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Gastric Myoelectrical Differences between Parkinson's Disease and Multiple System Atrophy

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Abstract: The electrogastrogram (EGG) was recorded for 24 hours in 17 Parkinson's disease (PD) patients, 17 multiple system atrophy (MSA) patients, and 8 healthy control subjects to elucidate the differences in the EGG findings between the two diseases. Eight EGG segments (3 preprandial, 3 postprandial, and 2 sleep segments) were selected from the total recording for spectral analysis, from which we obtained the dominant frequency (DF), instability coefficient of DF (ICDF), and low (LFR%), normal (NFR%), and high (HFR%) range power percentages of the total power. PD patients showed irregular slow waves, high HFR%, and high ICDF, whereas MSA patients showed regular slow waves and low ICDF. Although DF and NFR% increased after meal in controls, postprandial increases in DF and NFR% were less significant in both patient groups compared to the controls. The PD patients presented gastric dysrhythmias indicating gastric pacemaker disturbances. The MSA patients showed regular slow waves with low variability of the slow wave rhythm (low ICDF), which might have resulted from the involvement of gastric autonomic nerve function. © 2009 Movement Disorder Society

Key words: gastric myoelectrical activity; electrogastrogram; Parkinson's disease; multiple system atrophy; autonomic nervous system

Gastric myoelectrical activity is composed of gastric slow waves (electrical control activity) and spike/second potentials (electrical response activity) at three cycles per min (cpm). The gastric slow waves originating from the pacemaker cells on the major curvature of the stomach[1] can be measured noninvasively using a cutaneous electrogastrogram (EGG) recorder and placing electrodes on the abdominal skin.[1,2] The rhythmicity and amplitude of the gastric slow waves are used as EGG parameters, and rhythmicity in particular has high reliability and reproducibility.[3] EGG abnormalities have been reported to predict delayed gastric emptying,[4] and EGG recording is clinically used to evaluate gastric motility. Numerous EGG studies have been performed in several gastric disorders such as functional dyspepsia,[5] diabetic gastropathy,[6] and achalasia.[7] However, EGG study in neurodegenerative diseases such as Parkinson's disease (PD) and multiple system atrophy (MSA) has not been performed well.

PD is a progressive neurologic disorder and its primary neuropharmacologic feature is striatal dopamine deficiency, which develops as a result of nigrostriatal dopaminergic neuronal degeneration. The presence of Lewy bodies in the substantia nigra and other subcortical nuclei is a neuropathologic diagnostic indication of PD.[8] Autonomic symptoms, such as constipation, urinary dysfunction, and orthostatic hypotension, are common in PD patients.[9] Upper gastrointestinal (UGI) symptoms, including nausea and abdominal fullness, occur in about 30 to 70% of PD patients.[10,11] Gastric emptying studies have reported delayed emptying time in PD patients.[12,13]

MSA is a sporadic neurodegenerative disorder that includes four domains: autonomic failure/urinary dysfunction, parkinsonism, cerebellar ataxia, and corticospinal dysfunction.[14] MSA is pathologically characterized by α-synuclein-positive glial cytoplasmic inclusions.[15] Autonomic failure is a primary characteristic

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TABLE 1. *Participant profiles*

		MSA			PD		
	Control n = 8	Total n = 17	With UGI symptoms n = 3	Without UGI symptoms n = 14	Total n = 17	With UGI symptoms n = 6	Without UGI symptoms n = 11
Age (yr)	63 ± 8	64 ± 7	70 ± 11	63 ± 6	66 ± 8	68 ± 5	64 ± 10
Male:Female	5:3	13:4	3:0	10:4	6:11	2:4	4:7
Disease duration (yr)		3.2 ± 1.2	2.7 ± 0.6	3.4 ± 1.3	6.1 ± 3.6	5.0 ± 1.9	3.4 ± 1.3
Disease severity (Hoehn + Yahr)		2.3 ± 1.0	1.7 ± 0.5	2.4 ± 1.0	3.2 ± 0.5	3.0 ± 0	3.2 ± 0.6
UGI symptom							
Nausea		3 (18%)	3 (100%)	0 (0%)	6 (35%)	6 (100%)	0 (0%)
Abdominal fullness		1 (6%)	1 (33%)	0 (0%)	5 (29%)	5 (83%)	0 (0%)
Autonomic dysfunction							
Orthostatic hypotension[a]		10 (59%)	2 (67%)	8 (57%)	7 (41%)	3 (50%)	4 (36%)
Constipation		14 (82%)	3 (100%)	11 (79%)	17 (100%)	14 (82%)	3 (100%)
Urinary dysfunction		16 (94%)	3 (100%)	13 (93%)	1 (6%)	1 (11%)	0 (0%)

