J Neurol (2011) 258:421–426
DOI 10.1007/s00415-010-5769-z

ORIGINAL COMMUNICATION

Is there a delayed gastric emptying of patients with early-stage, untreated Parkinson's disease? An analysis using the ^{13}C-acetate breath test

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Received: 6 July 2010 / Revised: 15 August 2010 / Accepted: 20 September 2010 / Published online: 12 October 2010

Abstract During the pre-symptomatic stage of Parkinson's disease (PD), the idiopathic PD related abnormal synuclein immunostaining is confined to the medulla oblongata and olfactory bulb, according to Braak. In the study of the enteric nervous system of PD, it has reported that Lewy bodies were found in the Auerbach's and Meissner's plexuses. These lesions may cause dysfunction of the gastrointestinal tract (GI) as pre-clinical symptoms of PD. However, because L-dopa therapy itself may worsen the symptoms of the digestive tract function, it is needed to evaluate the gastrointestinal tract function in patients with early-stage, untreated (de novo) PD. In the present study, using the ^{13}C-acetate breath test (^{13}C-ABT), we investigated gastric emptying in 20 untreated, early-stage PD patients and 40 treated, advanced-stage PD patients, and 20 healthy volunteers. Gastric emptying was examined by the ^{13}C-ABT [the half emptying time (HET), the peak time of the ^{13}C% dose-excess curve (T_{max})]. The T_{max} and HET of gastric emptying as assessed using the ^{13}C-ABT was significantly delayed in untreated, early-stage PD patients as compared to the controls ($P < 0.001$). The T_{max} and HET of gastric emptying were not significantly delayed in untreated, early-stage PD patients as compared to treated, advanced-stage PD patients. The results demonstrated that delay in gastric emptying did not differ between untreated, early-stage and treated, advanced-stage PD patients. Gastric emptying of untreated, early-stage PD is already delayed. Delayed gastric emptying may be one of markers of the pre-clinical stage of PD.

Keywords Parkinson's disease · Gastric emptying · Untreated (de novo) early-stage · ^{13}C-acetate breath test

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Introduction

Patients with Parkinson's disease (PD) often complain of gastrointestinal (GI) tract symptoms such as heartburn, nausea, vomiting, and full abdomen sensation [1–3]. Some studies have reported on the dysfunction of the GI tract in PD patients [1, 2, 4, 5].

During the pre-symptomatic stage of PD, the idiopathic PD related abnormal synuclein immunostaining is confined to the medulla oblongata and olfactory bulb, according to Braak [6]. The most likely causes of GI tract symptoms are degenerations of the dorsal vagal nucleus and the intramural plexus of the whole intestine [7]. These degenerations are likely to develop prior to the degeneration of dopaminergic neurons of the substantia nigra [7]. Therefore, in the previous study, it was reported that delayed gastric emptying was common in patients with early-stage, treated PD [1, 2, 4]. However, because L-dopa therapy itself may worsen the symptoms of delayed gastric emptying [8, 9], their interpretation of the results of their study is limited. Gastric emptying of patients with treated PD may be affected by L-dopa therapy. It was not clear whether there is the delayed gastric emptying of patients with early-stage,

untreated PD. It is needed to evaluate the function of the GI tract in patients with early-stage, untreated PD.

Recently, the ^{13}C-acetate breath test (^{13}C-ABT) has been widely recognized as useful for evaluating gastric emptying because it is less invasive than isotope or acetaminophen methods [10]. It was reported that the ^{13}C-ABT was a reliable and non-invasive tool for the analysis of gastric emptying rates of liquid phases without radiation exposure [11]. Though the ^{13}C-ABT is an isotopic method, it uses a stable isotope not emitting ionizing radiation and is feasible methods for PD patients [12].

The aim of this study is to compare the gastric emptying between patients with early-stage, untreated PD and patients with advanced-stage, treated PD, and healthy volunteers using the ^{13}C-ABT. We tested whether there is the delayed gastric emptying of patients with early-stage, untreated PD.

