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A study of the non-motor symptoms in early Parkinson's disease with olfactory deficits

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Abstract. – OBJECTIVE: The aim of this study is to determine characteristics of non-motor symptoms (NMS) in early Parkinson's disease (PD) with olfactory deficits and to analyze the feasibility of diagnosing PD based on olfactory deficits.

PATIENTS AND METHODS: 62 patients without olfactory deficits in early PD (PD group), 58 patients with olfactory deficits in early PD (olfactory deficits group) and 60 healthy examined people (control group) were selected successively.

RESULTS: It was found that there was no statistical significance in the difference in ages and courses of disease among the three groups ($p > 0.05$). The percentage of males in the olfactory deficits group markedly increased, the NM-Quest score rose, the rate of cases complicated with a sleep disorder and constipation also increased significantly ($p < 0.05$). The comparison of depression occurrence rates and other NMS, as well as BUA levels in olfactory deficits group and PD group, showed no significant difference ($p > 0.05$). According to the relevant analysis, olfactory deficits were positively correlated with the occurrence of cpRBD and constipation ($p < 0.05$), while they showed no obvious correlation with depression, other NMS or the BUA level ($p > 0.05$). The degree of olfactory deficits was also positively correlated with the occurrence of cpRBD and constipation ($p < 0.05$). The prevalence rate of postural instability/gait difficulty (PIGD) in olfactory deficits group was noticeably higher than that in PD group, and olfactory deficits showed a positive correlation with the occurrence of PIGD ($p > 0.05$). A combination of NMS-Quest and Sniffin's Sticks was applied to the diagnosis of PD, and it yielded an AUC of 0.795 (sensitivity of 79.3%, specificity of 89.6%, with cutoff scores of 13.5 and 25.5 respectively). The sensitivity, specificity and accuracy all increased markedly.

CONCLUSIONS: The early PD may emerge with olfactory deficits and multiple other non-motor symptoms, and a joint application of NMS-Quest and olfactory rating can serve as a reference for the diagnosis of early PD.

Key Words:
Early Parkinson's disease, Olfactory deficits, Non-motor symptoms, NMS-Quest, UPDRSIII, HAMD, cpRBD, Blood uric acid, ROC curve.

Introduction

Parkinson's disease (PD) is a neurodegenerative disease which causes senile dementia secondary to Alzheimer's disease (AD)[1-3]. Except for some cardinal signs of the disease such as resting tremor, rigidity, bradykinesia and slow gait, various non-motor symptoms (NMS) including decreased olfactory function, depression, anxiety, sleep disorder, constipation and cognitive impairment may also occur at an average high rate of 30% to 65%[4], which depends on the course of PD[5]. Some NMS appear before the typical symptoms[6] such as olfactory deficits, pain and depression. In some it occurs simultaneously with motor symptoms[7] such as delusion, difficulty in swallowing and tumbling; and some aggravate as the motor symptoms get severe[8] such as salivation and sleep impairment. The occurrence and development mechanism of NMS in PD still remains unclear, and it can only be partially explained by the Braak et al hypothesis[9]. At present, there is no specific medicine or treatment to intervene the NMS[10]. A great number of researches have been conducted to analyze the types and occurrence of NMS in PD. It was found that olfactory dysfunction might occur in patients with early PD and develop with the ongoing course of the disease, and thus can serve as an important reference index for PD screening and intervention at the early stage[11,12]. Through analyzing the characteristics of NMS in early PD with olfactory deficits, this study attempts to explore the feasibility of diagnosing PD based on olfactory deficits.

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Patients and Methods

Patients

In this study, objects were consecutively selected from the patients who came to the hospital from January 2015 to January 2016 and were diagnosed with early PD including 62 patients without olfactory deficits (PD group) and 58 patients with olfactory deficits (olfactory deficits group). The diagnosis of PD was in accordance with the UK PD Society Brain Bank Clinical Diagnostic Criteria[13]. Subtype analysis of motor symptoms was conducted according to the method proposed by Jankovic et al[14], as the sum of "tremor items" in the Unified Parkinson's Disease Rating Scale Part III (UPDRSIII) divided by the sum of "postural instability and gait disorder (PIGD) items" in UPDRSIII. The ratio ≥ 1.5 would be classified as tremor dominant, and ratio ≤ 1.0 would be PIGD dominant. The severity of the disease was described using Hoehn and Yahr (H-Y) staging[15] in UPDRS-V, with H-Y ≤ 2 being classified as a mild disease, and H-Y > 2 as moderate and severe disease.