[a]Systolic blood pressure fall > 20 mm Hg.
MSA, multiple system atrophy; PD, Parkinson's disease; UGI, upper gastrointestinal.

of MSA, and orthostatic hypotension and urinary dysfunction are other diagnostic criteria.[16] Although UGI symptoms are uncommon in MSA, these disorders can develop into a clinical problem.[17] Two studies have reported gastric emptying time in MSA patients, and presented contrasting results: one study showed a shortened[17] while the other showed a delayed[13] gastric emptying time.

PD patients have been reported to have gastric electrical dysrhythmia.[18,19] No EGG study has been conducted in MSA patients, except for that by Suzuki et al.,[20] in which regular slow waves were recorded in the MSA patients. Although the EGG characteristics of MSA patients are still unclear, there is a possibility that EGG findings in MSA are different from those in PD. We recorded EGG activity in PD and MSA patients to elucidate the differences in EGG findings between the two diseases.

SUBJECTS AND METHODS

Subjects

Seventeen PD patients (6 males and 11 females; age 66 ± 8.3 years), 17 MSA patients (13 males and 4 females; age 64 ± 7.3), and 8 healthy control subjects with no history of gastrointestinal diseases (5 males and 3 females; age 63 ± 8.3) were enrolled in our study after obtaining their informed consent. All patients fulfilled the diagnostic criteria for PD[21] or MSA.[14] Incidences of gastric and autonomic symptoms are shown in Table 1. The patients were classified on the basis of severity of PD according to Hoehn and Yahr staging of PD[22] as follows: 1 patient was classified as stage I, 13 as stage II, and 3 as stage III. The severity of MSA was assessed using clinical stratification of spinocerebellar degeneration, a system established by the Ministry of Health, Labor, and Welfare of Japan[23] as follows: 3 patients were assessed as Grade 1, 8 as Grade 2, 5 as Grade 3, and 1 as Grade 5. One PD patient had received no medication. Sixteen PD patients had received antiparkinsonian agents: 10 had received only levodopa/dopa decarboxylase inhibitor (DCI) (150–600 mg/day) and 6 patients received combination therapy of levodopa/DCI (300–1,000 mg/day) and dopamine agonist (n = 3, cabergoline 2–4 mg/day; n = 1, pergolide 0.75 mg/day). Four MSA patients received no medicines. Six MSA patients received taltirelin hydrate (10 mg/day). Seven MSA patients received antiparkinsonian agents: 4 of these received only levodopa/DCI (200–300 mg/day) and 3 received combination therapy of levodopa/DCI (300–450 mg/day) and dopamine agonist (n = 2, cabergoline 3 mg/day; n = 1, bromocriptine 7.5 mg/day). One received only amantadine hydrochloride (150 mg/day). None of the patients had received anticholinergic drugs. All the patients continued their medication under observation. All participants gave their informed consent. The experiments conformed to the Declaration of Helsinki.

EGG Measurement

Gastric myoelectrical activity was measured for 24 hours using a portable four-channel EGG recorder (Nipro EG; Nipro, Japan) at a sampling rate of 1 Hz. Five surface electrodes (Vitrode J; Nihon Kohden, Japan) were placed on the abdominal skin surface as

described previously.[20] During the study, all the subjects were instructed to abstain from alcohol and smoking and were instructed to stay in a recumbent position for 60 minutes before and after each meal. They were also instructed to follow their normal daily activities, including light physical exercise and regular sleep, and to record their activities along with the accurate time and duration of the activity in an activity report sheet.

EGG Analysis

The EGG data were downloaded to a personal computer and analyzed using EGS2 Ver.1.31 software (Gram, Japan). Based on the daily activity report, we selected eight segments for analysis from the 24-hour EGG recording. Three 20-minute segments were selected 15 to 45 minutes before (prebreakfast, prelunch, and predinner EGG segments) and after (postbreakfast, postlunch, and postdinner) each meal. We chose two 20-minute segments from the recording conducted during sleep: an early-sleep segment selected 1 to 2 hours after going to bed and a late-sleep segment selected 1 to 2 hours before waking up.

