Assessment of small intestinal bacterial overgrowth in Alzheimer's disease

Jingwei Sim[a]; Yu Tien Wang[b,c]; Kaysar Mamun[d,e]; Sze Yan Tay[f]; Kinjal Doshi[f], Shahul Hameed[a,e,f]; Simon Kang-Seng Ting[a,e,f*]

Abstract

There is great interest in crosstalk between the gastrointestinal and immune systems. Small intestinal bacterial overgrowth (SIBO) is a bowel disorder prevalent among patients with Parkinson's disease; SIBO treatment has been shown to modulate neurological inflammation, motor and cognitive outcomes there. However, to date, no link between Alzheimer's dementia and SIBO has been established. This pilot study sought to estimate the prevalence of SIBO in Alzheimer's dementia in the outpatient setting in Singapore General Hospital. It entailed performing a hydrogen breath test and objectively scoring gastrointestinal symptoms and their severity in 48 patients, comparing symptom scores and mean breath test values in those with mild to moderate Alzheimer's against age- and sex-matched controls that did not fulfill DSM-V criteria for probable Alzheimer's. Here, the prevalence of positive breath tests and symptoms of SIBO were no greater among Alzheimer's patients than in controls. This suggests that the gut microbiome changes and increased bowel inflammation seen in previous studies on Alzheimer's patients are likely effected through pathways other than SIBO, and are likely more complex than a mere increase in small bowel bacterial volume. Rather, future research could be directed along the lines of qualitative changes in small bowel microbiota, or pathologies in other parts of the gastrointestinal tract such as the colon or stomach, aspects which are not adequately captured by the hydrogen breath test.

Keywords: Alzheimer's disease; dementia; gut-brain axis; small intestinal bacterial overgrowth; microbiome.

Acta Neurol Taiwan 2021;30:102-107

INTRODUCTION

Research has proposed that crosstalk between the gastrointestinal and immune systems drives neurodegeneration. Metabolites and neuromodulators released from immune cells and microbiota can alter

From the [a]National Neuroscience Institute, Singapore; [b]Department of Gastroenterology & Hepatology, Singapore General Hospital; [c]Singapore and Nobel Gastroenterology Centre, Gleneagles Hospital, Singapore; [d]Department of Geriatric Medicine, Singapore General Hospital, Singapore; [e]Duke-NUS Graduate Medical School Singapore, Singapore; [f]Department of Neurology, Singapore General Hospital, Singapore

Received August 26, 2020. Revised August 30, 2020.
Accepted May 20, 2021.

Correspondence to: National Neuroscience Institute@SGH, Neuroscience Clinic, Block 3, Singapore General Hospital, Outram Road, Singapore 169608, simon.ting.k.s@singhealth.com.sg

gut permeability, gut peptide and bile acid signaling, which have been found to affect microglia maturation, astrocyte activity and blood-brain barrier permeability[1–3]. Evidence supports a role for the 'brain-gut-microbiota' axis in the neuroinflammation seen in Alzheimer's disease. For instance, lipopolysaccharide and Escherichia coli fragments co-aggregate with brain plaques[4], where amyloid accumulation may in fact act as a buffer against neuroinflammation. Stool samples from Alzheimer's patients show a less diverse microbiome[5] and raised calprotectin levels[6]. There is anecdotal evidence that some gut-brain associations have therapeutic value – for one, Helicobacter pylori eradication improves cognition in Alzheimer's patients[7].

Small bowel intestinal overgrowth (SIBO) is a gastrointestinal disorder common in patients with Parkinson's disease[8]. There are multiple mechanisms by which SIBO could affect neuroendocrine pathways and cause neural inflammation – for instance, by altering gut permeability, distension and nutrient metabolite release[9,10]. It has showed promise as a therapeutic target in Parkinson's disease – where SIBO predicts worse motor fluctuations rescuable by rifaximin[10]. This led some to wonder if SIBO might also be a promising therapeutic target in Alzheimer's dementia. No study thus far has associated SIBO with Alzheimer's, although a link could potentially account for the cognitive improvements seen after rifampin treatment[11]. Here, we describe an observational study to estimate SIBO prevalence in Alzheimer's.