Inclusion criteria were: (1) Age 18 to 80 years; (2) The total course of disease were no more than 6 months according to the exact clinical symptoms and diagnosis time, and H-Y ≤ 2; (3) Treated only with medication, without any other physical or biological treatments such as acupuncture physiotherapy or electrostimulation; 4) With cognitive and comprehending abilities to finish the questionnaires and rating scales in this study; with complete data which can be used for statistical analysis.

Exclusion criteria were: (1) With essential tremor, PD caused by cerebrovascular diseases, encephalitis, medication, trauma, etc., Parkinsonism-Plus; (2) With motor or non-motor symptoms caused by other clear reasons; (3) With other neurological or psychiatric disorders, pain diseases, diseases complicated with multiple organ (heart, lung, liver, kidney) diseases, alcoholic addiction and use of sedative hypnotics; (4) With nasal or paranasal sinus diseases or operation history, obstructive pulmonary disease, cold history within 3 weeks and other diseases that influence olfactory sensation; (5) With poor compliance.

This work has been approved by the Ethics Committee of the hospital and gained informed consent from the patients and their relatives. During the same period, 60 healthy persons receiving physical examination were selected (control group).

Research Methods and Observation Index

Non-motor symptoms questionnaire (NMS-Quest) was adopted to analyze types and incidence rate of 30 NMS including olfactory dysfunction, sleep disorder, constipation, depression, anxiety, cognitive impairment, illusion, autonomic dysfunction, pain, sexual disorder, etc. In terms of scoring, 1 point was assigned for one symptom, and 0 point for the absence of the symptoms. Thus, higher score signifies higher NMS. Olfactory function tested with the method of Sniffin's Sticks in three categories including olfactory threshold, odor discrimination and odor identification. A total score of over 28 points was classified as a normal olfactory function, a score between 16 and 28 points was olfactory deficits, and score under 16 points was olfactory loss. Depression rating was conducted according to the Hamilton Depression Scale (HAMD), and scores of 20 or higher indicated depression. The occurrence rate of clinically probable rapid eye movement sleep behavior disorder (cpRBD) was estimated according to International Classification of Sleep Disorders-Revised (ICSD-R), namely the presence of limb or body movements associated with dreams, and at least one of the following: (1) harmful or potentially harmful sleep behaviors during sleep; (2) dreams that appear to be "acted out"; (3) sleep behaviors that disrupt sleep continuity. The prevalence rate of chronic constipation was judged based on Rome III Diagnosis Criteria for Constipation. Constipation would be diagnosed if 2 or more symptoms out of 6 symptoms (straining, lumpy/hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction/blockage, manual maneuvers to facilitate defection, less than 4 defections each week) occurred in the latest 3 months at a frequency of more than 25%, and the course of disease had lasted for over 6 months. Blood uric acid (BUA) levels were analyzed with conventional biochemical methods.

Statistical Analysis

SPSS 19.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for data statistics. The measurement data were shown by mean ± standard deviation. Comparison between groups was done using One-way ANOVA test followed by Post Hoc Test (LSD). Comparison among multiple groups was analyzed using one-way ANOVA, and Ccomparison between two groups

was made by *t*-test. Enumeration data were shown by % and inter group comparison was tested by X^2. X2 was also used for analysis of qualitative data; the sensitivity and specificity of diagnosis were shown by the receiver operating characteristics (ROC) curve, and the accuracy of diagnosis was analyzed through the area under the curve (AUC). If $p < 0.05$, the difference was statistically significant.