Methods

Patients

Our study population consisted of 60 patients with an initial diagnosis of PD on the basis of the UK Parkinson's Disease Society Brain Bank Clinical diagnostic criteria [13, 14] and 20 healthy volunteers (control group). The control group was ten men and ten women, median age 69.0 years (range 63–73 years). The patients were divided into two groups: 20 patients with early-stage, untreated PD [eight men and 12 women; median age 70.5 years (range 54–82 years); disease duration 0.9 years (range 0.3–2.5 years)] and 40 patients with advanced-stage, treated PD [14 men and 26 women; median age 67.0 years (range 42–86 years); disease duration 6.0 years (range 3.0–31.0 years)]. Each group of the PD patients was consecutively consulted at our hospital. Modified Hoehn and Yahr classification of the patients with early-stage, untreated PD was stage 1–2, according to the Unified Parkinson's Disease Rating Scale [15, 16]. Modified Hoehn and Yahr classification of the patients with advanced-stage, treated PD was stage 3–4. All PD patients with early-stage were not treated with any medications at first visit, and were followed up for at least 1 year after this study in order to rule out atypical parkinsonism. All PD patients with advanced-stage were being treated with antiparkinsonian medications (long-term L-dopa therapy). No patient was treated with drugs that might alter gastric emptying. None of the PD patients had basic diseases such as liver dysfunction, renal failure, cardiopulmonary disease, diabetes mellitus, GI disease or history of gastric surgery. Clinical characteristics (including age, gender, body mass index) were not significantly different among the PD groups with early-stage and with advanced-stage, or the control group. The results of blood examinations were within normal range. In addition, there were no differences between the PD groups in terms of pepsinogen I, II, and serum gastrin levels, hemoglobin A1c (HbA1c), which might affect gastric motility [17]. The positive ratio of immunoglobulin G anti-Helicobacter pylori antibody did not differ significantly between the PD groups and no patients had past history of peptic ulcer. The positive ratio of orthostatic hypotension (OH) [18] and coefficient of variation of R-R intervals ($CV_{R\text{-}R}$) [19], heart/mediastinum (H/M) ratio of I-[123]-metaiodo-benzylguanidine (MIBG) scintigraphy [20] were not significantly different between the PD groups.

Informed consent was obtained from each subject prior to participation in this study. The study protocol was approved by the Ethical Committee of Gifu University, and was carried out in accordance with the 1975 Declaration of Helsinki.

Gastric emptying examination

The GE examination was carried out using the ^{13}C-breath test according to Ghoos [10] with slight modifications. PD patients and healthy volunteers were tested after an overnight fast of 12 h. All PD patients did not take any antiparkinsonism drug over 24 h. Early in the morning, PD patients and healthy volunteers took the liquid test meal (Racol: TM, 200 kcal/200 ml; Otsuka Pharmaceuticals Co., Ltd., Tokyo, Japan) containing 100 mg ^{13}C-sodium acetate. Thereafter, an expiration breath sample was collected every 10 min for 4 h and analyzed for $^{13}CO_2$ using an IR spectrophotometer (UBiT-IR300; Otsuka Electronics Co., Ltd., Tokyo, Japan). During the examination, all subjects were in a sitting position.

The principle of ^{13}C-ABT is ingestion of a liquid test meal containing ^{13}C-acetate, gastric emptying, absorption from the digestive tract, metabolism in the liver (production of $^{13}CO_2$), expiration from the lung, and increase of $^{13}CO_2$ in expired breath.

Mathematical analysis

The data were used for mathematical curve fitting. A best fit curve of expired $^{13}CO_2$ was constructed for each subject. The %-$^{13}CO_2$ cumulative excretion in the breath was assessed using a non-linear regression formula [21, 22]: $y = m\ (1 - e^{-kt})^{\beta}$ to fit the curve of the cumulative ^{13}C recovery. The %-$^{13}CO_2$ excretion per hour was fitted to the formula $mkbe^{-kt}\ (1-e^{-kt})^{\beta-1}$. T is time and m, k, and β are constants. The value of m represents the total cumulative $^{13}CO_2$ recovery when the time is infinite. The half emptying time (HET) was calculated using the formula: $\mathrm{HET} = -1/k\ \ln(1 - e^{-1/\beta})$. T_{max} is the peak time of the ^{13}C%–dose-excess curve (%–dose/h) based on a time

profile of the $^{13}CO_2$ excretion rate. The parameters were estimated with Excel software (Microsoft Co., Ltd., Redmond, WA).

Statistical analysis

Categorical variables were compared using Fisher's exact probability test. Other variables were expressed as median (range). Medians were compared using Mann–Whitney's *U* test. All analyses were carried out on StatView statistical software, version 5.0 (Abacus Concepts, Inc., Berkeley, CA). A *P* value less than 0.05 was considered significant.

Results

Controls and early-stage, untreated PD patients (Figs. 1, 2)

The examinations were safely carried out in all PD patients and controls. The T_{max} was significantly delayed in patients with early-stage, untreated PD (median 1.17 h, range 0.67–1.83 h) as compared with the controls (median 0.83 h, range 0.67–1.00 h) ($P < 0.001$). The HET was significantly delayed in patients with early-stage, untreated PD (median 2.04 h, range 1.75–3.07 h) as compared with the controls (median 1.44 h, range 1.30–1.64 h) ($P < 0.001$). There was absolutely no overlap in the range of the HET between controls and early-stage, untreated PD patients.