Visual Inspection

We inspected raw EGG recordings and determined whether the gastric slow wave was regular. The slow waves were considered regular when they were rhythmical for more than 80% of the total analysis time.

Overall Power Spectrum Analysis

We performed power spectral analysis for each EGG segment using a fast Fourier transform (FFT) with an analysis range 1.6 to 9.0 cpm. The frequency at which the overall power spectrum displayed peak power in the range 2.0 to 4.0 cpm was defined as the dominant frequency (DF).[1] The frequency ranges were classified into low (1.6–2.0 cpm; LFR), normal (2.0–4.0 cpm; NFR), and high (4.0–9.0 cpm; HFR) frequency ranges. We calculated the ratios of LFR (LFR%), NFR (NFR%), and HFR (HFR%) components as percentages of total power.

Instability Coefficient of Dominant Frequency

We performed a running spectral analysis to obtain the instability coefficient of the dominant frequency (ICDF). During running spectral analysis, we applied FFT to consecutive 256-s signal stretches with 75% overlap. ICDF was defined as the ratio of standard deviation to the mean value of the EGG peak frequencies obtained by running spectrum analysis.[2]

Effect of Meal on EGG

To evaluate the effect of meal on EGG, we compared the average values of preprandial data (prebreakfast, prelunch, and predinner data) with that of postprandial (postbreakfast, postlunch, and postdinner data).

Statistical Analysis

All data are expressed as mean ± SD. Analysis of variance (ANOVA) was performed to compare the three groups. For the cases in which the values showed significant differences in ANOVA, we used the post hoc Scheffe's test to compare the three groups. We used Wilcoxon's signed rank sum test to compare the preprandial values with postprandial values and the

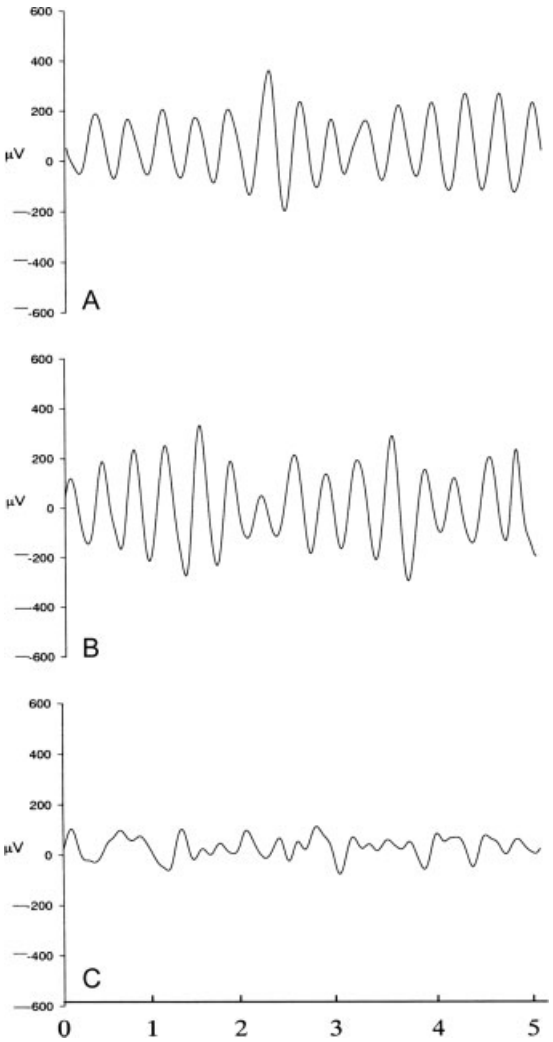

FIG. 1. Raw electrogastrographic recordings in a healthy control (**A**), multiple system atrophy (MSA) (**B**), and Parkinson's disease (PD) (**C**) patients in the fasting state.

