

# Rapid improvement in Alzheimer's disease symptoms following fecal microbiota transplantation: a case report

Journal of International Medical Research

48(6) 1–6

© The Author(s) 2020

Article reuse guidelines:

[sagepub.com/journals-permissions](http://sagepub.com/journals-permissions)

DOI: 10.1177/0300060520925930

[journals.sagepub.com/home/imr](http://journals.sagepub.com/home/imr)



Sabine Hazan 

## Abstract

Alzheimer's disease (AD), the most common form of dementia, is a leading cause of death and a major cause of morbidity in older people. The disease is characterized by progressive memory loss, cognitive impairment, and the cerebral accumulation of amyloid- $\beta$  peptide. Given the health and economic impacts of AD, treatments that target the underlying etiology of AD or modify the course of the disease are of significant interest. The gut microbiome has been increasingly implicated in the pathogenesis of several neurological diseases, including multiple sclerosis and Parkinson's disease. Furthermore, emerging evidence has demonstrated that there are alterations in gut microbiome composition in patients with AD, suggesting involvement of the microbiome–gut–brain axis. We present symptom improvement in a patient with AD following fecal microbiota transplantation for a *Clostridioides difficile* infection.

## Keywords

Alzheimer's disease, fecal microbiota transplantation, gastrointestinal microbiome, microbiota, neuroinflammation, *Clostridioides difficile*

Date received: 4 December 2019; accepted: 17 April 2020

## Introduction

Alzheimer's disease (AD) is a devastating neurodegenerative disease characterized by a deterioration in memory and other cognitive domains and the cerebral accumulation of amyloid- $\beta$  peptide. Advancing age is the

Ventura Clinical Trials, Malibu, CA, USA

### Corresponding author:

Sabine Hazan, Ventura Clinical Trials, 1835 Knoll Drive, CA 93003, USA.

Email: [sabinehazan@aim.com](mailto:sabinehazan@aim.com)



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

most significant risk factor for the disease, with incidence doubling every 5 years after the age of 65.<sup>1</sup> Approximately 46.8 million people worldwide currently have AD or a related dementia.<sup>2</sup> However, this number is expected to increase exponentially in the coming years, largely as a result of the ageing population.<sup>2</sup> The associated economic burden of AD is substantial; in 2015, the total estimated worldwide cost of dementia was US\$818 billion, which is projected to rise to US\$2.0 trillion by 2030 because of the increased prevalence of AD.<sup>2</sup> However, despite decades of research, the etiology of AD remains unknown and there are currently no preventative or disease-modifying treatments.

A growing body of experimental and clinical data implicates the gut microbiome in the pathogenesis of several neurological conditions, including autism spectrum disorder (ASD),<sup>3</sup> Parkinson's disease (PD),<sup>4</sup> and multiple sclerosis (MS).<sup>5,6</sup> More recently, alterations in gut microbiome composition have been observed in patients with AD,<sup>7</sup> suggesting a potential role for the microbiome in AD pathogenesis. This hypothesis has been supported by animal models;<sup>8,9</sup> for example, germ-free amyloid- $\beta$  precursor protein transgenic mice have markedly less cerebral amyloid- $\beta$  pathology compared with control mice with intestinal bacteria.<sup>8</sup> Certain bacteria within the gut microbiota are also capable of secreting large amounts of amyloids and lipopolysaccharides,<sup>10</sup> a hallmark feature of AD.

Fecal microbiota transplantation (FMT) is the infusion of fecal material from a healthy donor into the gastrointestinal tract of an individual with disease. This procedure represents the most powerful means of modulating the gut microbiome. The therapy has risen to prominence in the last decade following several outbreaks of severe *Clostridioides difficile* infection (CDI) in North America and Europe, which were caused in part by the emergence

of the hypervirulent NAP1/B1/027 strain. In these difficult-to-treat cases as well as in subsequent randomized, controlled trials, FMT has consistently achieved cure rates >90%.<sup>11</sup> Serendipitous improvements following FMT have since been reported in a number of extra-intestinal conditions, including ASD,<sup>3</sup> MS,<sup>12,13</sup> and myoclonus dystonia.<sup>14</sup> To our knowledge, ours is the first report of a patient who experienced rapid improvement in their AD symptoms following FMT for recurrent CDI.

