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BRIEF REPORT

Effects of Galactooligosaccharides on the Gut Microbiome in Patients with Alzheimer's Dementia

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Abstract

Background: Alterations of the gut microbiome may accelerate the course of Alzheimer's dementia through the enhancement of inflammatory and neurodegenerative processes. Prebiotic galactooligosaccharides increase the abundance of *Bifidobacterium* species and may have beneficial effects on disease progression.

Methods: In a group of Alzheimer patients taking a galactooligosaccharide preparation for 12 weeks, the effects on bacterial abundances and Shannon index of the gut microbiome as well as neurofilament light-chain serum concentration were assessed.

Results: There was an increase of the abundance of the genus *Bifidobacterium* and an increase of the Shannon index when taking galactooligosaccharides. The increase of the Shannon index was correlated with a decrease of the neurofilament light-chain serum concentration.

Discussion: These findings suggest a beneficial effect of galactooligosaccharides on the gut microbiome and an inhibition of neurodegeneration in patients with Alzheimer's dementia. Further clinical studies may be warranted.

Introduction

Alterations of the gut microbiome in Alzheimer patients have been observed by different researchers [1-3]. Reproducible alterations identified so far are a decrease in microbial diversity and changes in abundance of the genera *Bifidobacterium* and *Escherichia* [4]. Various mechanisms have been suggested by which gut microbiota may influence the course of Alzheimer's dementia. There may be anti-inflammatory effects of butyrate-producing species mitigating the course of the disease [5]. Other bacteria or bacterial components may lead to inflammation and increased permeability of the colon epithelium. They may consequently promote the transgression of bacteria or bacterial components into the systemic circulation and enhance inflammatory and neurodegenerative processes [6] as well as amyloid-β pathology [7].

Neurofilament light-chain (Nfl) is a part of the neuronal cytoskeleton and is released in the case of axonal damage [8,9]. CSF and serum levels of Nfl are highly correlated [8]. Nfl is increased in Alzheimer's dementia and mild cognitive impairment [10]. In patients with Alzheimer's disease, the level of Nfl is correlated with the extent and the further progression of cognitive impairment [11,12]. Therefore it may be used as a marker of neuronal destruction quantitatively reflecting neurodegeneration in Alzheimer's disease.

Prebiotics are substrates selectively utilized by host microorganisms conferring a health benefit [13]. Galactooligosaccharides (GOS), a component of human mother's milk, are complex carbohydrates and act as physiological prebiotics [14]. They are resistant to digestion in the upper gastrointestinal tract and reach the colon intactly. There they have a bifidogenic effect [15,16] and may mitigate the symptoms in inflammatory diseases of the colon [17] as well as of other organ systems [18]. They act as soluble decoy receptors, thus preventing the adhesion of pathogens to epithelial cells and they stimulate tight junctions. Thus, GOS may also help to mitigate inflammation und slow down neurodegeneration in Alzheimer's disease. Against this background, we conducted a pilot study on the effects of a GOS preparation (Dynabion®) in Alzheimer patients.

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Methods

The assessments were carried out in a group of out-patients with probable mild Alzheimer's dementia according to the NINCDS-ADRDA criteria [19]. None of them was suffering from inflammatory bowel disease or diabetes mellitus, had had an infectious disease during the last three months or had been under antibiotic treatment during the last six months.

The patients took app. 5 grams of a galacto-oligosaccharides powder daily with added small amounts of curcumin and berberine (Dynabion®) for 12 weeks. The powder was dissolved in a glass of water and taken before breakfast.

Stool samples were obtained before and at the end of the GOS intake, immediately frozen at -20 °C and later processed by means of PCR amplification and subsequent 16S-rRNA sequencing using the commercially available MiSeq® system (Illumina Inc.). Bacterial diversity was measured by means of the widely used Shannon index, which quantifies entropy and increases with the number of detected species and the evenness of their abundances [20]. Further we assessed the abundances of the genera *Bifidobacterium* and *Escherichia*, which have been reported to be significantly altered in Alzheimer's dementia [4]. At both time points, serum samples were obtained by peripheral venipuncture. Nfl was quantified by an ultrasensitive single molecule array (Simoa) on a Quanterix SR-X Analyzer using the NF-light® assay.

