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Analysis of Diagnostic Value of Electrogastrography for Parkinson's Disease and its Predictive Value for the Disease Progression

Zhining Li,[1] You Lv,[1] Xingyi Cao,[1] Liangqun Rong,[1] Xiue Wei,[1] Haiyan Liu,[1] Zhendong Wang[2] and Aiping Gong[1]

[1]Department of Neurology, The Second Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu, China
[2]Digestive Department, The Second Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu, China

The study aimed to evaluate the diagnostic and prognostic value of indexes detected by electrogastrography in Parkinson's disease patients. One hundred twenty early Parkinson's disease patients and 120 healthy controls were recruited, and underwent electrogastrography to detect dominant frequency (DF), instability coefficient of DF (ICDF), low frequency range (LFR), high frequency range (HFR), and normal frequency range (NFR). The receiver operating characteristic (ROC) curve was drawn for the diagnostic value analysis. The motor function was scored with the Unified Parkinson's Disease Rating Scale (UPDRS). Sniffin' Sticks test was used for the olfactory evaluation, and the TDI score consisting of odor threshold (T), odor discrimination (D) and odor identification (I) tests was calculated. The preprandial ICDF of Parkinson's disease patients was significantly higher than that of the control group, and decreased slowly during the late postprandial phase. The levels of LFR%, HFR% and NFR% in Parkinson's disease patients were higher than the control group during both the preprandial and late postprandial phase, and the changes of each index before and after meals were not obvious. Preprandial ICDF value and TDI score had the ability to distinguish Parkinson's disease patients with the AUC of 0.874 and 0.859 respectively. The ICDF detected by electrogastrography has high clinical value in the early diagnosis of Parkinson's disease, and the combination of ICDF and TDI can improve the diagnostic sensitivity and specificity of a single indicator. High ICDF levels during the preprandial phase are related to the poor prognosis of Parkinson's disease patients after treatment.

Keywords: electrogastrography; gastrointestinal dysfunction; instability coefficient of dominant frequency; Parkinson's disease
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Introduction

Parkinson's disease (PD) is a neurodegenerative disease characterized by the degeneration of dopaminergic neurons in the substantia nigra and the decrease of dopamine transmitters in the striatum (Jalakas et al. 2019). Recent studies have shown that PD patients usually show clinical symptoms when the number of cells in the substantia nigra is reduced by more than half and dopamine levels in the putamen by more than four-fifths (https://doi.org/10.1016/j.ebiom.2017.09.009). And tissue degeneration in certain parts of the brain is irreversible. Therefore, effective drug therapy should be taken at the early stage of PD to reduce irreversible degeneration of brain tissue and improve the prognosis of patients.

The main clinical manifestations of PD patients are static tremor, bradykinesia, muscle rigidity and postural disorder (Honarmand Tamizkar et al. 2021). However, non-motor disorders such as cognitive dysfunction, mental disorders, sleep disorders, autonomic nervous function and sensory disorders also have a higher incidence of PD (Nielsen and Skovbolling 2021). Gastrointestinal dysfunction is an important clinical manifestation of PD patients, with an occurrence rate of 70-80% (Kuai et al. 2021), which

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Correspondence: Aiping Gong, Department of Neurology, The Second Affiliated Hospital of Xuzhou Medical University, No. 32 Meijian Road, Xuzhou, Jiangsu 221000, China.
e-mail: gong_aiping@163.com

causes psychological and physical harm to patients, as indicated by multiple studies. Gastrointestinal dysfunction even appears before the neurological symptoms of PD patients, and the severity of gastrointestinal dysfunction is closely related to the severity of PD (Liu et al. 2020). Therefore, gastrointestinal function assessment may have certain clinical value in the early diagnosis of PD.

Electrogastrogram (EGG) is a noninvasive test that records gastric electrical activity according to the body surface projection position of the upper abdomen stomach (Wolpert et al. 2020). The upper part of the gastric body in the greater curvature is the starting point area of gastric electricity. The periodic electrical activity starts from here and spreads to the pylorus direction. The slow wave frequency of human is 3 times per min. A large number of studies have confirmed that EGG can record and reflect the gastric motility (Tokmakci 2007; Sha et al. 2009; Herbert et al. 2012). The dominant frequency (DF) of EGG can reflect the slow wave frequency of stomach and determine the maximum contraction frequency of stomach (Duboc et al. 2020). The relative changes of amplitude before and after meal in EGG were related to the contraction of stomach. Normal gastric electrical rhythm is related to normal gastric motility, while abnormal rhythm is related to gastric motility disorder (Rajamanuri et al. 2021). The instability coefficient of DF (ICDF) refers to the variation of slow wave (SW) frequency, which is calculated as the ratio of the standard deviation to the mean of SW frequency, which may increase in patients with gastrodynamic diseases (Czerwionka-Szaflarska and Parzecka 2006).