METHODS

Here, an observational study was conducted to estimate SIBO prevalence in Alzheimer's. 48 participants aged 65-85 years were recruited from both neurological and geriatric outpatient clinics in Singapore General Hospital from 2016 to 2018.

Inclusion criteria for Alzheimer's disease patients included (1) fulfilling Diagnostic and Statistical Manual of Mental Disorders version five (DSM-V) diagnostic criteria for 'probable Alzheimer's disease', (2) age 60-85, (3) Mini mental state examinations (MMSE) score 13-23 (mild to moderate stage), and (4) having a reliable caregiver who can provide collaborative history. Exclusion criteria were (1) presence of major psychiatric conditions such as major depression or schizophrenia, (2) BMI >35, (3) presence of malignancy, ischaemic heart disease, diabetes mellitus, thyroid dysfunction or renal impairment (as determined by study investigators), (4) previous surgery or anatomical anomalies which may alter GI motility (as assessed by investigators), and (5) unable to give or no consent available. All Alzheimer's patients fulfilling inclusion criteria had been diagnosed by specialists from neurology or geriatric departments specializing in dementia. They had also received neuroimaging in the form of either computed tomography or magnetic resonance imaging that excluded other structural lesions of the brain. 21 participants met criteria for Alzheimer's disease. 27 others did so for the control group. All participants had caregivers that could provide a corroborative history. None had been diagnosed previously with intestinal disorders.

A Gastrointestinal Symptom Rating Scale was administered using a fifteen-item questionnaire[12] modified recently for use in a Japanese study on Parkinson's patients[13]. Each category of symptoms is scored 0-6 with a higher score representing a greater subjective impact on the respondent, scores were then summed in five domains of symptoms (abdominal pain, indigestion, reflux, diarrhea, constipation).

The patients were advised to avoid foods with complex carbohydrates one day before the test as per guideline recommendations[14], which would otherwise confound hydrogen measurements. They then fasted for twelve hours, and were instructed to avoid physical exertion two hours prior. A glucose hydrogen breath test was then performed, whereby participants were given an oral glucose load of 1g/kg, expired hydrogen/methane levels measured with gas chromatography (BreathTracker SC Quintron) every twenty minutes for a three-hour time period. The examination was performed by technicians but interpreted and reported by gastroenterologists, and performed within three months of recruitment. A positive breath test was defined as an increase of hydrogen and/or methane >12ppm above baseline. A week before the test, medications that could affect gut pH or motility, including laxatives, suppositories, prokinetics, opiates, anticholinergics, antibiotics and non-steroidal anti-inflammatories were omitted as recommended by the assay manufacturer. Subjects on stable doses (exceeding

six months) of antidepressants, oral contraceptives and anti-lipid medications were allowed to continue on these. A Wilcoxon rank sum test with continuity correction for continuous variables and chi-square test for categorical variables was applied. Data analysis was performed in Stata V13.1 (College Station, TX, USA) with level of significance set at 0.05.

Written consent was obtained from all participants and the study was approved by the Singhealth Centralised Institutional Review Board.

RESULTS

The demographics of study participants with Alzheimer's disease (n=21) and controls (n=27) are reflected in Table 1. These two groups differed significantly only in MMSE scores and years of education. 2 of 21 Alzheimer's cases (9.5%) and 5 of 27 controls (18.5%) had positive hydrogen breath tests (Table 1), as defined by an increase of hydrogen and/or methane >12ppm above baseline. The rate of positive breath tests did not differ significantly between both groups, nor did their mean raw breath test values (Figure 1). The finding of a positive breath test in 9.5% of our controls is consistent with the prevalence of SIBO in populations studied overseas[9].

The Gastrointestinal Symptom Rating Scale score – both total score and score by domain of symptoms – did not differ significantly between the Alzheimer's and control groups. Gastrointestinal Symptom Rating Scale scores in controls were similar to those reported in another east Asian population[13].