### Case report

An 82-year-old man presented for opinion and management of recurrent CDI following hospitalization for methicillin-resistant *Staphylococcus aureus* pneumonia. The patient had previously failed several courses of antibiotics for CDI, including vancomycin, vancomycin with metronidazole, fidaxomicin, and bezlotoxumab, with relapse confirmed via symptom recurrence and positive stool test.

At the time of presentation, the patient was under the care of his primary care physician and his neurologist for the treatment of AD, following a gradual 5-year decline in memory and cognition. The patient was taking memantine (28 mg once daily) and donepezil (23 mg once daily). The patient's dementia symptoms included confusion, memory loss, depression, and flattened affect. On his most recent Mini-Mental State Examination (MMSE) administered by the neurologist, the patient scored 20, indicating mild cognitive impairment. This result reflected the gastroenterologist's findings and was within the expected range for patients with AD. The patient's wife reported that he no longer appeared to enjoy socializing, and required considerable assistance with basic tasks such as food preparation, bathing, and taking his medication. Neuropsychiatric testing revealed significant impairments in the areas of

memory and semantic language abilities, nonverbal learning, and divided attention and response inhibition. His scores in these areas were within the first through fifth percentiles for function.

Following a detailed discussion regarding the potential risks and benefits associated with the procedure, the patient underwent a single 300 mL FMT infusion (per the Borody method)<sup>15</sup> using stool from the patient's 85-year-old wife as a donor. The patient's wife was intellectually acute, with normal affect and stable mood. Following the procedure, the patient's CDI symptoms resolved, and repeat stool testing 2 months later was negative.

At the follow-up visit 2 months post-FMT, the patient's wife reported improvements in the patient's mental acuity and affect. The MMSE was re-administered by the gastroenterologist (and subsequently by the neurologist) and the patient scored 26, indicating normal cognition. Four months post-FMT, the patient reported continued improvement in memory, with no progression in symptoms. The patient now remembered his daughter's birthday, which he had not been able to recall previously, and was able to correct the physician's recollections of his symptoms. Six months post-FMT, the patient reported a marked improvement in mood, was more interactive, and showed more expressive affect. Readministration of the MMSE revealed that the patient's score had further increased to 29.

Because no study was conducted, no ethics approval or consent was required. Verbal consent was obtained from the patient for the publication of the report; however, this was merely a courtesy because all data have been de-identified.

## Discussion

To our knowledge, this is the first report of a case of rapid reversal of AD symptoms in a patient following FMT for recurrent CDI.

Improvements in AD symptoms occurred as early as 2 months post-FMT and continued to the 6-month follow-up visit (the date of the last follow-up), with no noted reversion of symptoms. The resolution of symptoms occurred in a stepwise manner: first, there was increased mental acuity and improved affect observed at 2 months post-FMT, and this was followed by marked improvements in memory and mood by 4 and 6 months post-FMT, which were accompanied by more expressive affect. These findings paralleled improvements in the patient's MMSE scores, which increased to within the range of normal cognition by 2 months post-FMT. Eradication of CDI was also confirmed at the 2-month follow-up visit, via the resolution of symptoms and a negative stool test.

The central role of the gut microbiome in neurological dysfunction has been increasingly recognized, and alterations in gut microbiome composition have consistently been reported in ASD,<sup>3</sup> PD,<sup>4</sup> and MS.<sup>5,6</sup> Rapid and dramatic improvements have also been observed in several of these conditions following manipulation of the gut microbiome, including with FMT, which further supports a causal association. In an open-label study in 18 children with ASD, 2 weeks of vancomycin treatment followed by daily FMT infusions for 7 to 8 weeks resulted in significant improvements in core ASD symptoms, which persisted at the 2-year follow-up.<sup>3</sup> Furthermore, in a case series of three patients with MS and underlying gastrointestinal symptoms, 5 to 10 days of FMT infusions resulted in a profound reversal of major neurological symptoms, and led to longstanding disease remission.<sup>12</sup> Similarly, a 61-year old female with secondary progressive MS achieved disease stability for over 10 years following FMT for recurrent CDI.<sup>13</sup> In addition, in a patient with myoclonus dystonia, significant

