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ALS Untangled No. 21: Fecal transplants

The ALSUntangled Group

Fecal microbiota transplantation (FMT) is a technique whereby stool from a healthy donor is delivered into the GI tract of a sick patient. On behalf of PALS who requested it, we herein review the evidence for using FMT to treat ALS.

Rationale

The human intestinal tract contains between 1×10^{13}–1×10^{14} microorganisms, belonging to over 7000 different strains, and containing over 3 million unique genes (1,2). Thus, gut microbes outnumber our own cells by an order of magnitude and could possess 150 times more genes than the entire human genome. Modern sequencing and metagenomic techniques have enabled characterization of the complex human 'fecal microbiome'. Humans can be divided into three distinct 'enterotypes', based on the relative profiles of gut microorganisms. Disruption of the normal microbial homeostasis has been directly implicated in the pathogenesis of ulcerative colitis, Crohn's disease, celiac disease, diabetes, obesity, and certain allergies (reviewed in (2)). Both animal and human studies have also shown that the gut microbiome is altered in obesity, and germ-free mice are resistant to diet induced obesity (3,4). Recognizing the potential importance of this rapidly expanding field, the National Institutes of Health have established the Human Microbiome Project to study the complexity of the gut microflora and its roles in health and disease (http://commonfund.nih.gov/hmp/).

FMT, also called fecal bacteriotherapy, has been reported in dozens of publications, mostly for treating patients with recurrent Clostridium difficile diarrhea, for which it has had unanimously excellent results. FMT was first reported as an effective therapy for pseudomembranous colitis by Eisenman et al. in 1958 (5), although donor stool transplantation as a treatment for diarrhea was documented as far back as 4th century China (reviewed in (6)). A recent randomized clinical trial published in the New England Journal of Medicine used duodenal infusion of donor feces for recurrent C. difficile diarrhea. The study was stopped at interim analysis after only 43 patients had been randomized, because almost all of the patients in the control groups had recurrence, whereas FMT was effective in 81% after a single infusion, and two out of the three other patients after a subsequent infusion (7).

The goal of FMT is restoration of normal healthy gut flora homeostasis. The composition of the gut microbiome is presumably influenced by our environment, thus spouses or other cohabitating family members are preferred as stool donors. The donors are screened for stool and blood-born pathogens, a stool sample is obtained, homogenized in a blender, filtered, re-suspended, then delivered either by nasogastric tube, enema, or colonoscopy into the recipient (8).

Patients with neurodegenerative and neuroimmunologic disorders often suffer from chronic constipation. As the use of FMT to treat recalcitrant constipation has expanded, case reports have accumulated in which patients with neurologic and autoimmune disorders have seen marked improvements in their non-GI symptoms with FMT (6). These have inspired further investigations into the potential role of a 'brain-gut axis' employing bidirectional communication via neuronal, hormonal, immunologic and toxic signaling. Proposed mechanisms include 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 (6,9–11).

FMT is generally considered most effective in treating constipation caused by chronic clostridial infections. Interestingly, several pathogenic clostridial strains are well known to cause neuromuscular disease, such as C. botulinum and C. tetani – which produce neurotoxins that can infect lower motor

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neurons, and in the case of tetanus, utilize retrograde signaling to the CNS. Given the well characterized pathogenicity of these clostridial strains, the frequency of constipation in many chronic neurologic disorders, and published case reports in which FMT and/or antibiotic regimens targeting clostridial infections appeared to serendipitously attenuate neurologic symptoms, some researchers have postulated that neurotoxins produced by related species may be neuro-pathogenic. Longstreth et al. specifically hypothesized that ALS may be caused by an as-yet-unidentified motor neuron toxin produced by a clostridial species in susceptible patients (12). Unlike recurrent C. difficile diarrhea, in which the normal fecal microbiome has been severely altered, it is possible that a pathogenic microbial composition in neurologic diseases such as ALS might be more resilient to change and thus antibiotics/probiotics previously trialed may not be effective (10).