DISCUSSION

If we infer the proportion of Alzheimer's disease subjects having SIBO based on the proportion of our controls, by modest estimates, at least 69 patients would have been needed in the Alzheimer's group to reach a power of 80% at one-sided significance level of 0.05. Therefore, the present study is underpowered to conclude that Alzheimer's has absolutely no association with SIBO. However, there are still valuable takeaways from the dataset.

Whereas the prevalence of SIBO is strongly enriched among Parkinson's disease patients (25-67% prevalence in Parkinson's)[9], the prevalence of SIBO in Alzheimer's and control groups did not differ in this study. This is also reflected in current literature. In a meta-analysis of 56 studies[15], Parkinson's disease conferred an odds ratio of 3.36 for gastrointestinal disorders ranging from constipation, SIBO, inflammatory bowel disease to irritable bowel syndrome - whereas the odds ratio in Alzheimer's was only 1.52. Of the seven studies showing

Table 1. Study participants with Alzheimer's disease (n=21) versus controls (n=27) differed only in MMSE scores and years of education. The frequency of positive hydrogen breath tests and their values did not differ between groups in this study. Numbers reflect mean values (± standard deviation) of each group, or the number of participants in each group (percentage).

	Alzheimer's disease, mean value or number of participants	Controls, n=27	p
Age (years)	69.1 (± 9.4)	66.3 (± 5.0)	0.06
Number of male subjects per group	7 (33%)	11 (40.7%)	0.60
Number of ethnic Chinese per group	19 (90.5%)	26 (96.3%)	0.51
Duration of formal schooling (years)	6.9 (± 4.0)	11.9 (± 2.6)	<0.01
MMSE score	17.0 (± 5.5)	28.7 (±1.0)	<0.01
Number of positive hydrogen breath tests per group	2 (9.5%)	5 (18.5%)	0.38
Hydrogen breath test value (change in ppm)	4.0 (± 5.8)	6.8 (± 12.0)	0.37
Total Gastrointestinal Symptom Rating Scale score for abdominal pain and discomfort, reflux, diarrhea and constipation domains	2.1 (± 2.0)	2.15 (± 1.6)	0.38

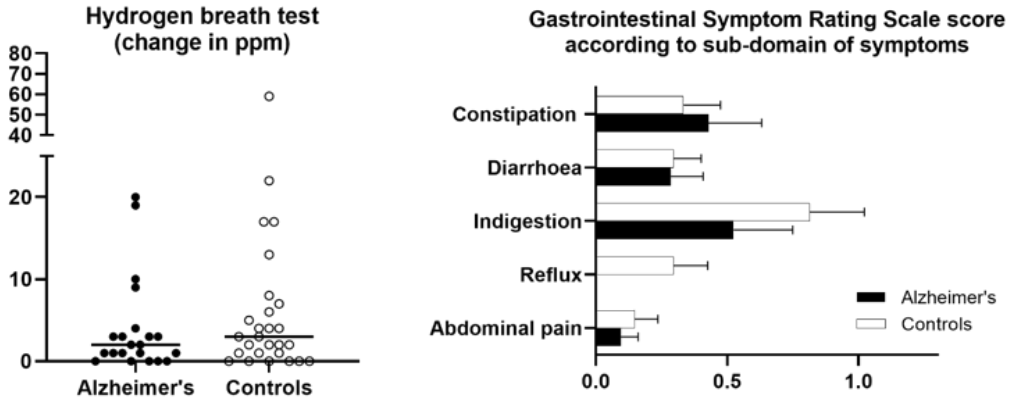

Figure 1. Hydrogen breath test values and Gastrointestinal Symptom Rating Scale score by domain of symptoms did not significantly differ in the Alzheimer's group compared to controls. Each point in the hydrogen breath test plot represents a single research subject, while the horizontal line represents the group mean. On the right, each bar represents average score per domain of symptoms (summed from 3-4 ratings within a single questionnaire) +/- SD per group - no single gastrointestinal symptom domain was overrepresented within the Alzheimer's group.

an effect of Alzheimer's on gastrointestinal disorders, five of these showed a link with Helicobacter pylori infection. It is conceivable – even exciting – that Alzheimer's disease and Parkinson's disease affect the gastrointestinal tract differently, perhaps analogous to different neuroinflammatory pathways. Since Helicobacter pylori colonization is prevalent among Alzheimer's patients[7], the specific effects of this on the gut microbiome could be explored in future studies.