improvement in tremor and functional deficits were reported following the manipulation of gut microbiota with vancomycin, rifaximin, and metronidazole for chronic diarrhoea.<sup>14</sup> In another study, a 71-year old male with longstanding constipation and PD experienced a rapid and dramatic reduction in PD symptoms, including an absence of persistent tremors, glabellar tap reflex, and cogwheel rigidity, when his constipation was treated with vancomycin, metronidazole, and colchicine.<sup>16</sup>

Gut bacteria may contribute to the pathogenesis of AD via a number of mechanisms. Microbe-mediated bidirectional communication pathways exist between the gut and the central nervous system, and many of the neurotransmitters that regulate mood and cognition in the brain, such as gamma-aminobutyric acid (GABA) and dopamine, are also synthesized and catabolized by gut bacteria. GABA dysfunction has been shown to play a role in AD,<sup>17</sup> and abnormally high GABA concentrations have recently been identified in reactive astrocytes of post-mortem AD patients.<sup>18</sup> Molecular mimicry is a well-documented strategy that is commonly employed by pathogens to gain a competitive advantage over their host. It occurs when similarities between microbial proteins and host peptides result in the cross-activation of autoreactive T or B cells and a loss of self-tolerance.<sup>19</sup> Rheumatic fever after *Streptococcus pyogenes* infection is a classic example of this; antigen cross-reactivity between streptococcal M protein and cardiac myosin results in the targeting of myocardial tissue.<sup>19</sup> However, a number of other well-documented molecular mimicry events exist, and a recent database study catalogued 261 validated host-microbial mimicry interactions.<sup>20</sup> Although the focus to date has been on the role of molecular mimicry as a cause of autoimmune diseases, this mechanism may also be exploited in the development of AD. The progressive

accumulation of  $\beta$ -amyloid protein plaques between neurons represents a hallmark of AD. However, the initiating factor responsible for the development and propagation of these prion-like proteins is unknown. Amyloids are secreted by a wide range of pathogenic and non-pathogenic bacteria, and play an important role in cell adhesion and biofilm formation.<sup>10</sup> Similarities between the tertiary structure of microbe-derived amyloids and  $\beta$ -amyloid in AD may trigger antigen cross-reactivity, thus potentially initiating the formation of AD. Interestingly, both microbe-derived amyloids (such as curli) and AD-related  $\beta$ -amyloid are recognized by the same Toll-like receptor (TLR)2/TLR1 complex.<sup>21</sup> Finally, dysbiosis itself may contribute to the development of AD. A dysbiosis-induced increase in gut permeability may potentially lead to persistent systemic inflammation, disruption of the blood-brain barrier, and ultimately neurodegeneration.

Neuroinflammation plays a central role in the pathogenesis of AD,<sup>22,23</sup> and is characterized by elevated levels of pro-inflammatory cytokines,<sup>23</sup> nuclear factor  $\kappa\beta$  signalling,<sup>24</sup> and aggregation of activated microglia in damaged areas.<sup>25</sup> The influence of the gut microbiome on neuroinflammation in AD remains poorly understood, as do the exact mechanisms of action of FMT in this disease. However, the potent immunomodulatory effects of FMT are well recognized. FMT has been demonstrated to ameliorate chronic intestinal colitis in both humans and animal models via the downregulation of pro-inflammatory cytokines, promotion of anti-inflammatory responses, and inhibition of nuclear factor  $\kappa\beta$  activity.<sup>26-28</sup> In addition, similarly beneficial effects have since been observed in several other conditions with an inflammatory component.<sup>13,29,30</sup> Thus, FMT may have a positive effect on cognitive function in AD via alterations in the levels of circulating cytokines.

Alternatively, by restoring the previously impaired intestinal barrier function, FMT may prevent the translocation of neuroactive compounds and metabolites within the central nervous system that regulate mood and cognition and contribute to inflammation. However, further studies are urgently required to elucidate the exact mechanisms by which FMT may ameliorate symptoms in AD.