Relevant animal data

There are no published animal data investigating FMT as a treatment for ALS. There are limited animal data on alterations in the gut microbiome in other neurologic disorders. For example, studies with germ-free animals or animals given specific gut infections iatrogenically have implicated the fecal microbiome in certain mood disorders, cognition, and pain syndromes (reviewed in (9)). Experimental autoimmune encephalomyelitis (EAE), an animal model for multiple sclerosis, does not develop in germ-free mice, and subsequent colonization with fecal microbiota causes them to develop demyelination (13,14). The colonic microbiome is also altered in a mouse model of Alzheimer's disease, evaluated by fatty acid methyl ester analysis (15).

There are animal data demonstrating that clostridial toxins, such as tetanus toxin, can be transported to the CNS despite an intact blood-brain barrier and without invoking an immune mechanism. For example, the non-toxic C fragment of tetanus toxin is known to be transported in a retrograde fashion to the CNS, and thus has been studied as a potential vehicle to target therapies for neurodegenerative disorders. In one study, naked DNA encoding the non-toxic C fragment of tetanus toxin was injected intramuscularly into SOD1-G93A mice, and was transported retrograde and trans-synaptically back to the spinal cord (confirmed by Western blot), and surprisingly had therapeutic benefits in the ALS mice (16). The authors hypothesized that the therapeutic benefit may be related to intrinsic neuroprotective properties of this non-toxic fragment, which were also demonstrated in vitro, possibly due to similarities between the tetanus toxin and certain endogenous growth factors that utilize transynaptic transport pathways.

Relevant human data

There are no published clinical trials or even case reports of FMT use in PALS. Only a single PALS has reported trying FMT on PatientsLikeMe, with a one-time dose, 'slight' perceived effectiveness, and no side-effects. An informal poll of ALSUntangled providers and FMT experts resulted in only a single anecdotal report of a patient with ALS who was treated with repeated FMT for chronic constipation and saw his ALS symptoms improve. The patient was a professional athlete and the stool donor a 'fan'. He reportedly "got out of the wheel chair and was said to be able to dance" with his wife, though later declined. No neurologic evaluation, ALSFRS-R, pulmonary spirometry, nor other data are available, and the case has not been published.

Borody et al. in Australia at the Centre for Digestive Diseases (www.cdd.com.au) and Probiotic Therapy Research Centre (www.probiotictherapy.com.au) have used FMT and/or antibiotic regimens designed to treat constipation, ulcerative colitis, and other bowel disorders, and noted serendipitous improvements in several extra-intestinal conditions. These have included case reports and small case series of patients with Parkinson's disease, multiple sclerosis, and myoclonus dystonia (10,17–19). There are also case reports suggesting improvement in chronic fatigue syndrome, Alzheimer's disease, and autism (2,10), and the intestinal microbiota is altered in children with autism compared to healthy controls (20). A patient with both myasthenia gravis and ulcerative colitis (UC) received a proctocolectomy for her UC, after which she experienced complete remission of her myasthenia; at a three-year follow up, she was asymptomatic and had a normal EMG (21).

In ALS, constipation is common and presumed multifactorial – related to dehydration, lack of dietary fiber intake, and decreased physical activity (22). However, a study using radio-opaque markers found that ALS patients have substantially delayed gastric emptying and colonic transit times compared to healthy controls even if they did not complain of GI symptoms; this abnormal colonic motility did not correlate with bulbar involvement or disease duration (23). Recent studies have also suggested a relationship between prediagnostic body fat and ALS risk (24), interesting in the light of recent human and animal data on the role of the fecal microbiome in obesity.