In the current study, early PD patients were enrolled and underwent EGG. The indexes detected by EGG were compared between PD patients and healthy controls before and after treatment.

Materials and Methods

Study subjects

One hundred and twenty patients with early PD (duration of motor symptoms < 3 years) admitted to our hospital were selected as the research object. Inclusion criteria are as follows: the patients meet the diagnostic criteria of PD established by the National Extrapyramidal Conference; the patient's Hoehn-YAHR grade was I-II; the patients did not receive any treatment before enrollment; the patients were informed of the study subject, voluntarily participated in it and signed the informed consent; this study was approved by the Ethics Committee of The Second Affiliated Hospital of Xuzhou Medical University. Exclusion criteria are as follows: secondary PD caused by drugs, tumor, infection, trauma, cerebrovascular disease, etc.; brain CT examination showed obvious bilateral basal ganglia calcification, lacunar infarction of striatum, abnormal white matter and hydrocephalus; with mental illness. A total of 120 healthy subjects were selected as the control group.

Electrogastrogram examination

The subjects stopped using gastric motility drugs and antiacid drugs within 3 days, and abstained from irritating food, greasy food, tobacco and alcohol. The subjects were fasting for more than 8 h. According to the projection of gastric body and gastric antrum on the body surface, the electrodes were placed on the corresponding parts of the upper ventral body surface, and a conductive lake was coated between the electrodes and the skin. EGEG-8D type 8-channel gastroenteroelectrograph produced by Hefei Keli Photoelectric Technology Co., LTD., Hefei, China was used to monitor the electrogastrogram on fasting and postprandial. The patient was placed in supine position to complete the standard meal and to avoid electrode position changes as much as possible. A total of 75 min of electrogastrogram was recorded, including 35 min before meal and 40 min after meal (including feeding time). In the 75 min, three 20-min clips were selected, including preprandial (10-30 min) and early (35-55 min, including meal intake time) and late (55-75 min) postprandial states.

Observational index

The indicators of electrogastrogram mainly include DF and frequency range. The frequency ranges were divided into three groups, including low frequency range (LFR, 1.6-2.0 cpm), high frequency range (HFR, 4.0-9.0 cpm), and normal frequency range (NFR, 2.0-4.0 cpm). In addition, motor function of all patients was scored with the Unified Parkinson's Disease Rating Scale (UPDRS) before and 6 months after treatment.

Olfactory test

The Sniffin' Sticks test is purchased from Burghart Messtechnik GmbH, Holm, Germany. It consists of three tests of smell function, including Odor threshold (T) test, Odor discrimination (D) test and Odor identification (I) test. The patient's eyes were closed during the measurement of the odor threshold and the odor discrimination threshold to prevent visual recognition of the reagent. The sum of the above T, D and I scores is the total TDI score, namely the total olfactory score.

Statistical analysis

SPSS 21.0 was applied for the data analysis, and the data were expressed as mean value and standard deviation (SD). The sample size estimation was based on preliminary data, and calculated by using a two independent proportions power analysis with alpha = 0.05 and a power of 90% (beta = 0.1). And the results indicated at least 68 individuals are needed for each group. Comparisons between groups were done via paired sample T test or ANOVA analysis. The receiver operating characteristic (ROC) curve was drawn for the diagnostic value evaluation. Youden Index (Youden index = sensitivity + specificity −1) was calculated, and the best sensitivity and specificity were achieved by using the optimal diagnostic threshold. Pearson's correlation was

performed for the association analysis.

Results

Basic clinical information of the study subjects

One hundred and twenty PD patients and another 120 healthy controls were recruited in the present study. As shown in Table 1, the two study groups were age and sex-matched ($P > 0.05$). In addition, their body mass index (BMI) showed no significant difference between the PD and control groups ($P > 0.05$). The mean course of all PD patients was 1.62 ± 0.85 years, in which 41 cases were tremor type, 27 were stiffness type and 52 were mixed type.

