that demonstrated the effectivity of FMT in these functional disorders that are lacking an otherwise good medical therapeutic intervention. We conclude that randomized controlled trials are required to ground FMT as a possible therapy for these difficult-to-treat conditions.

Keywords

Microbiota, Microbiome, Irritable Bowel Syndrome, Functional Disorders, Dysbiosis, Chronic Fatigue Syndrome

1. Case Presentation

A 58-year-old patient presented to our outpatient clinic complaining of severe diffuse pain, insomnia, diarrhea, abdominal pain, bloating, photophobia, hypersensitivity to odor, noise, light touch, tinnitus and palpitations. He suffered from cognitive impairment: memory loss, concentration deficit and depression with suicidal thoughts.

Most of his symptoms started 18 years earlier at the age of 40. He was diagnosed with fibromyalgia, IBS and CFS. On his physical examination, typical tender points for fibromyalgia were accessed. He underwent lactose, glucose, fructose and sorbitol breath tests, stool cultures, serological testing for inflammatory bowel disease and celiac, fecal calprotectin level test, upper endoscopy and colonoscopy. As all 4 breath tests were positive, the patient was diagnosed with small intestinal bacterial overgrowth (SIBO). ASCA IgA was also mildly positive and he underwent a video capsule endoscopy that was normal.

Throughout the years, the patient was treated with selective serotonin reuptake inhibitors (SSRIs), serotonin antagonist and reuptake inhibitors (SARIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), gamma-aminobutyric acid (GABA), pregabalin, tramadol, Omega 3, Cognitive Behavioral Therapy (CBT), medical cannabis, St. John's wort (*Hypericum perforatum*), acupuncture, medicinal hot springs, hydrotherapy, mild exercise, all without considerable effect.

After a personal tragedy, the disease progressed and the patient became disabled and stopped working. He spent most of his days in bed, unable to perform minimal physical activity; his insomnia has worsened despite treatment with melatonin and sleeping pills. Memory impairment had become severe, with memory loss of close relatives and friends, and marked disorientation. Social security has granted the patient 70% general disability and a complete (100%) occupational disability.

The patient sent his own stool samples for microbial next generation sequencing analysis at a commercial lab. The results demonstrated high levels of *Streptococci* (Table 1). Stool culture, done at the same time, was positive for *Candida*. He was treated with Hydroxychloroquine and Rifampicin, VSL#3 (probiotic), dietary change to low carbohydrates and low sugar diet, reporting mild and short standing improvement.

The patient was interested in FMT as an experimental treatment for his mixed symptoms caused by fibromyalgia, CFS and IBS. Given that this type of treatment is not approved for these indications, he used an online protocol for FMT screening and preparation. His son was screened for HIV, HCV, fecal parasites and bacterial cultures. Stool was homogenized with a food processor and was self-instilled using an enema. Within 24 hours he experienced dramatic improvement of symptoms that lasted for 6 weeks. Four consecutive FMTs resulted with the same transient improvement of symptoms, lasting for approximately 6 weeks each. The improvement from the sixth course lasted for over 9 months and included additional treatment for SIBO with FODMAP and rifaximin.

Table 1. Fecal microbiota analysis performed prior and post fecal microbial transplantation (FMT). A 16S rDNA genome sequencing demonstrating microbial composition alterations at the “Genus level” following FMT.

Phylum	Family	Genus	% of total (Pre FMT)	% of total (Post FMT)	
Firmicutes (gram+)	Lachnospiraceae	Anaerostipes	7.92*	0.09	
		Coprococcus	0.72	1.66	
		Dorea	6.85	0.61	
		Moryella	0	0	
		Roseburia	32.11	3.01	
		Sporobacterium	0	0	
		Syntrophococcus	0	0	
		Ruminococcaceae	Acetanaerobacterium	0	0
			Acetivibrio	1.22*	0
			Ethanoligenens	0	0
	Faecalibacterium		0.08	5.65	
	Papillibacter		0	0	
	Ruminococcus		1.27*	4.51	
	Sporobacterium		0	0	
	Subdoligranulum		0.17	0	
	Clostridiaceae		Butyricoccus	0	0
			Clostridium	0	1.58
		Lactonifactor	0.08*	0	
	Eubacteriaceae	Naaerofustis	0	0	
		Eubacterium	0	4.91*	
	Blautia	Blautia	21.51	10.92	
		Howardella	Howardella	0	0
	Lactobacillaceae	Lactobacillus	0.2	0.25	
	Enterococcaceae	Enterococcus	0	0.03*	
	Streptococcaceae	Lactococcus	0	0	
		Streptococcus	26.39*	0.15	
	Leuconostocaceae	Leuconostoc	0	0.01	
	Erysipelotrichaceae	Catenibacterium	0	0	
		Coprobacillus	0.54	0.5	
		Holdemania	0	0	
Turcibacter		0*	0.04*		
Veillonellaceae	Dialistr	0	0		
	Megamonas	0	0		
	Megasphaera	0	2.26*		
Oscillospiaceae	Oscillibacter	0.29	0		
Staphylococcaceae	Staphylococcus	0	0		
Bacteroidetes (gram-)	Bacteroidaceae	Bacteroides	0.42	21.11*	
	Rikenellaceae	Alistipes	0	0	
	Porphyromonadaceae	Barnesiella	0	0	
		Odoribacter	0	0.04	
		Parabacteroides	0	1.04	