Costs and potential side-effects

Risks appear minimal with FMT if the donor has been properly screened for infectious organisms. Colonoscope insertion has a small risk of perforation. Some patients may develop transient GI complaints or altered bowel habits for several days after FMT (personal communication, Olga Aroniadis,

Montefiore Medical Center). In a 2012 multicenter long-term follow-up study on FMT for recurrent C. difficile, four patients developed an autoimmune disease at some time after FMT, but there was no clear relation to the FMT (25). If carried out by one's self at home, the cost for 10 consecutive treatments with FMT is about $800, which includes laboratory tests to screen the donor, the cost of a blender, a strainer, enema bags/bottles, and miscellaneous items (personal communication, Mark Davis, Director, Bright Medicine Clinic). In the Bright Medicine Clinic, Davis maintains a 'donor bank' and charges ~$4000 for 10 days of treatment.

Conclusions

There is rapidly expanding evidence implicating alterations in the fecal microbiome in wide-ranging human diseases, including potential contributions via a gut-brain signaling axis in neurodegenerative and neuroimmunologic disorders. Proposed mechanisms such as immune modulation and the production of neurotoxins by clostridia or other microbiota could bypass an intact blood-brain barrier. To date, there are no data directly implicating the fecal microbiome in ALS, nor published case reports of FMT being tried in PALS. Data in other neurodegenerative and neuroimmunologic disorders are largely circumstantial, comprising a handful of published case reports. Therefore, ALSUntangled does not recommend FMT as a treatment for ALS at this time. However, it is plausible that the fecal microbiome plays a role in some neurologic disorders, including ALS. Given the lack of effective therapies and the relatively low cost and low risk of FMT – if performed by experienced clinical centers we support further investigations in this developing field. A reasonable next step would be a detailed molecular analysis of gut bacteria in ALS patients; certainly these are the types of studies being advocated by the NIH Human Microbiome Project. If alterations are detected in the gut microbiome of ALS patients, a following step would be properly controlled studies in animal models, such as ALS mice. These studies could employ the same germ-free, and/or probiotic treatment regimens published in mouse models of EAE, Alzheimer's disease, and obesity.

The ALSUntangled Group currently consists of the following members: Lyle Ostrow, Richard Bedlack, Orla Hardiman, Terry Heiman-Patterson, Laurie Gutmann, Mark Bromberg, Gregory Carter, Edor Kabashi, Tulio Bertorini, Tahseen Mozaffar, Peter Andersen, Jeff Dietz, Josep Gamez, Mazen Dimachkie, Yunxia Wang, Paul Wicks, James Heywood, Steven Novella, L.P. Rowland, Erik Pioro, Lisa Kinsley, Kathy Mitchell, Jonathan Glass, Sith Sathornsumetee, Hubert Kwiecinski, Jon Baker, Nazem Atassi, Dallas Forshew, John Ravits, Robin Conwit, Carlayne Jackson, Alex Sherman, Kate Dalton, Katherine Tindall, Ginna Gonzalez, Janice Robertson, Larry Phillips, Michael Benatar, Eric Sorenson, Christen Shoesmith, Steven Nash, Nicholas Maragakis, Dan Moore, James Caress, Kevin Boylan, Carmel Armon, Megan Grosso, Bonnie Gerecke, Jim Wymer, Bjorn Oskarsson, Robert Bowser, Vivian Drory, Jeremy Shefner, Noah Lechtzin, Melanie Leitner, Robert Miller, Hiroshi Mitsumoto, Todd Levine, James Russell, Khema Sharma, David Saperstein, Leo McClusky, Daniel MacGowan, Jonathan Licht, Ashok Verma, Michael Strong, Catherine Lomen-Hoerth, Rup Tandan, Michael Rivner, Steve Kolb, Meraida Polak, Stacy Rudnicki, Pamela Kittrell, Muddasir Quereshi, George Sachs, Gary Pattee, Michael Weiss, John Kissel, Jonathan Goldstein, Jeffrey Rothstein, Dan Pastula, Gleb Levitsky, Mieko Ogino, Jeffrey Rosenfeld, Efrat Carmi, Craig Oster, Christina Fournier, Paul Barkhaus, Eric Valor, Brett Morrison.

Note: this paper represents a consensus of those weighing in. The opinions expressed in this paper are not necessarily shared by every investigator in this group.

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