Differences of Shannon index, bacterial abundances and Nfl serum concentrations before and during GOS

Figure 1: Effects of galactooligosaccharides on the gut microbiome. (A) Effect of galactooligosaccharides on the abundance of *Bifidobacterium*. The abundance of the genus *Bifidobacterium* (in%, logarithmic axis division) is shown for each individual patient before and after taking galactooligosaccharides for 12 weeks; (B) Effect of galactooligosaccharides on the Shannon index. The Shannon index is shown for each individual patient before and after taking galactooligosaccharides for 12 weeks.

intake were assessed by paired Student's t-tests. Bacterial abundance values had been ln-transformed in order to normalize distributions. The relationships between gut microbiota and serum concentration of Nfl were analyzed by means of Spearman rank-correlation coefficients. Given the exploratory nature of this study, no adjustment for multiple testing was performed.

Results

The assessments were carried out in 10 Alzheimer patients, 5 women and 5 men at ages between 71 and 85 years (mean: 78 years) with a body mass index (BMI) between 19.7 and 29.3 (mean: 25.2). Their MMSE scores were between 18 and 26 (mean: 21.2). The duration of dementia ranged between 15 and 36 months (mean: 24.4 months).

After GOS intake, the abundance of the genus Bifidobacterium increased from 1.33% (mean; range: 0.004-8%) to 1.70% (mean; range: 0.001 to 5%) ($p = 0.042$), mainly in the patients with initially low abundances (Figure 1a). There was also an increase of the Shannon index from 2.64 ± 0.69 (mean ± SD) to 2.98 ± 0.47 ($P = 0.047$). The increase was found particularly in the patients with initially low Shannon indices (Figure 1b). The abundance of the genus Escherichia and the serum concentration of Nfl were not significantly altered.

After taking GOS, there was a significant negative correlation between the changes of the Shannon Index and those of the Nfl serum concentration ($r = 0.750$; $p = 0.021$) (Figure 2). No significant correlations between the abundances of Bifidobacterium or Escherichia and the Nfl serum concentration could be ascertained.

Discussion

A bifidogenic effect of GOS has been reported in healthy elderly subjects [15,21] and in patients with ulcerative colitis [17]. We could confirm this finding in patients with Alzheimer's disease. *Bifidobacterium*, which is reduced in the gut microbiome of elderly subjects [22,23], protects the colonic mucus layer enhancing mucus production [24] through the modulation of goblet cells [25].

The increase of *Bifidobacterium* when taking GOS has health promoting effects. The production of the pro-inflammatory cytokines IL-6, IL-1β, and TNF-alpha is reduced [21]. We also observed an increase of microbial diversity reflected by an increase of the Shannon index. The increase of the Shannon index was correlated with a decrease of the neuronal destruction marker Nfl. Thus, taking GOS may inhibit neurodegeneration in patients with Alzheimer's disease. In particular, patients with a