The gold standard for diagnosing SIBO involves obtaining bacterial cultures from jejunal aspirates, but the hydrogen breath test is more widely used in clinical practice as it is non-invasive. As emphasized in our study protocol via instructions to caregivers and subjects, diet and medications need to be strictly controlled, to improve the reliability of the breath test. A study of the motor effects of rifaximin treatment on Parkinson's patients with SIBO16 illustrated that the same breath test repeated on real-world subjects over time could change even with placebo treatment, suggesting that a single breath test may not be sufficient to exclude or confirm SIBO status. In the future, the approach of studying stool cultures directly for their microbiome signatures would be more specific, and may improve the reliability of our assessment of SIBO. Another explanation for why we did not find a link between Alzheimer's and breath test values could be that the hydrogen breath test is a quantitative test of small bowel bacterial volume. What other studies had demonstrated were qualitative changes in the small bowel microbiome, where the comparison of stool cultures between Alzheimer's and control patients may have been more useful. Alternatively, it is plausible that Alzheimer's has more significant effects on other segments of the gastrointestinal tract – such as the gastric or colonic mucosa – where changes in flora may not be adequately captured by a hydrogen breath test. This is in line with studies that have shown a promising effect of Helicobacter pylori eradication on cognition in Alzheimer's disease[15].

There are also limitations with the current study's inclusion criteria. We defined dementia clinical severity based on MMSE score, and we understand the limitation of MMSE as being significantly dependent on one's level of education. Our study population is a diverse population that comprises multiple ethnicities with largely uneducated or poorly-educated elderly, given our local historical context. However, a previous local study has shown that the MMSE is still a reliable tool in identifying dementia for the local population[17]. However, other alternatives such as the Clinical Dementia Rating scale[18] should be considered in future studies, which might give a more specific clinical severity rating.

Moving forward, it would also be important to

determine if any differences in gastrointestinal disease and microbiota translate into clinical symptoms reported by Alzheimer's patients. While some studies report increased constipation and fecal incontinence, others suggest that the microbiome changes were actually asymptomatic [5]. Unexpectedly, in our dataset the prevalence of reflux symptoms tended to be lower in the Alzheimer's group (although this did not reach significance), and given the suggested link between Alzheimer's disease and Helicobacter pylori in the literature, perhaps questionnaires that probed into symptoms of upper gastrointestinal tract disorders could be of higher yield.

The gastrointestinal tract still represents an attractive neuroinflammatory target in Alzheimer's disease. Better powered studies are required to determine if there is any association between Alzheimer's and classical SIBO. While gastrointestinal dysfunction in Alzheimer's could still be clinically significant, a more critical eye needs to be cast on the tools we use to assess these differences.

ACKNOWLEDGMENTS

This work was supported by the SingHealth Foundation Research Grant SHF/FG555P/2014.

