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Factors associated with Parkinson's disease patients with hyposmia in Chines e han population: a case-control study.

Lin Wu[1,2], Yi-Ming Liu[3*]

[1]Department of Neurology, Qilu Hospital of Shandong University, Jinan, Shandong 250012, PR. China

[2]Department of Neurology, People Hospital of Rizhao City, Rizhao, 276800, PR. China

[3]Department of Neurology, Qilu Hospital of Shandong University, Jinan, Shandong 250012, PR. China

Abstract

Background: Hyposmia is important for early and differential diagnosis of Parkinson's Disease (PD); however its mechanism remains unclear. The aim of this retrospective study is to identify the clinical phenotypic associated with hyposmia in Chinese han PD patients.
Methods: We used 16-item odor identification test from Sniffin' Sticks (SS-16) to evaluate the olfactory function of 120 Chinese Han PD patients (including 62 PD patients without hyposmia (PDOH) and 58 PD patients with hyposmia (PDH) and compared them with 60 Healthy Controls (HC). We analyzed the correlation between hyposmia with disease related characteristics including motor symptoms (Tremor-Dominant (TD) type and Postural Instability and Gait Difficulty (PIGD) type) and other common Non-Motor Symptoms (NMSs) (constipation, depression and level of serum uric acid).
Results: Compared to HC, constipation, depression and level of serum uric acid showed significant difference in PDH (χ^2=37.465, P=9.3E10; tD=4.32, P=0.005; tD=3.742, P=0.01, respectively) or PDOH (χ^2=17.391, P=3.0E5; tD=4.166, P=0.006; tD=2.780, P=0.03, respectively). Constipationwas significantly associated with PDH compared to PDOH (χ^2=5.534, P=0.02), while depression and level of serum uric acid were negative(tD=0.162, P=0.89; tD=0.961, P=0.37, respectively). Patients with TD type was significantly more than those with PIGD type between PDH and PDOH (χ^2=6.487, P=0.01).
Conclusions: Tremor-dominant type and constipation may be associated with hyposmia in Chinese han PD patients, not depression and level of serum uric acid.

Keywords: Parkinson's disease, Olfactory dysfunction, Non-motor symptoms, Tremor, Constipation.

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Introduction

In 1975, Ansari and Johnson firstly reported olfactory dysfunction in Parkinson's Disease (PD) [1], which has been validated by several studies in recent years. Hyposmia is one of the common Non-Motor Symptoms (NMSs), which played a vital role in the early or differential diagnosis of PD [2]. It may occur in early stage of the disease or even before the motor symptoms. However, the clinical phenotypic characteristics in Chinese han PD patients with hyposmia were not known.

About 65% ~ 90% PD patients had olfactory impairment [3-6]. In early studyies, hyposmia was thought be an independent feature of PD and unrelated to disease stage, disease duration or neurologic signs [4]. However, a recent investigation from Japan reported that, olfactory identification scores of patients with akinetic-rigid type were lower than those with tremor-dominant type [7]. Except for hyposmia, some other NMSs such as constipation and depression may also precede the motor symptoms in epidemiological studies [8-10]. Otherwise, Jenner reported that serum uric acid might have protective function for PD patients [11].

As most previous investigations came from Japan, Europe and America, few of them could not reflect Chinese han population. Therefore, we conducted this case-control study to characterize the association between the motor or non-motor symptoms and hyposmia in Chinese han PD patients.

Materials and Methods

Participants

In this case-control study, a total of 180 adults including 62 PD patients without hyposmia (PDOH), 58 PD patients with hyposmia (PDH) and 60 Healthy Controls (HC) were studied. The age and sex matched among the three groups. Blood samples were obtained from unrelated Han Chinese individuals in the Qilu Hospital of Shandong University, Shandong, China between January 2011 and July 2014. All the patients met the Criteria of the United Kingdom Brain Bank [12] and none of

them had got functional neurosurgery for PD. Patients were excluded if they:

- Had nasal sinus diseases or olfactory diseases such as chronic sinusiti, acute upper respiratory tract infection, nose surgery or nasal polyposis
- Had PD caused by cerebrovascular disease, cerebritis, drugs or injuries
- Exhibited heart, lung, liver or kidney disease
- Had family history of PD

The study was approved by the Ethics Committee of Qilu Hospital of Shandong University. All individuals included in the study obtained written informed consents.

Clinical profiling

The motor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS III) was used to evaluate motor symptoms [13]. Depressive symptom was assessed by 17-item Hamilton Rating Scale for Depression (HAMD-17) [14]. Constipation was defined as ROME III criteria [15]. Serum Uric Acid was measured by standard clinical laboratory techniques (Roche Diagnostic, Mannheim, Germany).

Statistical analysis

The independent sample t-test and chi-square analysis were employed for comparing group means and categorical data, respectively. Statistical comparisons employed one-factor ANOVA and LSD post-hoc multiple comparisons test using age, age of onset, disease duration and level of serum uric acid among groups. All P-values were 2-sided and P-values <0.05 were taken to indicate statistical significance. SPSS 20.0 software was used for statistical analysis.