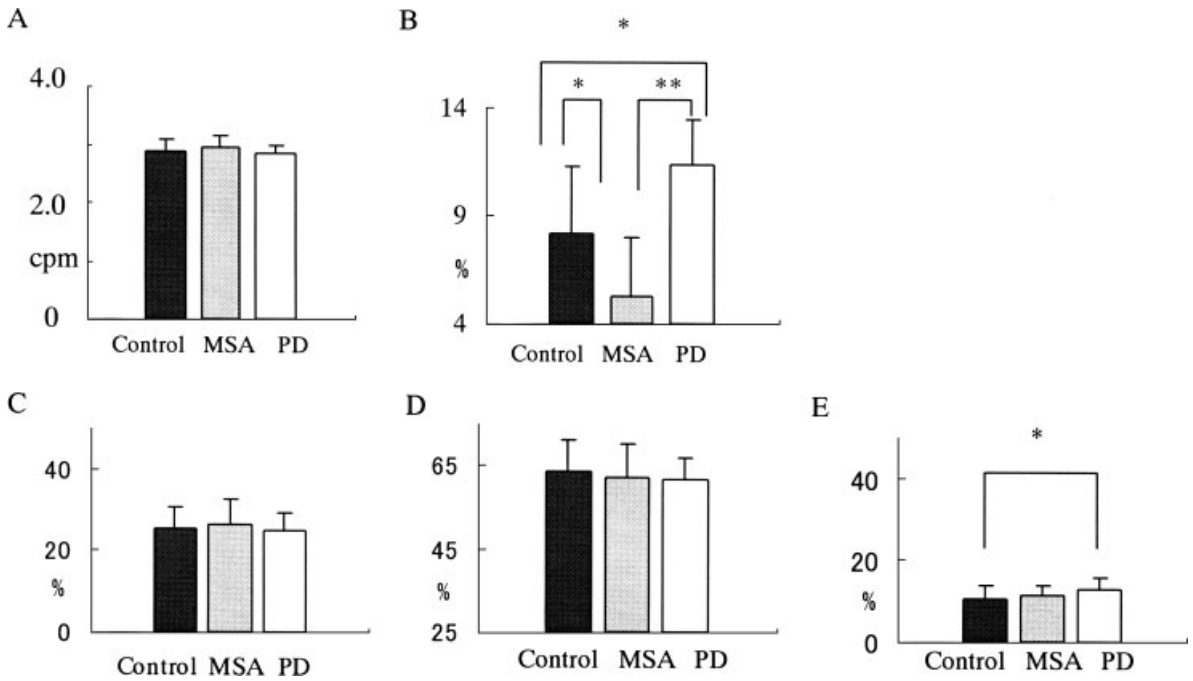

FIG. 2. Eight-segment averages for dominant frequency (**A**), instability coefficient of dominant frequency (**B**), low-frequency range (LFR%) (**C**), normal-frequency range (NFR%) (**D**), and high-frequency range (HFR%) (**E**) of control, multiple system atrophy (MSA), and Parkinson's disease (PD) patients. $*P < 0.05$; $**P < 0.01$.

Mann-Whitney test to compare the two patient groups. Spearman rank-correlation coefficient was used to estimate whether each EGG parameter correlated with the disease duration, severity of disease, and L-dopa dose. Statistical significance was considered when $P < 0.05$.

RESULTS

Visual Inspection

All control and MSA patients showed regular slow waves in raw EGG, whereas all PD patients showed irregular slow waves (Fig. 1A–C).

Dominant Frequency

No significant differences were detected in the average DF of the eight segments among the PD (2.87 ± 0.12 cpm), MSA (2.95 ± 0.21 cpm), and control (2.87 ± 0.2 cpm) groups (Fig. 2A). Figure 3A shows the circadian change in DF. In control group, DF did not change after waking up, and increased after each meal. DF after a meal was similar to that during sleep. Although MSA patients showed circadian changes in DF similar to those of the controls, the DF responses to meal intake in the MSA patients were lower than those in the controls. In PD patients, DFs were maintained at an almost constant level through 24 hours. The postprandial average DF was higher than the preprandial average in each group. Increase in DF because of meals was significantly smaller in PD patients than in controls whereas in MSA patients, it was not significantly different from that in controls (Table 2).

Instability Coefficient of Dominant Frequency

The ICDF average of the eight segments in MSA patients (5.3% ± 2.8%) was significantly lower than that in controls (8.2% ± 3.1%, $P < 0.05$) and PD patients (11.3% ± 2.1%, $P < 0.01$). The ICDF average in PD patients was significantly higher than that in controls ($P < 0.05$) (Fig. 2B). ICDF was maintained at a constant level for 24 hours in each group (Fig. 3B). The postprandial ICDF average was not significantly different from the preprandial ICDF average in each group. No significant differences were detected in ICDF changes caused by meals among the PD, MSA, and control groups (Table 2).