Controls and advanced-stage, treated PD patients (Figs. 1, 2)

In all patients with advanced-stage, treated PD, the blood concentration of L-dopa was below 25 ng/ml (below the detection level) at start of examination. The T_{max} of GE

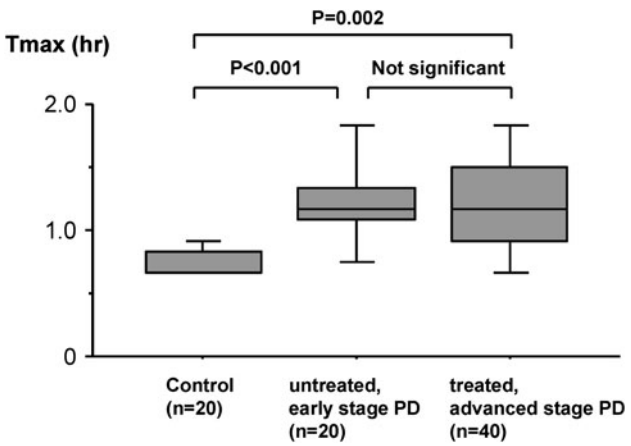

Fig. 1 T_{max} in control, PD patients with untreated, early-stage and those with treated, advanced-stage

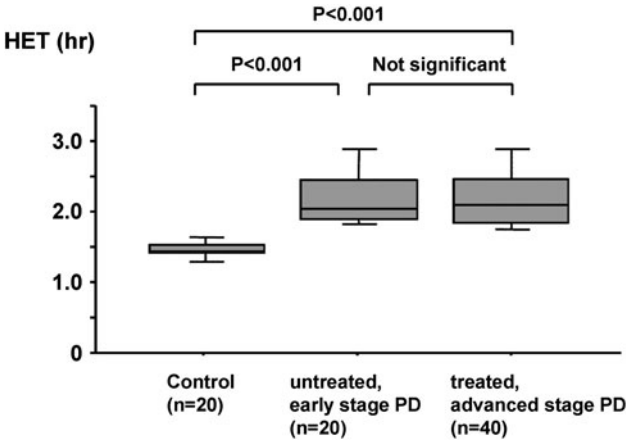

Fig. 2 HET in control, PD patients with untreated, early-stage and those with treated, advanced-stage

using the ^{13}C-ABT was significantly delayed in patients with advanced-stage, treated PD (median 1.17 h, range 0.50–2.17 h) as compared with the controls (median 0.83 h, range 0.67–1.00 h) ($P = 0.002$). The HET was significantly delayed in patients with advanced-stage, treated PD (median 2.09 h, range 1.60–3.30 h) as compared with the controls (median 1.44 h, range 1.30–1.64 h) ($P < 0.001$). There was virtually no overlap between controls and advanced-stage, treated PD patients.

PD patients with untreated early-stage and treated advanced-stage (Figs. 1, 2; Table 1)

The T_{max} was not significantly delayed in PD patients with early-stage (median 1.17 h, range 0.67–1.83 h) as compared with those with advanced-stage (median 1.17 h, range 0.50–2.17 h) ($P = 0.58$). The HET was not significantly delayed in PD patients with early-stage (median 2.04 h, range 1.75–3.07 h) as compared with those with advanced-stage (median 2.09 h, range 1.60–3.30 h) ($P = 0.77$).

Discussion

In the present study we have shown two novel important points. Firstly, we demonstrated that gastric emptying is significantly delayed in early-stage, untreated PD patients. Secondly, delayed gastric emptying does not differ between patients with early-stage, untreated PD as compared to those with advanced-stage, treated PD.

PD patients sometimes complain of upper GI symptoms such as heartburn, nausea, vomiting, and full abdomen sensation [1–3]. With respect to the pathological background of PD, during the pre-symptomatic stage of PD, the idiopathic PD related abnormal synuclein immunostaining

Table 1 Clinical characteristics of PD patients with untreated, early-stage and those with treated, advanced-stage

	Untreated, early-stage PD ($n = 20$)	Treated, advanced-stage PD ($n = 40$)	P value
Age (years)	70.5 (54–82)	67.0 (42–86)	0.49
Gender (male/female)	8/12	14/26	0.78*
BMI (kg m^{-2})	20.5 (17.8–27.9)	20.3 (16.8–27.1)	0.56
Duration (years)	0.9 (0.3–2.5)	6.0 (3.0–31.0)	<0.001
Duration with L-dopa (years)	0	5.5 (2.5–30.0)	<0.001
L-dopa (mg)	0	400 (100–750)	<0.001
Upper GI symptoms	6	11	0.99*
OH	9	21	0.78*
$CV_{R\text{-}R}$	1.70 (0.83–4.64)	1.71 (0.67–5.14)	0.43
MIBG (H/M ratio)	1.45 (1.13–2.56)	1.49 (1.27–1.95)	0.80