Comparison of EGG-related parameters between the two groups

As shown in Fig. 1A, the DF value of PD patients was lower than the control group at any moment, but the difference was not significant ($P > 0.05$), and DF decreased in both groups in the postprandial period after meal intake. PD patients exhibited high ICDF values than the controls during both preprandial and late postprandial phase, but the difference was significant only during preprandial phase, and it did not reach the significant level during the late preprandial phase (Fig. 1B, $P < 0.001$). It can be seen that meal intake led to the increase of ICDF in the early phase for both groups (Fig. 1B). Also significantly high levels of LFR% were detected in PD patients in both preprandial and late postprandial phase (Fig. 1C, $P < 0.01$). In addition, PD cases also owned low NFR% and high HFR% than the control group, but the difference did not reach a significant level (Fig. 1D, E, $P > 0.05$). In conclusion, the influences of eating on EGG indexes of PD patients were slighter than that of controls.

Diagnostic value of ICDF and TDI score

As shown in Fig. 2A, ICDF levels were compared

Table 1. Comparison of general data between the Parkinson' disease (PA) and control groups.

Items	Control group (n = 120)	PD group (n = 120)	*P* value
Age, years	60.95 ± 5.19	60.13 ± 6.09	0.255
Sex, n (%)			0.699
Male	62 (51.67)	59 (49.17)	
Female	58 (48.33)	61 (50.83)	
BMI, kg/m^{-2}	22.90 ± 2.85	22.71 ± 3.24	0.629
Course of disease, Years	–	1.62 ± 0.85	–
classification, n (%)			–
Tremor type	–	41 (34.17)	
Stiffness type	–	27 (22.50)	
Mixed type	–	52 (43.33)	

Data are shown as n (%) or mean ± SD. Comparisons between the two groups were done via chi square test or one way ANOVA analysis.
BMI, body mass Index.

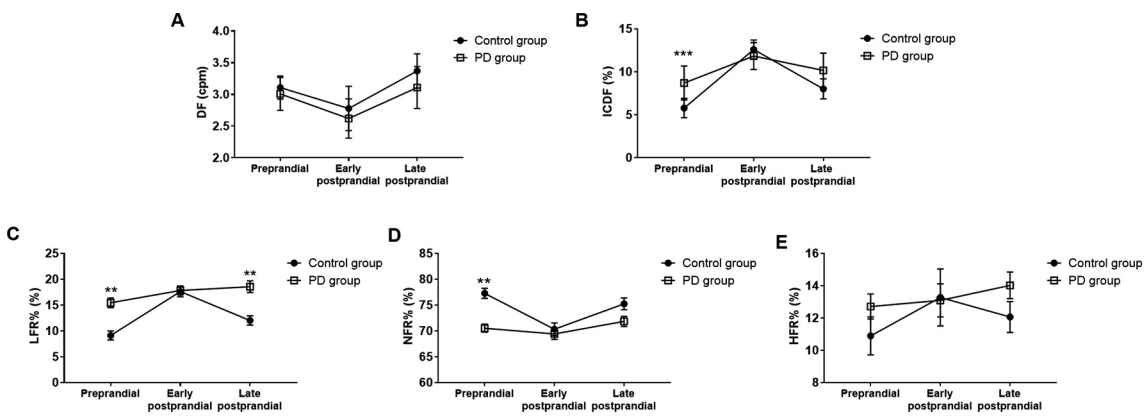

Fig. 1. Comparison of EGG-related parameters between the Parkinson's disease (PD) patients and control groups. The changes of indexes detected by EGG during the preprandial, early and late postprandial phase, including dominant frequency (DF) (A), instability coefficient of dominant frequency (ICDF) (B), low frequency range (LFR)% (C), normal frequency range (NFR)% (D) and high frequency range (HFR)% (E). $^{**}P < 0.01$; $^{***}P < 0.001$, in comparison with control group.

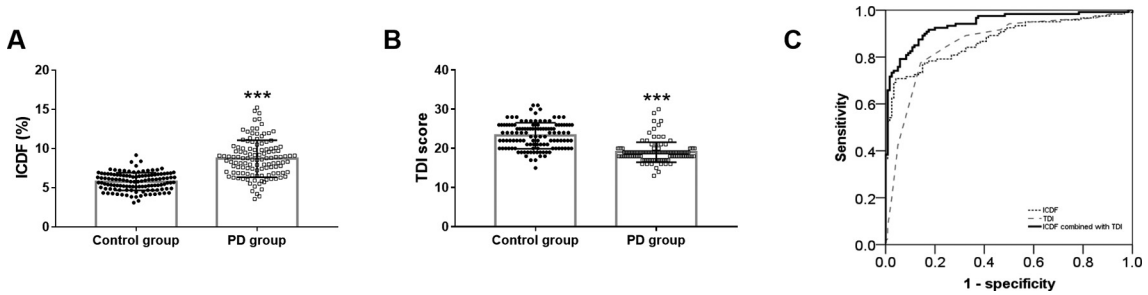

Fig. 2. Diagnostic value of instability coefficient of dominant frequency (ICDF) and TDI score in Parkinson's disease (PD). A. Increased ICDF in PD patients during the preprandial phase. B. Decreased TDI score in PD patients. C. ROC curves of ICDF, TDI score and their combination. ***$P < 0.001$.