Continued

	Prevotellaceae	Prevotella	0	17.64*
		Xylanibacter	0	0
Actinobacteria (gram+)	Bifidobacteriaceae	Bifidobacterium	0*	5.23
	Actinomycetaceae	Actinomyces	0	0.01
	Micrococcineae	Rothia	0	0
	Coriobacteriaceae	Asaccharobacter	0*	0*
		Collinsella	0	6.73
		Olsenella	0	0
		Slackia	0	1.47*
Proteobacteria (gram-)	Enterobacteriaceae	Escherichia/Shigella	0	0.45
		Klebsiella	0	0
	Sutterellaceae	Cutterella	0	0.31
	Desulfovibrionaceae	Lawsonia	0	0

*Abnormal % of total microbiota as defined by the reference of the commercial lab.

The patient reported marked improvement with total resolution of fatigue and depression, marked improvement of insomnia, oversensitivity to touch, odor and noise. Cognitive impairment has also improved. A physical examination by a rheumatologist (JN A) was normal with no evidence of synovitis or tender fibromyalgia points, concluding that all his symptoms had improved. The patient returned to full employment and is now asymptomatic for over a year.

A second stool microbial analysis demonstrated significant changes compared to the first analysis (Table 1, Table 2). Most marked was a decrease in the proportion of the Firmicutes phylum from 99.35% to 36.17% and an increase in the Bacteroidetes phylum from 0.42% to 39.82% post FMT. At the genus level, fecal *Streptococcus* proportion fell from 26.39% to 0.15% and *Bifidobacterium* increased from 0% to 5.23%. Additional changes included bacterial diversity index that was reduced from 3.21 to 2.55 post FMTs and a negative stool culture for *Candida*.

2. Discussion

Functional disorders, such as fibromyalgia, CFS and IBS, affect many patients and are frequently associated. These disorders clinically differ with an unclear pathogenesis.

Fibromyalgia affects up to 2% of general population [1]. Pain is a predominant symptom of fibromyalgia. However, fatigue, non-refreshed sleep, mood disturbance and cognitive impairment are common, and have an important influence on quality of life [2]. The European league against Rheumatism (EULAR) recommendations, for the management of fibromyalgia were published in 2016: Graduated approach aiming at improving health-related quality of life by non-pharmacological modalities is advised as first line therapy [3].

CFS is diagnosed after at least 6 months of unexplained fatigue [4]. CBT and graded exercise therapy (GET) have shown moderate effectiveness [5].

Table 2. Fecal microbiota analysis performed prior and post fecal microbial transplantation (FMT). A 16S rDNA genome sequencing demonstrating microbial composition alterations at the “Phylum” and “Family” level following FMT.

	% Pre FMT	% Post FMT
Firmicutes	99.35	36.17
<i>Lachnospiraceae</i>	47.6	5.37
<i>Ruminococcaceae</i>	2.74	10.16
<i>Clostridiaceae</i>	0.08	1.58
Bacteroidetes	0.42	39.82
Actinobacteria	0	13.44
Proteobacteria	0	0.76

IBS is a functional disorder characterized by abdominal pain or discomfort associated with defecation or change in bowel habits according the Rome criteria [6]. IBS usually causes long-term symptoms, which may occur in episodes. The symptoms interfere with daily life and social functioning in many patients. The prevalence of IBS in Europe and North America is estimated to be 10% to 15% [7].

There is a marked overlap between these conditions. The prevalent theory suggests that CNS dysfunction of unknown origin causes over responsiveness to sensory perception stimuli that are within the normal range among healthy individuals in patients suffering from fibromyalgia, CFS, IBS and other functional disorders [8]. Investigations using standardized criteria reported 42% - 70% of fibromyalgia patients meeting IBS criteria [9] [10] and one study demonstrated 92% IBS in patients diagnosed with CFS [11]. Many patients report being diagnosed with fibromyalgia and later the diagnosis is converted to CFS and vice versa.