Frequency Ranges

There were no significant differences in LFR% and NFR% averages of the eight segments among the PD (24.9% ± 4.3%, 62.0% ± 5.0%), MSA (26.4% ±

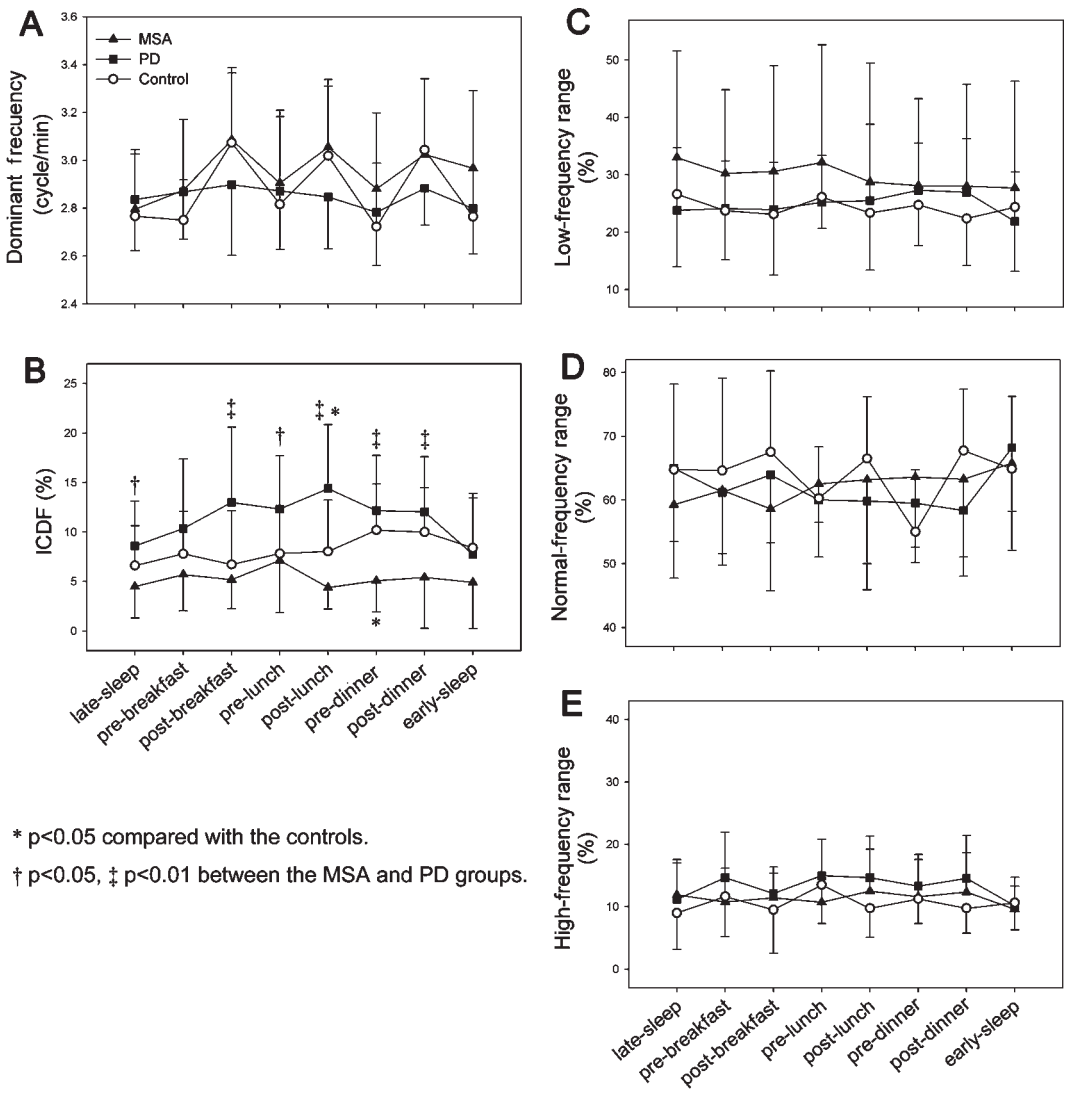

FIG. 3. Changes during 24 hour in each group for dominant frequency (DF) (**A**), instability coefficient of dominant frequency (ICDF) (**B**), low-frequency range (LFR%) (**C**), normal-frequency range (NFR%) (**D**), and high-frequency range (HFR%) (**E**) of control, multiple system atrophy (MSA), and Parkinson's disease (PD) patients.