To our knowledge, this is the first documented case of a rapid reversal of AD symptoms in a patient following FMT for recurrent CDI. Although this is only a preliminary report, the remarkable resolution of AD symptoms following FMT for CDI is instructive and adds to the evidence that suggests a causal association between the gut microbiome and neurological dysfunction. Given the probable role of the gut microbiome in the pathogenesis of AD, modulation of the microbiome represents a promising avenue of treatment. A randomized, double-blind, placebo-controlled trial is currently underway to evaluate the efficacy of oral FMT in AD, the results of which are eagerly anticipated.

### Acknowledgements

Third-party writing assistance was provided by Jordana Campbell, BSc, of Biocite Medical Writing Services.

### Declaration of conflicting interest

Sabine Hazan has a pecuniary interest in Ventura Clinical Trials and ProgenaBiome.

### Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

### ORCID iD

Sabine Hazan  <https://orcid.org/0000-0002-2870-2106>

### References

1. Hirtz D, Thurman DJ, Gwinn-Hardy K, et al. How common are the “common” neurologic disorders? *Neurology* 2007; 68: 326–337. DOI: 10.1212/01.wnl.0000252807.38124.a3.
2. Alzheimer’s Disease International. World Alzheimer report 2015: the global impact of dementia, <https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf> (2015).
3. Kang DW, Adams JB, Coleman DM, et al. Long-term benefit of microbiota transfer therapy on autism symptoms and gut microbiota. *Sci Rep* 2019; 9: 5821. DOI: 10.1038/s41598-019-42183-0.
4. Minato T, Maeda T, Fujisawa Y, et al. Progression of Parkinson’s disease is associated with gut dysbiosis: two-year follow-up study. *PLoS One* 2017; 12: e0187307. DOI: 10.1371/journal.pone.0187307.
5. Umeton R, Eleftheriou E, Nedelcu S, et al. The gut microbiome in relapsing multiple sclerosis patients compared to controls. (P2.355). *Neurology* 2018; 90: P2.355.
6. Miyake S, Kim S, Suda W, et al. Dysbiosis in the gut microbiota of patients with multiple sclerosis, with a striking depletion of species belonging to clostridia XIVa and IV clusters. *PLoS One* 2015; 10: e0137429. DOI: 10.1371/journal.pone.0137429.
7. Vogt NM, Kerby RL, Dill-McFarland KA, et al. Gut microbiome alterations in Alzheimer’s disease. *Sci Rep* 2017; 7: 13537. DOI: 10.1038/s41598-017-13601-y.
8. Harach T, Marungruang N, Duthilleul N, et al. Reduction of Abeta amyloid pathology in APPPS1 transgenic mice in the absence of gut microbiota. *Sci Rep* 2017; 7: 41802. DOI: 10.1038/srep41802.
9. Minter MR, Zhang C, Leone V, et al. Antibiotic-induced perturbations in gut microbial diversity influences neuroinflammation and amyloidosis in a murine model of Alzheimer’s disease. *Sci Rep* 2016; 6: 30028–30028. DOI: 10.1038/srep30028.
10. Zhou Y, Blanco LP, Smith DR, et al. Bacterial amyloids. *Methods Mol Biol* 2012; 849: 303–320. DOI: 10.1007/978-1-61779-551-0\_21.