Results

Comparison of Types and Occurrence Rate of NMS

There was no statistical significance in the difference in ages and courses of disease among the groups ($p > 0.05$). The percentage of males in the olfactory deficits group markedly increased, the NM-Quest score rose, the rate of cases complicated with sleep disorder and constipation increased ($p < 0.05$). The comparison of occurrence rates of depression among the three groups was also statistically significant, while the difference between olfactory deficits group and PD group was not statistical significance. The comparison of the incidence of another NMS, as well as BUA levels among three groups, was also statistically significant ($p > 0.05$) as shown in Table I.

Correlation Between Olfactory Deficits and Other NMS

The olfactory deficits group was selected based on the method of Sniffin's Sticks, with 49 cases of olfactory deficits and 9 cases of smell loss. Relevant analysis showed that olfactory deficits were positively associated with the occurrence of cpRBD and constipation (r = 0.325, $p = 0.027$; r = 0.356, $p = 0.024$), and showed no correlation with the occurrence of depression and other NMS as well as the BUA level ($p > 0.05$). The degree of olfactory loss was also positively associated with cpRBD and constipation (r= 0.523, $p = 0.008$; r = 0.566, $p = 0.002$).

Relation Between Olfactory Deficits and Motor Symptoms

According to UPDRSIII, there were 37 tremor-dominant cases and 25 PIGD-dominant cases (40.3%) in PD group. Further, there were 24 tremor-dominant cases and 34 PIGD-dominant cases (58.6%) in olfactory deficits group. Inter-group difference was statistically signifi-

Table I. Comparison of types and occurrence rate of NMS.

Group	Cases	Male/ Female	Average age (year)	Average course of disease (month)	NMS-Quest rating	Olfactory dysfunction [case (%)]	Sleep disorder	Constipation	Depression	Others	UA (μmol/L)
PD	62	34/28	67.8 ± 8.2	3.3 ± 1.2	15.3 ± 4.2	–	5 (8.1)	8 (12.9)	16 (25.8)	5 (8.1)	423.5 ± 56.2
Olfactory deficits	58	42/16	67.2 ± 8.6	3.4 ± 1.3	18.2 ± 4.5	58 (100)	13 (22.4)	16 (27.6)	18 (31.0)	6 (10.3)	416.3 ± 53.9
Control	60	30/30	65.6 ± 8.5	–	3.4 ± 1.1	3 (5.0)	2 (3.3)	3 (5.0)	5 (8.3)	2 (3.3)	426.2 ± 55.7
F (X2)		6.761	0.432	0.536#	4.625	106.587	11.760	12.126	9.910	2.485	0.321
p		0.034	0.567	0.725	0.037	0.000	0.003	0.002	0.007	0.289	0.424

#, *t*-test.

cant (X2 = 4.015, p = 0.045), and the relevant analysis showed that olfactory deficits were positively correlated with PIGD ($p < 0.05$).

Analysis of ROC Curve

When NMS-Quest rating score was used for the diagnosis of PD, it yielded an AUC of 0.623 (95% CI: 0.251-0.864) with 62.5% sensitivity, 72.4% specificity and a cutoff score of 16.4. When the method of Sniffin's Sticks was adopted for the diagnosis of PD, it yielded an AUC of 0.567 (95% CI: 0.162-0.903) with 42.3% sensitivity, 63.7% specificity and a cutoff score of 21.2. When a combination of NMS-Quest and Sniffin's Sticks was applied to the diagnosis of PD, and it yielded an AUC of 0.795 (95% CI: 0.442-0.951) with 79.3% sensitivity and 89.6% specificity and cutoff scores of 13.5 and 25.5 respectively (Figure 1).

Discussion

The pathogenesis of NMS in PD is quite complicated. It might be related to the motor symptoms or the pathological basis of PD, or with the use of anti-PD drugs, and might be also associate with senility[16]. According to the Braak staging, Braak Stage 1 was characterized by degeneration of the olfactory bulb and the anterior olfactory nucleus, and this may manifest clinically as olfactory dysfunction. In Braak Stage 2, the degenerative process progresses gradually to the lower brainstem and the medulla oblongata, and causes autonomic nervous dysfunction. While the degeneration of raphe nuclei, locus coeruleus and pedunculopontine nucleus leads to sleep/wake cycle dysfunction and sleep disorder. A triad of cardinal motor symptoms including tremor, rigidity and bradykinesia occur in the Braak Stage 3 and 4. In Stage 5 and 6, there is the presence of Lewy bodies in the limbic system and mature neocortex in patients. Further, it leads to neurological symptoms[9] such as depression, cognitive impairment, and optical illusion may also emerge in this period[9]. However, the Braak staging still remains to be further clarified.