6.2%, 62.2% ± 8.16%), and control (25.4% ± 5.2%, 63.9% ± 7.3%) groups (Fig. 2C,D). The average HFR% of the eight segments in the PD patients (13.2% ± 2.9%) was significantly higher than that in the controls (10.6% ± 3.3%, $P < 0.05$) (Fig. 2E). Moreover, NFR% did not change after waking up and increased after each meal in the controls. NFR% after meals was similar to that during sleep. LFR% and HFR% showed changes opposite to that of NFR% in the controls. LFR%, NFR%, and HFR% were maintained at an almost constant level for 24 hours in the PD and MSA groups (Fig. 3C–E). In the controls, the postprandial average NFR% was significantly higher than the preprandial average NFR%, and the postprandial average LFR% and HFR% were significantly lower than the preprandial average LFR% and HFR%. No significant differences were detected in the pre and postprandial averages of LFR%, NFR%, and HFR% among the three groups.

The LFR% reduction caused by meals in the PD patients was significantly smaller than that in controls, whereas in the MSA patients, it was not significantly different from that in controls. The increase in NFR% caused by meals in the MSA patients were significantly

TABLE 2. *Preprandial and postprandial values and amounts of change in dominant frequency (DF), instability coefficient of dominant frequency (ICDF), low-frequency range (LFR%), normal-frequency range (NFR%), and high-frequency range (HFR%)*

	Control	MSA	PD
DF (cpm)			
Preprandial	2.76 ± 0.21	2.89 ± 0.25	2.85 ± 0.16
Postprandial	3.05 ± 0.26**	3.06 ± 0.21**	2.93 ± 0.19*
Change	0.29 ± 0.26	0.17 ± 0.15	0.08 ± 0.16‡
ICDF (%)			
Preprandial	8.60 ± 4.53	5.96 ± 4.03	11.62 ± 6.00
Postprandial	8.25 ± 5.03	4.99 ± 3.40	13.14 ± 6.55
Change	−0.35 ± 4.19	−0.97 ± 2.79	1.52 ± 4.92
Low-frequency range (%)			
Preprandial	27.88 ± 5.6	30.18 ± 16.74	25.47 ± 8.31
Postprandial	22.96 ± 6.54*	29.12 ± 18.96	25.55 ± 10.62
Change	−4.92 ± 4.17	−1.06 ± 5.26	−0.08 ± 4.97
Normal-frequency range (%)			
Preprandial	59.96 ± 8.27	62.53 ± 9.59	60.24 ± 9.34
Postprandial	67.25 ± 8.23*	61.67 ± 12.74	60.71 ± 11.95
Amount of change (Δ)	7.29 ± 5.25	−0.86 ± 7.34†	0.47 ± 7.14
High-frequency range (%)			
Preprandial	12.13 ± 4.04	11.02 ± 5.01	14.31 ± 5.98
Postprandial	9.67 ± 3.36*	12.08 ± 5.66	13.76 ± 5.89
Change	−2.46 ± 2.42	1.06 ± 4.99	−0.55 ± 0.18

MSA, multiple system atrophy; PD, Parkinson's disease; DF, dominant frequency, ICDF, instability coefficient of dominant frequency.
*$P < 0.05$; **$P < 0.01$; compared to before the meal; Wilcoxon's signed rank-sum test.
†$P < 0.05$; ‡$P < 0.01$; compared to the control group; Scheffe's test.

smaller than those in controls. There were no significant differences in HFR% changes caused by meals among the three groups (Table 2).

Correlation between Clinical Features and EGG Findings

The 17 PD patients were classified into 6 patients with UGI symptoms (2 men, age 68.2 ± 5.2, disease duration 5.0 ± 1.9 years) and 11 without UGI symptoms (4 men, age 64.2 ± 9.6, disease duration 6.7 ± 4.2 years). The 17 MSA patients included 3 with (3 men, age 69.7 ± 10.6, disease duration 2.7 ± 0.6 years) and 14 without UGI symptoms (10 men, age 63.2 ± 6.3, disease duration 3.4 ± 1.3 years). UGI symptoms included nausea and abdominal fullness (Table 1). No significant differences were observed in DF, ICDF, LFR%, NFR%, and HFR% between the subgroups with and without UGI symptoms in each patient group. DF, ICDF, LFR%, NFR%, and HFR% did not significantly correlate with L-dopa dose, disease severity, or disease duration in any patient group.

