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SHORT COMMUNICATION

Gastrointestinal function in dementia with Lewy bodies: a comparison with Parkinson disease

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Abstract

Purpose To investigate gastrointestinal function in dementia with Lewy bodies and Parkinson disease.

Methods We examined gastric emptying and colonic transit time in 19 dementia with Lewy bodies and 46 Parkinson disease patients.

Results Gastric emptying was longer in dementia with Lewy bodies than in Parkinson disease ($p = 0.014$). Colonic transit time tended to be longer in dementia with Lewy bodies than in Parkinson disease. There was no relationship between gastric emptying and colonic transit time, nor between gastric emptying, colonic transit time and age.

Conclusion Gastric emptying was prolonged in dementia with Lewy bodies compared to Parkinson disease.

Keywords Dementia with Lewy bodies · Parkinson disease · Gastric emptying · Colonic transit time · Constipation

Introduction

Dementia with Lewy bodies (DLB) is the second most common age-related form of neurodegenerative dementia after Alzheimer's [1]. Although the precise incidence remains unknown, it is estimated that around one in every ten cases of dementia is attributable to abnormal aggregates of alpha-synuclein, i.e., Lewy bodies [2, 3]. The aggregated alpha synuclein proteins damage cellular machinery and ultimately destroy neurons, secondarily leading to losses of the chemical messengers dopamine (for motor, as seen in Parkinson disease [PD] [4]) and acetylcholine (for cognitive function). DLB is typically associated with significant fluctuations in symptoms, as well as greater incidence of hallucination than in Alzheimer's [1–3]. Oversensitivity to neuroleptics is another critical feature. One aspect of the disease is that levodopa treatment in DLB patients is less effective than in PD patients. It is well known that PD entails significant gastrointestinal (GI) tract dysfunction [5–8]. GI symptoms are one of the most common nonmotor symptoms (NMS) in patients with PD involving the whole GI tract (GIT), such as nausea, vomiting, constipation, etc. Slowed gastric emptying and disturbed electrogastrography underlie upper GIT dysmotility. Since levodopa is absorbed through proximal ileum, upper GIT dysmotility affects levodopa absorption [9] and may lead to delayed on, no-on and malignant syndrome. Loss of phasic rectal contraction, slowed colonic transit time, decreased abdominal contraction and paradoxical sphincter contraction on defecation are all features of lower GIT dysmotility. These may lead to volvulus, intussusception, intestinal pseudo-obstruction (ileus), stercoral ulcer and other GI emergency. Furthermore, constipation serves as a risk factor for PD as well as an early prodromal NMS of PD. Therefore, the question arises as to whether DLB has more significant GI tract dysfunction than PD. However, no such studies have been available thus far. In order to answer this question, we describe the results of our GI function tests in DLB and compare them with those in PD.

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Methods

This is a cross-sectional, single-institution study. The inclusion criteria were patients diagnosed with DLB [1] or PD [4]. The term Parkinson's disease dementia (PDD) is used when dementia appears more than 1 year after the onset of typical PD, whereas the term dementia with Lewy bodies refers to a dementia onset before or within 1 year after parkinsonism onset [1]. In this study, we did not use the one-year rule; we diagnosed DLB when apparent dementia was present in the patient, in order to explore the relation between the GI dysfunction severity with dementia. All patients underwent standard neurological examination including the Unified Parkinson Disease Rating Scale (UPDRS) [4], and three sets of cognitive tasks, i.e., the Mini-Mental State Examination (MMSE, 0-30 scale, normal > 24) [10], the Alzheimer's Disease Assessment Scale cognitive test (ADAScog, 0-70 scale, normal < 10; general cognitive tasks), and the Frontal Assessment Battery (FAB, 0-18 scale, normal > 16; frontal executive tasks). A history of GI symptoms (nausea, vomiting, constipation, etc.) was also taken. In order to augment diagnostic accuracy, we performed metaiodobenzylguanidine (MIBG) myocardial scintigraphy in all patients [1].