Table 2. The diagnostic value of instability coefficient of dominant frequency (ICDF) and TDI for early Parkinson's disease (PD).

Items	AUC	95% CI	Sensitivity	Specificity	*P* value
ICDF	0.874	0.828-0.919	70.80%	95.80%	< 0.001
TDI	0.859	0.810-0.909	77.50%	85.80%	< 0.001
ICDF combined with TDI	0.94	0.910-0.970	87.50%	87.00%	< 0.001

TDI, odor threshold (T) test, odor discrimination (D) test and odor identification (I) test.
AUC, area under the curve; CI, confidence interval.

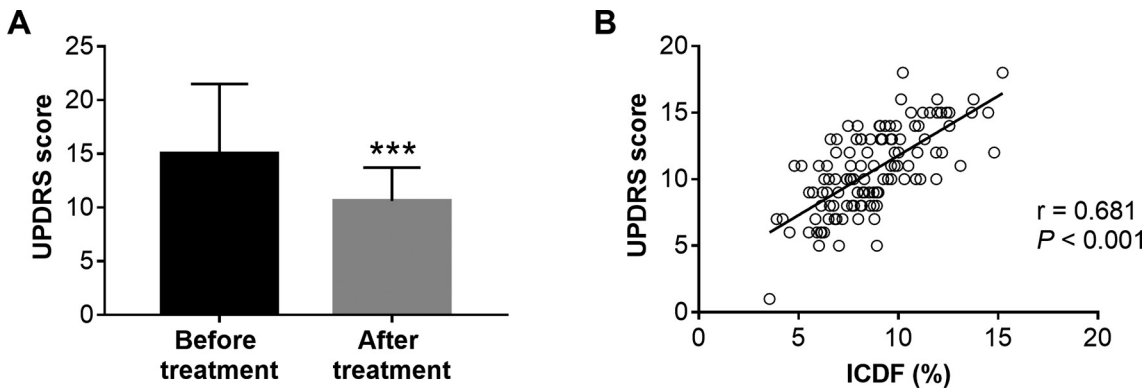

Fig. 3. Correlation of instability coefficient of dominant frequency (ICDF) with clinical prognosis. A. Patients' UPDRS score decreased significantly after 6 months of treatment. ***$P < 0.001$. B. ICDF levels during the preprandial phase were significantly correlated with the UPDRS score after 6 months of treatment.

between the case and control groups during the preprandial phase. A significantly increased level of ICDF was detected in PD patients in comparison with the control group ($P < 0.001$). In addition, decreased TDI score was identified in PD patients compared with the control group (Fig. 2B, $P < 0.001$). In light of the significant changes of the two scores between PD patients and healthy controls, their diagnostic value for PD was further examined by drawing ROC curve. As shown in Fig. 2C and Table 2, ICDF owned the diagnostic ability to identify PD cases from healthy people with the AUC of 0.874, the diagnostic sensitivity and specificity were 70.8% and 95.8% respectively. The AUC of TDI score was 0.859, with the sensitivity and specificity of 77.5% and 85.8% respectively. Furthermore, the combined diagnostic value of ICDF and TDI score was calculated. It can be seen that the sensitivity (87.5%) and specificity (87.0%) of the combined diagnosis of ICDF and TDI score were enhanced, and the AUC was 0.940.

Correlation of ICDF with clinical prognosis

After 6 months of treatment, the Patients' motor function was assessed by recording UPDRS scores. As shown in Fig. 3A, the paired sample t-test results demonstrated that patients' UPDRS score decreased significantly after 6 months treatment ($P < 0.001$). Patients' UPDRS score after 6 months treatment was used to evaluate the clinical prognosis of the patients, and its correlation with ICDF was calculated. Furthermore, Pearson's correlation analysis results demonstrated that ICDF levels during the preprandial phase were significantly correlated with the UPDRS score after 6 months of treatment (Fig. 3B, r = 0.681, $P < 0.001$).