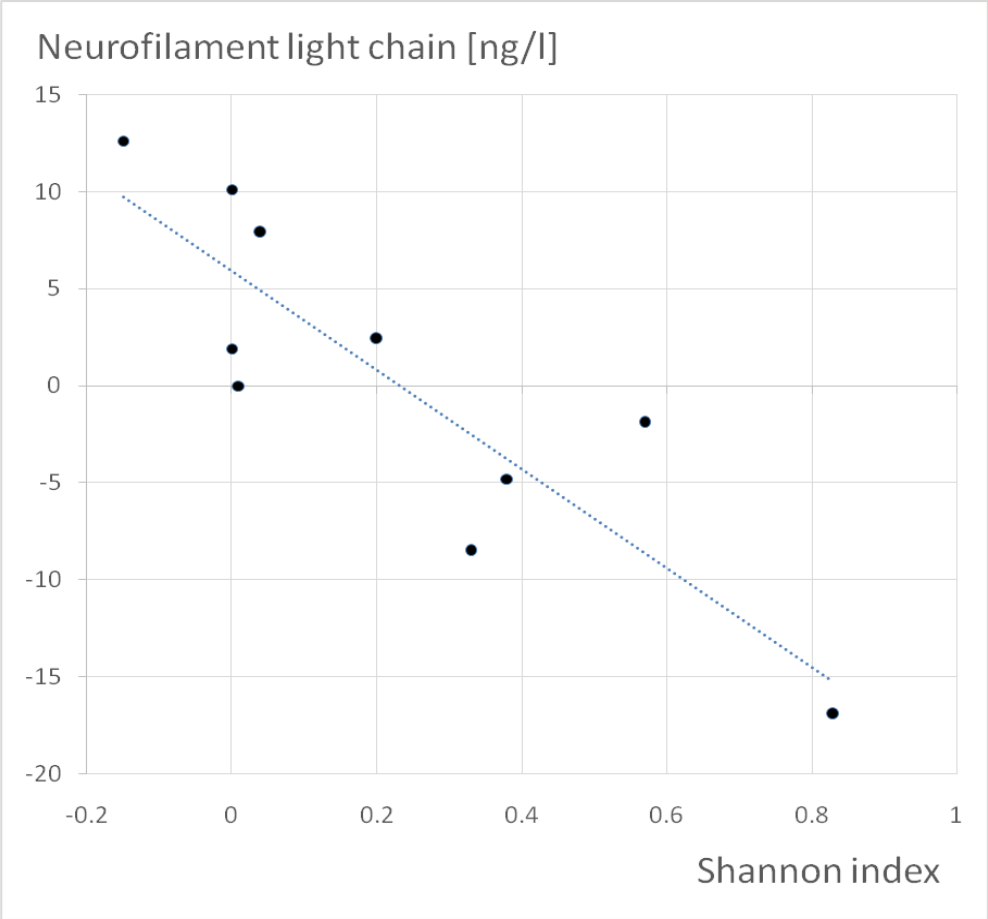

Figure 2: Correlation between the changes of Shannon index and Neurofilament light-chain when taking galactooligosaccharides. The changes of the serum concentration of neurofilament light-chain (in ng/l) are plotted over the changes of the Shannon index for each individual patient. The regression line is given.

dysbiosis of the gut microbiome, which is manifested by a low microbial diversity, may benefit from this treatment.

This assumption is supported by some clinical findings. Oligomannate, another prebiotic, has been extensively studied in Chinese Alzheimer patients [26] and has shown disease-modifying effects in this patient group [27]. A disease-modifying effect of *Bifidobacterium* has also been found in a double-blind controlled Japanese trial [28]. Adults with MCI at ages between 50 and 79 years, who were treated with a *Bifidobacterium* strain for 16 weeks, showed significant improvements in cognitive performance as reflected by the RBANS. Thus, controlled studies with GOS in patients with Alzheimer's disease may be warranted.

Author Contribution

Both authors have contributed to this study, accepted responsibility for the entire content of this manuscript and consented to its submission to the journal, reviewed all the results and approved the final version of the manuscript.