Variables expressed as median (range)

Medians were compared using Mann–Whitney's U test

PD Parkinson's disease, *BMI* body mass index, *GI* gastrointestinal tract, *OH* orthostatic hypotension, $CV_{R\text{-}R}$ coefficient of variation of R-R intervals, *MIBG* I-[123]-metaiodo-benzylguanidine scintigraphy, *H/M ratio* heart/mediastinum ratio

* Categorical variables were compared using Fisher's exact probability test

is confined to the medulla oblongata and olfactory bulb, according to Braak [6]. Neuronal degeneration occurring in the dorsal nucleus of the vagus may be responsible for the degeneration of the gastrointestinal myenteric plexuses. In the study of the enteric nervous system of PD, it has reported that Lewy bodies were found in the Auerbach's and Meissner's plexuses of the lower esophagus and stomach [23, 24]. Cytoplasmic inclusions similar to Lewy bodies were present in the ganglion cells of the colonic myenteric plexuses in PD patients [25]. The most likely causes of GI tract symptoms are degenerations of the dorsal vagal nucleus and the intramural plexus of the whole intestine [25]. These degenerations are likely to develop prior to the degeneration of dopaminergic neurons of the substantia nigra [7].

On the other hand, in lower GI symptoms, constipation has been identified as a rather frequent symptom in patients with PD ever since the first description of the disease [26–32]. Today, constipation is considered the most common manifestation of autonomic dysfunction in this disease occurring at a prevalence in the range of 70–80% [27, 30, 33, 34]. Constipation may precede development of PD [35]. It has been reported a prospective study which followed the bowel habits of 7,000 men for 24 years and reported that those with initial constipation (<1 bowel movement/day) had a threefold risk of developing PD after a mean interval of 10 years from initial constipation [35]. Involvement of the dorsal vagal nucleus, as would occur in Braak stage 1 may explain the pre-motor appearance of constipation [36]. It has been reported that motility of gut was controlled both by extrinsic inputs from the dorsal motor nucleus of the vagus and paravertebral sympathetic ganglia and by local reflexes mediated by intrinsic neurons of the enteric nervous system [37]. Both the enteric nervous system and the dorsal motor nucleus of the vagus are affected by Lewy body pathology at early stages of PD [37]. This early involvement provides insights into the pathophysiology of gastrointestinal dysmotility in GI disorder and may constitute an important step in the etiopathogenesis of Lewy body disease [37].

In the previous study, it was reported that delayed gastric emptying is common in patients with early-stage, treated PD [1, 2, 4]. However, because L-dopa therapy itself may worsen the symptoms of delayed gastric emptying [8, 9], their interpretation of the results of their study is limited. Gastric emptying of patients with early-stage, treated PD may be affected by L-dopa therapy. There is evidence to suggest that these complications in PD patients may be attributed to peripheral, pharmacokinetic mechanisms, mainly delayed gastric emptying as a side-effect of L-dopa [2, 38–40]. Dopaminergic agents also activate the vomiting center in the medulla via the chemoreceptor trigger zone, resulting in nausea, abdominal bloating, and vomiting [38].

In the present study, we tested whether there is the delayed gastric emptying of untreated patients with early-stage PD using ^{13}C-ABT. All PD patients were divided into two groups: those with untreated early-stage and those with treated advanced-stage. The patients with advanced-stage, treated PD were off drugs, including L-dopa, and the blood concentration of L-dopa was below the detection level at the start of examination. The two groups did not have significantly different blood parameters of gastric function such as pepsinogen I/II, serum gastrin, immunoglobulin G (IgG) anti-Helicobacter pylori antibody, hemoglobin A1c (HbA1c) [17] and neither was age of significant difference between the two groups [41]. The positive ratio of OH [18]

and $CV_{R\text{-}R}$ [19], H/M ratio of MIBG scintigraphy [20] were not significantly different between the PD groups. Under these conditions, there was not a difference in gastric emptying of PD patients with untreated, early-stage and those with treated, advanced-stage. And there is the delayed gastric emptying of untreated patients with early-stage PD. At the early-stage of PD, gastric emptying is already delayed similarly to the advanced-stage. Therefore, we speculate that delayed gastric emptying may be one of markers of the pre-clinical stage of PD.

In conclusion, our study demonstrated that gastric emptying is significantly delayed in untreated, early-stage PD patients as compared to controls, and that delayed gastric emptying does not differ between PD patients with untreated, early-stage and those with treated, advanced-stage. From a viewpoint of early diagnosis, it will be important to actually measure gastric emptying in PD patients in clinical settings. Our results demonstrated that from early-stage of PD, gastric emptying is already delayed similar to the advanced-stage. Delayed gastric emptying may be one of markers of the pre-clinical stage of PD.

Conflict of interest All authors report no disclosure.

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