REFERENCES

1. Houser MC, Tansey MG. The gut-brain axis: is intestinal inflammation a silent driver of Parkinson's disease pathogenesis? npj Park Dis. 2017;3(1). doi:10.1038/s41531-016-0002-0
2. Angelucci F, Cechova K, Amlerova J, Hort J. Antibiotics, gut microbiota, and Alzheimer's disease. J Neuroinflammation. 2019;16(1). doi:10.1186/s12974-019-1494-4
3. Lopes Da Silva S, Vellas B, Elemans S, et al. Plasma nutrient status of patients with Alzheimer's disease: Systematic review and meta-analysis. Alzheimer's Dement. 2014;10(4):485-502. doi:10.1016/j.jalz.2013.05.1771
4. Zhan X, Stamova B, Jin LW, Decarli C, Phinney B, Sharp FR. Gram-negative bacterial molecules associate with Alzheimer disease pathology. Neurology. 2016;87(22):2324-2332. doi:10.1212/WNL.0000000000003391
5. Vogt NM, Kerby RL, Dill-McFarland KA, et al. Gut microbiome alterations in Alzheimer's disease. Sci Rep. 2017;7(1). doi:10.1038/s41598-017-13601-y
6. Leblhuber F, Geisler S, Steiner K, Fuchs D, Schütz B. Elevated fecal calprotectin in patients with Alzheimer's dementia indicates leaky gut. J Neural Transm. 2015;122(9):1319-1322. doi:10.1007/s00702-015-1381-9
7. Kountouras J, Boziki M, Gavalas E, et al. Eradication of Helicobacter pylori may be beneficial in the management of Alzheimer's disease. J Neurol. 2009;256(5):758-767. doi:10.1007/s00415-009-5011-z
8. Gabrielli M, Bonazzi P, Scarpellini E, et al. Prevalence of Small Intestinal Bacterial Overgrowth in Parkinson's Disease. Mov Disord. 2011;26(5):889-892. doi:10.1002/mds.23566
9. Tan AH, Mahadeva S, Thalha AM, et al. Small intestinal bacterial overgrowth in Parkinson's disease. Park Relat Disord. 2014;20(5):535-540. doi:10.1016/j.parkreldis.2014.02.019
10. Fasano A, Bove F, Gabrielli M, et al. The role of small intestinal bacterial overgrowth in Parkinson's disease. Mov Disord. 2013;28(9):1241-1249. doi:10.1002/mds.25522
11. Loeb MB, Molloy DW, Smieja M, et al. A Randomized, Controlled Trial of Doxycycline and Rifampin for Patients with Alzheimer's Disease. J Am Geriatr Soc. 2004;52(3):381-387. doi:10.1111/j.1532-5415.2004.52109.x
12. Svedlund J, Sjödin I, Dotevall G. GSRS-A clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci. 1988;33(2):129-134. doi:10.1007/BF01535722
13. Yakabi K, Yamaguchi N, Ono S, et al. Open Label Trial of the Efficacy and Safety Profile of Rikkunshito used for the Treatment of Gastrointestinal Symptoms in Patients with Parkinson's Disease: A Pilot Study. Curr Ther Res - Clin Exp. 2017;87:1-8. doi:10.1016/j.curtheres.2017.07.003
14. Rezaie A, Buresi M, Lembo A, et al. Hydrogen and Methane-Based Breath Testing in Gastrointestinal Disorders: The North American Consensus. Am J Gastroenterol. 2017;112(5):775-784. doi:10.1038/

ajg.2017.46
15. Fu P, Gao M, Yung KKL. Association of Intestinal Disorders with Parkinson's Disease and Alzheimer's Disease: A Systematic Review and Meta-Analysis. ACS Chem Neurosci. 2020;11(3):395-405. doi:10.1021/acschemneuro.9b00607
16. Vizcarra JA, Wilson-Perez HE, Fasano A, Espay AJ. Small intestinal bacterial overgrowth in Parkinson's disease: Tribulations of a trial. Park Relat Disord. 2018;54:110-112. doi:10.1016/j.parkreldis.2018.04.003
17. Ng TP, Niti M, Chiam PC, Kua EH. Ethnic and educational differences in cognitive test performance on mini-mental state examination in Asians. Am J Geriatr Psychiatry. 2007;15(2):130-139. doi:10.1097/01.JGP.0000235710.17450.9a
18. Morris JC, Ernesto C, Schafer K, et al. Clinical dementia rating training and reliability in multicenter studies: The Alzheimer's Disease Cooperative Study experience. Neurology. 1997;48(6):1508-1510. doi:10.1212/WNL.48.6.1508