The exclusion criteria were (1) neurologic diseases other than DLB or PD, (2) comorbid diseases (diabetes, gastroesophageal reflux disease, abdominal surgery, etc.) that might affect gastric emptying, and/or (3) drugs (anti-cholinergic agents, etc.) and opioid abuse that might affect gastric emptying. We performed two GI function tests, i.e., gastric emptying (GE) and colonic transit time (CTT). The GE test (^{13}C-acetic acid expiration breath test) was performed in the morning, with overnight fasting and no medication for 8 h prior [9, 11, 12]. Breath samples were collected in a sitting position, 5, 10, 15, 20, 30, 40, 50, 60, 75, 90 min. after administration of a liquid test meal (200 kcal/200 ml) containing 100 mg ^{13}C-sodium acetate (Cambridge Isotope Laboratory Inc, USA). All breath samples were analyzed for $^{13}CO_2$ using an IR spectrophotometer (Otsuka Electronics Inc, Tokyo, Japan). The principle of the ^{13}C-acetic acid breath test is that after the liquid test meal containing ^{13}C-acetate is ingested, gastric emptying, absorption from the digestive tract and metabolism in the liver results in production of $^{13}CO_2$ and its expiration from the lungs in the expired breath. It has been reported that in normal subjects without any diseases of the lung, liver, or small intestine, T_{max} (^{13}C) correlates with the gastric emptying function. We then obtained T_{max} (^{13}C), i.e., the peak time of the ^{13}C-dose-excess curve, based on the measured change of the $^{13}CO_2/^{12}CO_2$ ratio [$\Delta^{13}CO_2$(‰)] [9, 11, 12].

The CTT test was performed using the repetitive ingestion method [8, 13]. We asked the subjects to ingest a small test capsule once a day for 6 days shortly after breakfast. The capsule contained 20 circular radiopaque markers (Sitzmark®). A week later, we took a plain abdominal X-ray. The markers were counted in three segments of the large bowel: the right colon, the left colon, and the sigmoid colon and rectum. One marker corresponds to 1.2 h (20 markers for 24 h) of transit time. We counted the number of markers in each segment of the large bowel. We multiplied these numbers by 1.2 to derive the colonic transit time in that part of the colon, i.e., the right CTT, left CTT and rectosigmoid CTT, respectively, and took the sum of these transit times as the total CTT. [8, 13] Statistical analysis was performed by the non-parametric Mann–Whitney's *U* test for samples with non-standard distribution. We performed correlation analysis between the values of T_{max} (^{13}C) and CTT, and between the values of T_{max} (^{13}C) and age in the individuals with PD or DLB. Informed consent was obtained from all patients and their caregivers, particularly of the elderly DLB patients, prior to participation in the study. This study was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki and its later amendments.

Results

We consecutively enrolled 19 untreated DLB patients (9 men, 10 women; mean age 77.4 ± 6.6 years [standard deviation]; mean disease duration 2.5 ± 1.4 years) and untreated 46 PD patients (21 men, 25 women; age 68.8 ± 7.3 years; duration 2.3 ± 3.0 years). Patients' clinical characteristics are shown in Table 1. None had comorbid disease or were

Table 1 Patients with PD and DLB

	PD (n = 46)	DLB (n = 19)	p value
Age (years)	68.8 ± 7.3	77.4 ± 6.6	< 0.001
Duration (years)	2.3 ± 3.0	2.5 ± 1.4	0.597
MIBG (delayed HM ratio)	1.95 ± 0.84	1.77 ± 0.94	0.452
Congnitive			
MMSE	27.2 ± 2.35	20.2 ± 2.46	< 0.0001
FAB	14.3 ± 2.41	10.9 ± 3.43	0.00159
ADAS	6.69 ± 3.34	12.1 ± 1.19	0.00078
Motor (UPDRS)			
Part I	0.81 ± 1.30	1.27 ± 1.19	0.1521
Part II	6.33 ± 3.96	10.3 ± 5.83	0.0555
Part III	14.4 ± 7.87	21.5 ± 13.0	0.1007
Part IV	0.08 ± 0.39	0.18 ± 0.40	0.5170
Total	21.5 ± 11.7	33.1 ± 18.9	0.0515

MIBG metaiodobenzylguanidine, *HM* heart-to-mediastinum ratio, *MMSE* mini-mental state examination, *FAB* frontal assessment battery, *ADAScog* Alzheimer's disease assessment scale cognitive subscale, *UPDRS* Unified Parkinson Disease Rating Scale

taking drugs that might affect GI function. The ages of the DLB patients were greater than those of the PD patients ($p < 0.0001$). The MIBG value did not differ between the two groups. The average score of the mini-mental state examination was lower in DLB (20.3 ± 2.5) than in PD (27.3 ± 1.9, $p < 0.0001$). Motor function as measured by UPDRS did not differ between the two groups.