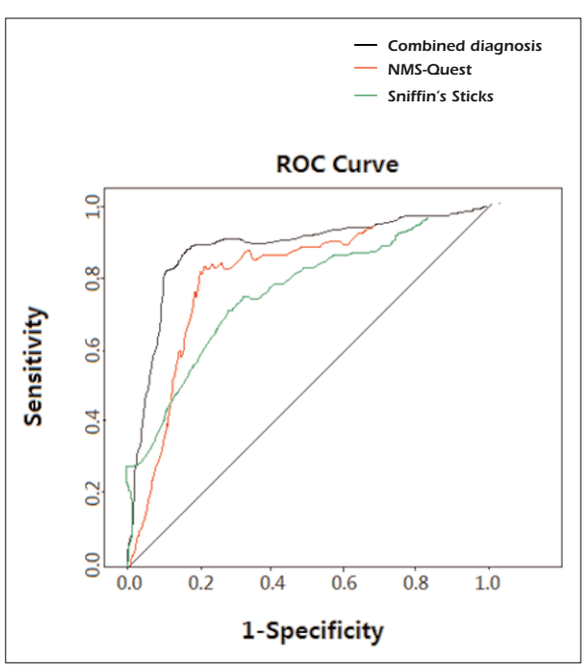

Figure 1.

Recent studies have shown[17] that olfactory dysfunction is closely connected with PD and even is the first sign of it, and the symptom aggravates with the ongoing course of the disease. Over 70% of PD patients are present with olfactory dysfunction[18]. Ross et al[19] followed 2263 normal elder people for five years, and found out that the people with olfactory dysfunction had 5.2-times the odds of developing PD compared with those without impaired olfaction, and olfactory disorder could predate PD by around 4 years, from which it can be seen that olfactory dysfunction is an independent risk factor for PD. Animal experiments[20] showed that olfactory dysfunction in PD is highly correlated with the reduced hippocampal and amygdala cholinergic activity and is poorly correlated with neurotransmitter activity, and has nothing to do with cortex cholinergic activity. Olfactory dysfunction in PD manifested as decrease and loss of olfactory function, with a low occurrence rate of phantosmia or parosmia. Olfactory impairment manifested as the overall impairment in abilities of odor threshold, odor identification, odor discrimination, odor memory and recognition, and the last damage occurs earlier and is more serious than the impairment of odor threshold[21]. PD always showed unilateral motor symptoms, but olfactory dysfunction was a bilateral symptom which differed in gender, with higher occurrence rate among male patients[22]. Besides, olfactory dysfunction was also influenced by a variety of factors including heredity, age, cognition, smoking, virus infection and trauma[23].

In this study, it can be concluded that there was no difference in the age and course of disease between the olfactory deficits group and the

PD group. As the proportion of male increase significantly, the NMS-Quest rating grew and the occurrence rate of complicating sleep disorder, as well as constipation, also increased. It indicated that male PD patients were more likely to present with olfactory deficits which may be accompanied by more NMS mainly represented by the increasing occurrence rate of sleep disorder and constipation, but was not related to the prevalence of depression or the changing BUA level. Olfactory deficits happened more often among patients with PIGD. According to the analysis of ROC curves, application of olfactory rating alone was inadequate for diagnosis of PD, while the combination of NMS-Quest and olfactory rating can remarkably improve the sensitivity, specificity and accuracy of the diagnosis.

Conclusions

To sum up, olfactory deficits and multiple other NMS may occur in early PD, and a joint application of NMS-Quest and olfactory rating can serve as a reference for the diagnosis of early PD.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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