References

1. Cattaneo A, Cattane N, Galluzzi S, Provasi S, Lopizzo N, et al. (2017) Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. Neurobiol Aging 49: 60-68.
2. Vogt NM, Kerby RL, Dill McFarland KA, Harding SJ, Merluzzi AP, et al. (2017) Gut microbiome alterations in Alzheimer's disease. Sci Rep 7: 13537.
3. Ling Z, Zhu M, Yan X, Cheng Y, Shao L, et al. (2020) Structural and functional dysbiosis of fecal microbiota in Chinese patients with Alzheimer's disease. Front Cell Dev Biol 8: 634069.
4. Hung CC, Chang CC, Huang CW, Nouchi R, Cheng CH (2022) Gut microbiota in patients with Alzheimer's disease spectrum: A systematic review and meta-analysis. Aging (Albany NY) 14: 477-496.
5. Ho L, Ono K, Tsuji M, Mazzola P, Singh R, et al. (2018) Protective roles of intestinal microbiota derived short chain fatty acids in Alzheimer's disease-type beta-amyloid neuropathological mechanisms. Expert Rev Neurother 18: 83-90.
6. Ghosh SS, Wang J, Yannie PJ, Ghosh S (2020) Intestinal barrier dysfunction, LPS translocation, and disease development. J Endocr Soc 4: bvz039.
7. Zhao Y, Dua P, Lukiw WJ (2015) Microbial sources of amyloid and relevance to amyloidogenesis and alzheimer's disease (AD). J Alzheimers Dis Parkinsonism 5: 177.
8. Bacioglu M, Maia LF, Preische O, Schelle J, Apel A, et al. (2016) Neurofilament light chain in blood and CSF as marker of disease progression in mouse models and in neurodegenerative diseases. Neuron 91: 56-66.
9. Khalil M, Teunissen CE, Otto M, Piehl F, Sormani MP, et al. (2018) Neurofilaments as biomarkers in neurological disorders. Nat Rev Neurol 14: 577-589.
10. Giacomucci G, Mazzeo S, Bagnoli S, Ingannato A, Leccese D, et al. (2022) Plasma neurofilament light chain as a biomarker of Alzheimer's disease in subjective cognitive decline and mild cognitive impairment. J Neurol 269: 4270-4280.
11. Zetterberg H, Skillbäck T, Mattsson N, Trojanowski JQ, Portelius E, et al. (2016) Association of cerebrospinal fluid neurofilament light concentration with alzheimer disease progression. JAMA Neurol 73: 60-67.
12. Olsson B, Portelius E, Cullen NC, Sandelius Å, Zetterberg H, et al. (2019) Association of cerebrospinal fluid neurofilament light protein levels with cognition in patients with dementia, motor neuron disease, and movement disorders. JAMA Neurol 76: 318-325.
13. Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, et al. (2017) Expert consensus document: The International scientific association for probiotics and prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol 14: 491-502.
14. Torres DPM, Gonçalves MdPF, Teixeira JA, Rodrigues LR (2010) Galacto-oligosaccharides: Production, properties, applications, and significance as prebiotics. Compr Rev Food Sci Food Saf 9: 438-454.
15. Ito M, Deguchi Y, Matsumoto K, Kimura M, Onodera N, et al. (1993) Influence of galactooligosaccharides on the human fecal microflora. J Nutr Sci Vitaminol (Tokyo) 39: 635-640.
16. Davis LMG, Martínez I, Walter J, Goin C, Hutkins RW (2011) Barcoded pyrosequencing reveals that consumption of galactooligosaccharides results in a highly specific bifidogenic response in humans. PLoS One 6: e25200.
17. Wilson B, Eyice Ö, Koumoutsos I, Lomer MC, Irving PM, et al. (2021) Prebiotic galactooligosaccharide supplementation in adults with ulcerative colitis: exploring the impact on peripheral blood gene expression, gut microbiota, and clinical symptoms. Nutrients 13: 3598.
18. Williams NC, Johnson MA, Shaw DE, Spendlove I, Vulevic J, et al. (2016) A prebiotic galactooligosaccharide mixture reduces severity of hyperpnoea-induced bronchoconstriction and markers of airway inflammation. Br J Nutr 116: 798-804.
19. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, et al. (2011) The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7: 263-269.
20. DeJong TM (1975) A comparison of three diversity indices based on their components of richness and evenness. Oikos 26: 222-227.
21. Vulevic J, Drakoularakou A, Yaqoob P, Tzortzis G, Gibson GR (2008) Modulation of the fecal microflora profile and immune function by a novel trans-galactooligosaccharide mixture (B-GOS) in healthy elderly volunteers. Am J Clin Nutr 88: 1438-1446.
22. Mueller S, Saunier K, Hanisch C, Norin E, Alm L, et al. (2006) Differences in fecal microbiota in different European study populations in relation to age, gender, and country: A cross-sectional study. Appl Environ Microbiol 72: 1027-1033.
23. Biagi E, Nylund L, Candela M, Ostan R, Bucci L, et al. (2010) Through ageing, and beyond: Gut microbiota and inflammatory status in seniors and centenarians. PLoS One 5: e10667.

24. Schroeder BO, Birchenough GMH, Ståhlman M, Arike L, Johansson MEV, et al. (2018) Bifidobacteria or Fiber Protects against diet-induced microbiota-mediated colonic mucus deterioration. Cell Host Microbe 23: 27-40.e7.

25. Bhatia S, Prabhu PN, Benefiel AC, Miller MJ, Chow J, et al. (2015) Galacto-oligosaccharides may directly enhance intestinal barrier function through the modulation of goblet cells. Mol Nutr Food Res 59: 566-573.

26. Wang X, Sun G, Feng T, Zhang J, Huang X, et al. (2019) Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression. Cell Res 29: 787-803.

27. Wang T, Kuang W, Chen W, Xu W, Zhang L, et al. (2020) A phase II randomized trial of sodium oligomannate in Alzheimer's dementia. Alzheimers Res Ther 12: 110.

28. Xiao J, Katsumata N, Bernier F, Ohno K, Yamauchi Y, et al. (2020) Probiotic Bifidobacterium breve in Improving cognitive functions of older adults with suspected mild cognitive impairment: A randomized, double-blind, placebo-controlled trial. J Alzheimers Dis 77: 139-147.