Discussion

In recent years, EGG has been applied more and more clinically as a research method of gastric motility physiology (Herbert et al. 2012). Due to the characteristics of non-invasive, painless, easy to accept and high repeatability, EGG detection can provide information for the diagnosis and treatment of many gastric diseases. It plays an important role in the study of digestive tract physiology, pathophysiology, pharmacology and clinical diagnosis and treatment of gastric diseases (Goodman 1952). EGG can objectively reflect the rhythm and power of gastric electricity. In the current study, we observed changes in several EGG parameters in early PD patients, including ICDF, LFR% and NFR%, reflecting patients' gastric dysfunction before treatment. Consistently, Goetze and Woitalla (2008) have suggested that about 16% of untreated PD patients had nausea and 43% had abdominal distension, which may be caused by gastric motility disorders. It is reported that nearly 70-80% of PD patients have gastric motility disorders (Kuai et al. 2021). Furthermore, gastric motility disorder can also affect the absorption of drugs in patients, leading to symptom fluctuations in PD patients (Greene et al. 2009). Therefore, gastric function examination of PD patients is very necessary for the treatment and long-term prognosis of patients.

PD is one of the main causes of disability in middle-aged and elderly people (Shichkina et al. 2020). Early diagnosis and treatment are crucial to control the progression of the disease and improve the prognosis of patients. It is previously reported that gastrointestinal dysfunction even appears before the neurological symptoms of PD patients, which may be associated with the disease severity (Parrella et al. 2019; Liu et al. 2020). Therefore, its early diagnostic value attracts our interest. In the present study, the EGG results indicated that the changes in electrogastric parameters in PD patients were small before and after meals. And in comparison with the control group, PD patients owned a remarkably increase trend of ICDF during preprandial phase. Furthermore, the ROC curve demonstrated the high diagnostic value of ICDF in identifying early PD patients from healthy controls. ICDF can reflect the variability of gastric electrical rhythm, which may attributable to the gastric dysmotility (Riezzo et al. 2013). Notably, Araki et al. (2021) have reported an increase of ICDF in PD patients compared with the healthy controls, which was consistent with the results observed in the present study. In addition, recently Araki et al. (2021) also evaluate the diagnostic value of ICDF in PD patients in a Japanese population. It is reported that preprandial ICDF can distinguish PD cases from healthy control with the AUC of 0.830 (Araki et al. 2021). Similarly, the present result also reported the diagnostic value of ICDF in PD, and the AUC was 0.874, which was just a little higher than the previous results. That might be the cause of the population difference.

It is known that impaired olfactory function is not only one of the most common non-motor symptoms of PD, but also one of the earliest preclinical symptoms of PD, even several years before the typical motor symptoms (Rossi et al. 2016). Changes in olfactory function of PD are caused by pathological changes in dopaminergic neurons in olfactory pathway. Therefore, the clinical value of olfactory function detection in the early (preclinical) diagnosis of PD has attracted much attention. Sniffin' Sticks olfactory test originated from Germany, and consisted of odor threshold test (T), odor discrimination test (D) and odor identification test (I) (Delgado-Losada et al. 2021). Olfactory test is widely used clinically because of its simplicity, cheapness and high sensitivity and specificity. In a previous study, Zhao et al. (2020) have tested the TDI score changes in PD patients to evaluate the patients' olfaction, and proposed it diagnostic ability for PD. The current findings presented that TDI score showed high identification ability for early PD patients with the AUC of 0.859, which was similar to the results from Zhao et al. (2020). Similarly, as Araki et al. (2021) reported, the AUC of OSIT-J for identifying early PD is 0.720, which is lower than the current results. But in the current study, we further calculated the combined diagnostic value of ICDF and TDI score. It can be seen that the sensitivity (87.5%) and specificity (87.0%) of the combined diagnosis of ICDF and TDI score were high, and the AUC reached 0.940. It is proposed that ICDF combined with TDI score has an important clinical value in the early diagnosis of PD patients.

The UPDRS is an effective tool for assessing the clinical severity of patients with PD (Yin et al. 2021). The higher the score, the more severe the PD's symptoms. In this study, the clinical progress of PD patients was evaluated by UPDRS after 6 months of treatment. Results showed that after 6 months of treatment, patients' UPDRS scores were significantly reduced, indicating significant efficacy. Furthermore, ICDF levels during the preprandial phase were positively correlated with the UPDRS score after 6 months of treatment. The results reflected that the clinical treatment effect is worse for gastrointestinal dysfunction patients. The reason may be that gastrointestinal dysfunction affects the absorption of drugs such as levodopa (Guebila and Thiele 2016).

In conclusion, gastrointestinal dysfunction commonly occurs in early PD patients. The ICDF detected by EGG has high clinical value in the early diagnosis of PD, and the combination of ICDF and TDI can improve the diagnostic sensitivity and specificity of a single indicator. High ICDF levels during the preprandial phase are related to the poor prognosis of PD patients after treatment.

Conflict of Interest

The authors declare no conflict of interest.

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