DISCUSSION

The PD patients showed irregular slow waves, which were objectively represented as high ICDF (dysrhythmia) and high HFR% (tachyrhythmia). The slow wave abnormality indicates gastric pacemaker dysfunction, because gastric slow waves originate from the pacemaker cells located in the greater curvature at the junction of the proximal and distal stomach. Interstitial cells of Cajal (ICC), located in the greater curvature of the stomach, are considered as gastric pacemaker cells because they generate rhythmic depolarizations with the same frequency as the slow waves.[24] Although no pathological study has been conducted on ICC in PD, Auerbach's and Meissner's plexuses of the alimentary tract, which are closely related to ICC,[25] have been reported to be involved in PD.[26,27] The irregular slow waves in the PD patients might have reflected the involvement of ICC, enteric plexuses, or both.

The MSA patients showed regular rhythmicity in slow waves. Suzuki et al.[20] also reported that MSA patients had regular slow waves, which indicates intact gastric pacemaker function. Autonomic lesions were central and preganglionic in MSA patients, whereas in PD patients, postganglionic neurons can also be affected along with central and preganglionic neurons. Obvious pathological change in the enteric nervous system has not been reported in MSA. With regard to the cardiac sympathetic innervation, postganglionic neurons are intact in MSA, whereas they are involved in PD.[28] Unlike in PD, the enteric nervous system might be intact in MSA. Moreover, the MSA patients in our study showed a low ICDF, which reflects a

reduction in the variability of the gastric pacemaker rhythm. Low ICDF in the MSA patients indicates involvement of the system mediating the slow wave rhythm. The autonomic nervous system, particularly the parasympathetic vagus nerve,[29] as well as enteric peptides,[30] play an important role in the control of the gastric pacemaker rhythm. In our study, ICDF reflected DF variability during a relatively short time, because we analyzed 20-minute EGG segments to obtain the ICDF. The enteric endocrine system is considered to regulate gastric motility for relatively longer periods, compared with the autonomic nervous system. Therefore, the ICDF value obtained is considered to mainly reflect neurogenic regulation. The dorsal motor vagal nucleus is involved in MSA.[31] Low ICDF values in our MSA patients might reflect an impaired gastric parasympathetic function.

Both DF and NFR% increased after meals in the controls, similar to that in previous studies.[18,19] The DF and NFR% responses to meal intake were reduced in the PD and MSA patients. In a previous study,[18] PD patients showed an absent or diminished DF response to meal intake. Suzuki et al.[20] did not refer to a DF response to meal intake in PD and MSA patients: however, the DF response to meal intake seems to have been diminished in their MSA patients compared with their healthy controls. The poor DF and NFR% responses after meals in our PD patients might be considered as indicators of impaired gastric pacemakers, because our results indicate gastric pacemaker dysfunction in PD. Another possibility is that involvement of parasympathetic nerves might have caused a diminished EGG caused by meal intake. DF increase in response to meals has been reported to be diminished after vagotomy.[32] The dorsal motor vagal nucleus is impaired in both PD[33] and MSA.[31]

Lindberg et al.[34] and Suzuki et al.[20] reported DF exhibited circadian rhythm in healthy subjects: DF was high during daytime and low during night while sleeping. Suzuki et al.[20] reported that the DF circadian rhythm was disrupted in MSA patients. DF in the fed state was higher than that in the fasting state or during sleep in our control patients, and DF in the fasting state was similar to that during sleep. Previous studies have demonstrated similar circadian rhythm of DF.[20,34] Our study did not show significant correlations between the EGG parameters and clinical background, including disease duration, severity, L-dopa dose, and UGI symptoms. There has been no report on the relationship between gastric motility and the clinical background in MSA. In PD, EGG abnormalities[35] and delayed gastric emptying time[10,36] might not be necessarily related to disease duration, severity, or L-dopa treatment. Many factors influence gastric electroactivity and motility. Aging[37] and antiparkinsonian medications[38] inhibit gastric motility. Furthermore, gastric emptying, suspected to be related to EGG findings,[4] might be accelerated in treated PD patients with motor fluctuations.[10] As a result, gastric motility might show high variability in PD patients,[11,36] making it difficult to reveal the relationship between EGG and clinical features in PD.

In conclusion, our PD patients showed irregular slow waves and high ICDF which indicates an impaired gastric pacemaker rhythm in PD. Our MSA patients showed regular slow waves and low ICDF which might reflect impaired vagal parasympathetic activity.

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