During the last decade, the importance of the enteric microbiome for health and disease conditions has emerged. Changes in the composition of gut microbiota (dysbiosis), have been associated with gastrointestinal, metabolic, autoimmune, allergic and neuropsychiatric disorders [12] and specifically in IBS patients [13] [14], fibromyalgia [14] and in CFS [15]. Moreover, interventions altering the enteric microbiota, such as probiotics therapy [16], and rifaximin [17] have shown efficacy in IBS patients.

FMT, which is the infusion of liquid filtrate feces from a healthy donor, into the gut of an affected recipient, has shown significant benefit for the treatment of *Clostridium difficile* infection (CDI) [18] [19] and is currently the recommended therapy for recurrent CDI [20]. FMT has also shown positive results for the treatment of inflammatory bowel disease [21] in multiple studies and have demonstrated some efficacy in non GI disorders, such as in Parkinson’s disease [22], myoclonus dystonia [23], multiple sclerosis [24], obesity, insulin resistance and metabolic syndrome [25]. In a study of 60 CFS patients treated with FMT, response rate was 70%. Twelve of the patients were contacted after 15 - 20 years, 7 reported full recovery and 5 reported no CFS symptoms for 1.5 and 3 years

following FMT [26].

In IBS patients, few studies, mostly case reports and case series, have demonstrated positive results for FMT [27] and it is currently tested in randomized controlled trials [NIH. clinical trialNCT02328547].

D-lactic acid producing *Enterococcus* and *Streptococcus* species were shown to be over-represented in CFS patients [28]. A recent study comparing microbiota of CFS patient to controls, observed significantly lower levels of *Faecalibacterium* and *Bifidobacterium* in the CFS population compared to healthy controls [15]. *Faecalibacterium* is known to have anti-inflammatory properties [29] and *Bifidobacterium*, commonly used as probiotics [30], was previously reported to reduce CRP levels in a cohort of CFS patients [31]. In addition, a significantly higher load of *Candida albicans* was found in CFS patients when in the acute phase of illness compared with when in remission [32]. Although the clinical significance of these findings is yet to be determined and although the fecal microbial analysis was not performed as a part of a clinical trial, some of the microbial alterations cited above are in line with the microbial alterations observed before and after FMT in our case. Specifically, the decrease of fecal *Streptococcus* and increased *Bifidobacterium* proportions and loss of fecal *Candida*, may support the beneficial properties of FMT.

Nevertheless, our results should be interpreted with caution, given that in addition to self FMTs, the patient underwent multiple additional interventions such as different dietary regimens, therapeutic trials with multiple medications, antibiotics and probiotics. These can also be responsible, at least partially, for the microbial alterations that were found, such as the decreased microbial diversity index that dropped from 3.21 to 2.55 perhaps due to antibiotics treatment.

Moreover, as in any treatment modality implemented for chronic pain, a significant placebo response must also be taken under consideration. However, the clinical improvement was clearly associated with the FMTs treatments.

No RCT's or case series have been published on FMT for fibromyalgia. To our knowledge, this is the first case of self-executed FMT resulting in full recovery of fibromyalgia and CFS. In the absence of satisfactory cognitive or pharmacological treatment for these disorders, few publications reported the experience of FMT for these indications.

Although there are no randomized control trials (RCTs) supporting this treatment, in a few case series on CFS and reports on fibromyalgia, FMT induced long term remission of CFS [26] and could be beneficial for fibromyalgia. This is a low risk procedure with mostly mild and short term complications [33] [34], with possible long term remission that may result in a significant cost effectiveness. A major concern is that the fame of FMT may lead patients to use a "do-it-yourself" approach (as in this case), without medical supervision, with possibly harmful consequences [35] [36]. A case of UC patient who suffered cytomegalovirus infection after performing FMT without donor screening was reported [37] and therefore we do not support performing FMT without appropriate medical care.

3. Conclusions

We have described a case of self-performed FMT, in which FMT was extremely beneficial in a severely ill patient who suffered from a combination of three functional disorders—fibromyalgia, CFS and IBS. The patient had high levels of *Candida* and *Streptococci* that have normalized after the FMT.

We conclude that FMT should be tested as a possible treatment for fibromyalgia and CFS. Controlled data regarding the microbiome characteristics of patients suffering from fibromyalgia should be obtained, and RCTs are required to ground FMT as a possible therapy for these difficult-to-treat conditions, to learn whether this approach is truly beneficial, who is the right target population, who should serve as donors and what is the right protocol of performing FMT for this patient population: number of FMTs, volume and optimal way of administration.

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