As shown in Fig. 1a, mean T_{max} (^{13}C) was significantly prolonged in DLB (63.2 ± 15.7 min) compared to PD (52.5 ± 15.5 min, $p = 0.014$). In particular, markedly prolonged cases [T_{max} (^{13}C) ≥ 75 min] were more common in DLB (eight patients, 42.1%) than in PD (seven patients, 15.2%) ($p = 0.019$). The median T_{max} (^{13}C) in healthy control is 44 min in our previous study (range, 23-64 min). [9].

As shown in Fig. 2, the total CTT in DLB (74.9 ± 51.9 h) was longer than that in PD (59.5 ± 43.1 h), but the difference did not reach statistical significance. Among CTT, rectosigmoid CTT was the longest in both DLB and PB. There was no relationship between the values of T_{max} (^{13}C) and CTT, or between the values of T_{max} (^{13}C) and age (Fig. 1b). The upper limit of total CTT in healthy control is 39 h in our previous study. [8].

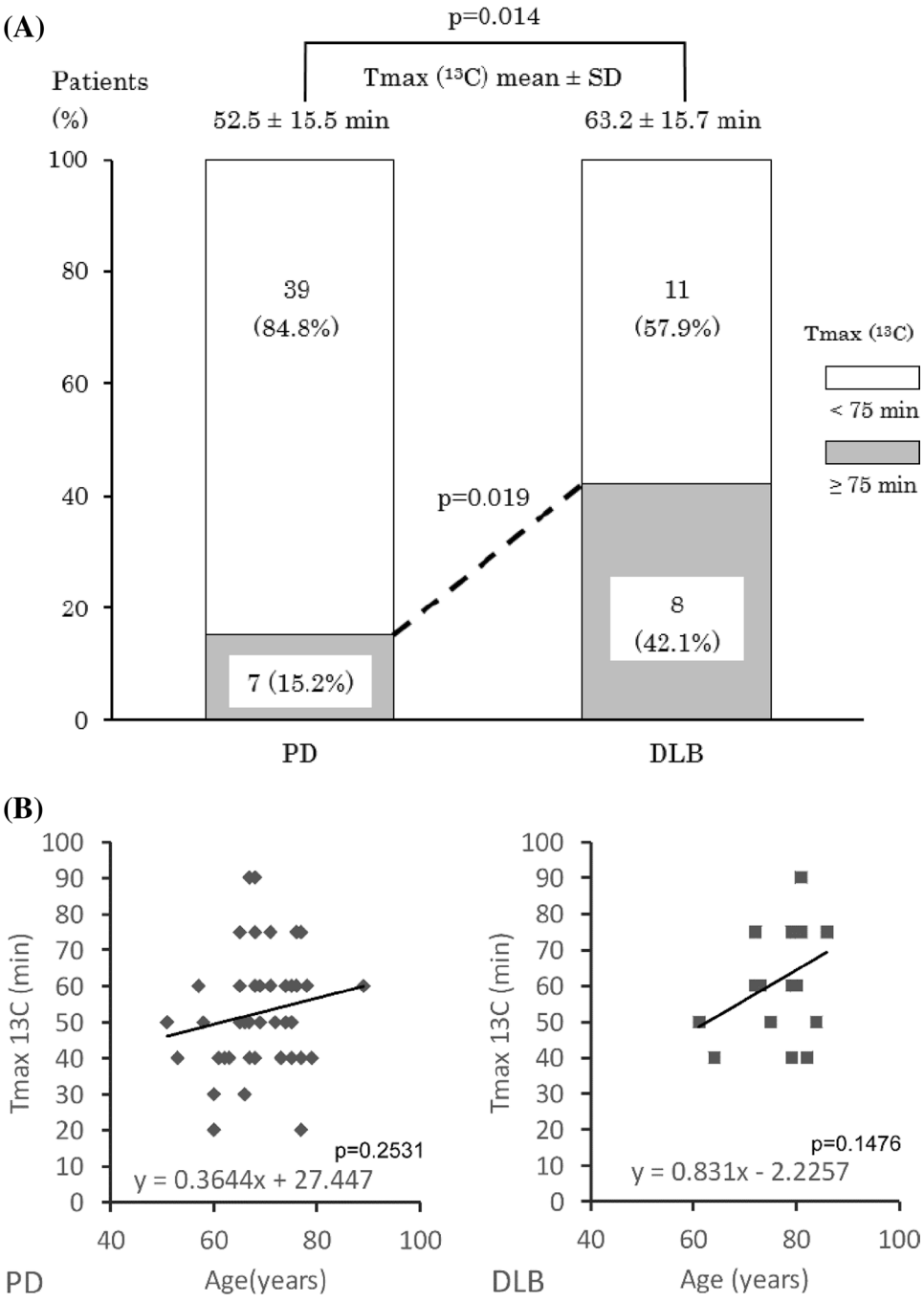

Fig. 1 Difference in gastric emptying between PD and DLB. **a** Mean T_{max} (^{13}C) in DLB was significantly prolonged compared with PD (63.2 ± 15.7 min in DLB vs. 52.5 ± 15.5 min in PD respectively, $p = 0.014$). The proportion of patients whose T_{max} ^{13}C was 75 min or longer was significantly larger in DLB than in PD. **b** The correlation between age and T_{max} (^{13}C) in the individuals with PD or DLB. There was no significant association in either group. Each symbol represents an individual in the group. Dashed lines represent the mean age of the participants of the groups. *PD* Parkinson disease, *DLB* dementia with Lewy bodies

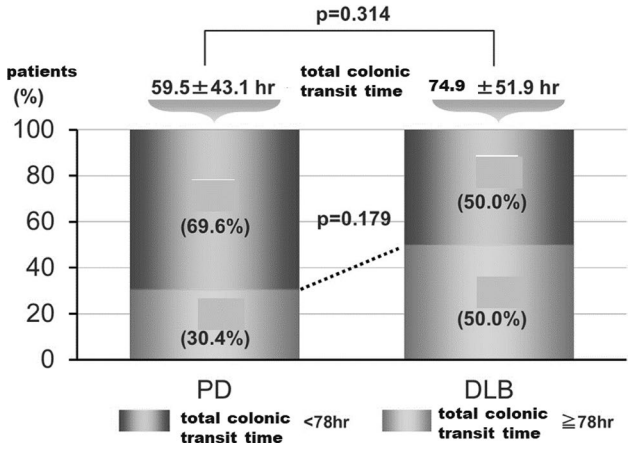

Fig. 2 Difference in colonic transit time between PD and DLB. Total CTT was longer in DLB (74.9 ± 51.9 h) than in PD (59.5 ± 43.1 h), but the difference did not reach statistical significance. *PD* Parkinson disease. *DLB* dementia with Lewy bodies

Discussion