11. Van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent clostridium difficile. *N Engl J Med* 2013; 368: 407–415. DOI: 10.1056/NEJMoa1205037.
12. Borody T, Leis S, Campbell J, et al. Fecal microbiota transplantation (FMT) in multiple sclerosis (MS): 942. *Am J Gastroenterol* 2011; 106: pS352.
13. Makkawi S, Camara-Lemarroy C and Metz L. Fecal microbiota transplantation associated with 10 years of stability in a patient with SPMS. *Neurol Neuroimmunol Neuroinflamm* 2018; 5: e459. DOI: 10.1212/NXI.0000000000000459.
14. Borody T, Rosen D, Torres M, et al. Myoclonus-dystonia affected by GI microbiota? *Am J Gastroenterol* 2011; 106: S352.
15. Leis S, Borody TJ, Jiang C, et al. Fecal microbiota transplantation: a 'How-To' guide for nurses. *Collegian* 2015; 22: 445–451. DOI: 10.1016/j.colegn.2014.08.002.
16. Borody T, Torres M, Campbell J, et al. Treatment of severe constipation improves Parkinson's disease (PD) symptoms. *Am J Gastroenterol* 2009; 104: S999.
17. Assefa BT, Gebre AK and Altaye BM. Reactive astrocytes as drug target in Alzheimer's disease. *Biomed Res Int* 2018; 2018: 4160247–4160247. DOI: 10.1155/2018/4160247.
18. Wu Z, Guo Z, Gearing M, et al. Tonic inhibition in dentate gyrus impairs long-term potentiation and memory in an Alzheimer's disease model. *Nat Commun* 2014; 5: 4159. DOI: 10.1038/ncomms5159 <https://www.nature.com/articles/ncomms5159#supplementary-information>.
19. Cunningham MW. Rheumatic fever, autoimmunity, and molecular mimicry: the streptococcal connection. *Int Rev Immunol* 2014; 33: 314–329. DOI: 10.3109/08830185.2014.917411.
20. Garg A, Kumari B, Kumar R, et al. miPepBase: a database of experimentally verified peptides involved in molecular mimicry. *Front Microbiol* 2017; 8: 2053. DOI: 10.3389/fmicb.2017.02053.
21. Rapsinski GJ, Newman TN, Oppong GO, et al. CD14 protein acts as an adaptor molecule for the immune recognition of Salmonella curli fibers. *J Biol Chem* 2013; 288: 14178–14188. DOI: 10.1074/jbc.M112.447060.
22. Azizi G and Mirshafiey A. The potential role of proinflammatory and antiinflammatory cytokines in Alzheimer disease pathogenesis. *Immunopharmacol Immunotoxicol* 2012; 34: 881–895. DOI: 10.3109/08923973.2012.705292.
23. Su F, Bai F and Zhang Z. Inflammatory cytokines and Alzheimer's disease: a review from the perspective of genetic polymorphisms. *Neurosci Bull* 2016; 32: 469–480. DOI: 10.1007/s12264-016-0055-4.
24. Chen CH, Zhou W, Liu S, et al. Increased NF- $\kappa$ B signalling up-regulates BACE1 expression and its therapeutic potential in Alzheimer's disease. *Int J Neuropsychopharmacol* 2012; 15: 77–90. DOI: 10.1017/S1461145711000149.
25. Sarlus H and Heneka MT. Microglia in Alzheimer's disease. *J Clin Invest* 2017; 127: 3240–3249. DOI: 10.1172/JCI90606.
26. Wang Z, Hua W, Li C, et al. Protective role of fecal microbiota transplantation on colitis and colitis-associated colon cancer in mice is associated with Treg cells. *Front Microbiol* 2019; 10: 2498–2498. DOI: 10.3389/fmicb.2019.02498.
27. Burrello C, Garavaglia F, Cribiù FM, et al. Therapeutic faecal microbiota transplantation controls intestinal inflammation through IL10 secretion by immune cells. *Nat Commun* 2018; 9: 5184. DOI: 10.1038/s41467-018-07359-8.
28. Khoruts A and Sadowsky MJ. Understanding the mechanisms of faecal microbiota transplantation. *Nat Rev Gastroenterol Hepatol* 2016; 13: 508–516. DOI: 10.1038/nrgastro.2016.98.
29. Chen D, Wu J, Jin D, et al. Fecal microbiota transplantation in cancer management: current status and perspectives. *Int J Cancer* 2019; 145: 2021–2031. DOI: 10.1002/ijc.32003.
30. Wang WW, Zhang Y, Huang XB, et al. Fecal microbiota transplantation prevents hepatic encephalopathy in rats with carbon tetrachloride-induced acute hepatic dysfunction. *World J Gastroenterol* 2017; 23: 6983–6994. DOI: 10.3748/wjg.v23.i38.6983.