It has been well documented that PD entails significant GI tract motor disorders, [5–8] which may affect levodopa absorption in the patients [9]. Some evidence has accumulated regarding the variety of mechanisms potentially underlying GI tract motor disorders in PD [14, 15]. Epidemiological studies in a Japanese-immigrant cohort in Hawaii, USA indicated a clear association between constipation and the future risk of developing motor signs (namely, PD) in Lewy body diseases (LBD) [16]. The interval between the onset of constipation (the first notification by the questionnaire) and the full manifestation of PD (development of motor signs) was more than 10–20 years in those studies. Also, serial pathology by Braak and colleagues showed that PD pathology in the brain starts in the dorsal vagal nucleus (which might regulate bowel function) earlier than in the substantia nigra (which regulates motor function). Gelpi et al. further reported that alpha-synuclein aggregates (the pathological hallmark of PD) tended to appear in the peripheral nerves earlier than in the brain: e.g., vagus nerve (86.7%), myenteric plexus (86.7%), cardiac sympathetic nerve (100%), etc. [14, 15]. In addition, epidemiological and experimental studies have suggested that environmental toxins (particularly pesticides in rural regions) may change microbiota (bacterial flora) in the bowel, triggering myenteric LBD pathology, and resulting in constipation. Also, once LBD pathology starts in the myenteric plexus, with a decreased vasoactive intestinal polypeptide (VIP) expression in submucosal neurons [17] etc., it is postulated that aggregated α-synuclein (a marker of LBD pathology) has the ability to be transmitted (like prions) from neuron to neuron, and spreads to the brain through sympathetic (thoracic and lumbar sympathetic trunk) and parasympathetic (vagal and pelvic) nerves [18–21]. The central nervous system further affects gut motility via the nigrovagal pathway, etc. [22].

As the study showed, patients with DLB, who have impaired cognitive function as measured by MMSE, AFB and ADAScog in addition to motor disorders, are significantly more likely to suffer from GI problems than previously thought. Gastric emptying (GE) in the DLB group was significantly longer than that in the Parkinson group. In contrast, we were unable to identify a significant difference in colonic transit time (CTT) between the two groups. To the best of our knowledge, this is the first report with such evidence. Pathological studies have shown Lewy bodies in the myenteric plexus (Meissner, Auerbach) early in the course of PD. Also in PD, previous GI function studies showed prolonged gastric emptying [5], decreased amplitude and loss of postprandial augmentation in the electrogastrogram [23] and prolonged colonic transit [4], indicating the important site of lesions being the periphery. Despite the demonstrated importance of GI dysfunction in PD, GI dysfunction appears to be more significant in DLB than in PD. In addition, we speculate that the GI pathology might be more significant in DLB than in PD. However, this is merely a speculation. Autopsy studies of the two disorders could help clarify the differences in lesions between them.

One limitation of this study is that the [13] C-acetate breath test evaluates the emptying of the liquid phase of the meal from the stomach. Typically, neuromuscular disorders that retard emptying of liquids are associated with even more severely delayed emptying of solids [24]. However, we could not evaluate emptying of solids in our patient cohort by the ^{13}C-acetate breath test. Also, the age in DLB was older than that in PD. While modest prolongation of gastric emptying occurs with ageing itself [24], fasting or fed gastric motility has been shown not to differ between young and old [25, 26]. We did not observe associations between T_{max} (^{13}C) and age. Therefore, the difference of T_{max} (^{13}C) between DLB and PD is likely to reflect the difference of the disease process in DLB and PD. Another limitation is the small sample size and lack of neurologically normal controls. In addition, we do not know the exact reason why no difference was noted in the lower GI (colonic transit time) between DLB and PD. One explanation might be that distal GI dysfunction is probably already evident in both patient groups. This is because distal GI dysfunction (constipation) is regarded as the very early feature in the course of PD [9]. However, this assumption needs further clarification with larger studies. In addition, it is reported that oral levodopa is deactivated by low-pH gastric acid but some moves on to the small intestine, where it is absorbed. Therefore, slowed GE may directly link to levodopa pharmacodynamics, leading to less levodopa absorption and delayed plasma levodopa peak. This seems why DLB with longer GE might have less response to

levodopa. Since GI function might affect levodopa absorption [9] leading to delayed-on, malignant syndrome and emergency pseudo-obstruction [27], we should pay close attention to the GI tract in our elderly DLB patients.

In conclusion, gastric emptying is prolonged in DLB compared to that in PD, although the older age in DLB might have contributed to the difference. CTT showed no difference between DLB and PD.

Author contributions Hirokazu Doi had a role in: acquisition, analysis and interpretation of data. Ryuji Sakakibara had a role in: study concept and design, acquisition of subjects and/or data, analysis and interpretation of data, and preparation of manuscript. Mitsutoshi Sato had a role in: acquisition, analysis and interpretation of data. Masayuki Masuda had a role in: acquisition, analysis and interpretation of data. Fuyuki Tateno had a role in: acquisition, analysis and interpretation of data. Yosuke Aiba had a role in: acquisition, analysis and interpretation of data. Masahiko Kishi had a role in: acquisition of subjects and/or data. Tomonori Yamanishi had a role in: review of data. Tatsuya Yamamoto had a role in: review of data. Katsuyoshi Matsuoka had a role in: acquisition of subjects and/or data.

Compliance with ethical standards

Conflict of interest None of the authors have any conflicts of interest to declare.

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