Results

Characteristics of the study participants

Table 1 showed the characteristics of the study participants. There was no difference in age, male/female, age of onset and disease duration among the three groups (PDOH, PDH and HC groups) (P>0.05).

Table 1. *Characteristics of the study participants.*

Variables	PDOH (n=62)	PDH (n=58)	HC (n=60)	P-value
Age	66.7 ± 6.4	65.1 ± 6.8	64.5 ± 7.1	0.920(F=0.085)
Male	33 (53.2)	32 (55.2)	35 (58.3%)	0.849 (χ^2=0.327)
Age of onset	59.2 ± 6.8	61.6 ± 7.6	-	-
Disease duration	3.3 ± 2.4	4.0 ± 3.2	-	-

PDOH: PD patients without hyposmia; PDH: PD patients with hyposmia; HC: Healthy Controls.

Correlation of clinical feature with PD

We studied the association of constipation and depression with PD patients. Compared to HC, constipation and depression in PDH or PDOH showed significant difference (P<0.05) (Table 2 and Table 3). Constipation was significantly different between the PDH and PDOH groups (P=0.02) (Table 3). However, there were no statistical differences in depression between the PDH and PDOH groups (P=0.89) (Table 2).

Table 2. *ANOVA and post-hoc multiple comparisons test analysis for depression and level of serum uric acid.*

Variables	PDOH	PDH	CH	P^a	P^b		
					PDOH vs PDH	PDOH vs CH	PDH vs CH
depression	5.40 ± 1.41	5.53 ± 0.95	1.97 ± 0.40	0.008(F=12.036)	0.89 (tD=0.162)	0.006 (tD=4.166)	0.005 (tD=4.328)
serum uric acid	276.87 ± 32.28	252.67 ± 29.69	346.86 ± 30.49	0.02(F=7.548)	0.37 (tD=0.961)	0.03 (tD=2.780)	0.01 (tD=3.742)

PDOH: PD patients without hyposmia; PDH: PD patients with hyposmia; HC: healthy controls. P^a, P-value was calculated by one-way ANOVA. P^b, P-value was calculated by LSD post-hoc multiple comparisons test.

Table 3. *Chi square analysis for abnormal gait and constipation.*

Variables	PDOH (n=62)	PDH (n=58)	CH (n=60)	P-value		
				PDOH vs PDH	PDOH vs CH	PDH vs CH
TD/PIGD	30/32	15/43	-	0.01(χ^2=6.487)	-	-
Constipation	22(35.5%)	33(56.9%)	3(5%)	0.02(χ^2=5.534)	3.0E5(χ^2=17.391)	9.3E10(χ^2=37.465)

PDOH: PD patients without hyposmia; PDH: PD patients with hyposmia; HC: Healthy Controls. TD: Tremor-Dominant. PIGD: Postural Instability and Gait Difficulty.

Association of motor symptom with PD

According to the method fo Jankovic [16], PD patients were divided into two subtypes:

- Tremor-Dominant (TD) type, score of average tremor/score of postural instability and gait difficulty ≥ 1.5
- Postural Instability and Gait Difficulty (PIGD) type, score of average tremor/score of postural instability and gait difficulty ≤ 1.0. Compared to PDOH, inviduals with TD were significantly more than those with PIGD in PDH (P=0.01).

Correlation of serum uric acid with PD

As serum uric acid might play a protective role for PD patients, we investigated the association between serum uric acid and PD patients. Serum uric acid showed significant difference among CH, PDOH and PDH groups. It was still significantly different in CH vs PDOH (p=0.03), CH vs PDH (p=0.01), but negative in PDOH vs PDH (p=0.37).

Discussion

In this study, we found constipation, depression and level of serum uric acid showed significant difference in PDH or PDOH compared to HC. Constipation was significantly associated with PDH compared to PDOH, while depression and level of serum uric acid were negative. Individuals with TD type were significantly more than those with PIGD type in PDH.

Constipation was one of the most common NMSs may precede the motor symptom. The main reason for constipation maybe the change of nervous system in the intestines, resulting in dysfunction of secrettion and movement [17]. In our study, the prevalence of constipation was 56.9% in PDH and 35.5% in PDOH, which were significantly higher than 5% in HC. Meanwhile, the prevalence rates were still significantly different between PDH and PDOH. This was consistent with previous study [18]. There were two possible explanations: Firstly, Braak pathological staging indicated that the disease generally begins distally from lower brainstem and olfactory bulb, implying constipation may associate with olfactory impairment in PD [19]. Secondly, accumulating evidence suggested that constipation was a premotor biomarkers for PD [8].

PD patients were divided into two subtypes: 1) TD type; 2) PIGD, according to the Jankovic's method [16] and UPDRS III [15]. Compared to PDH, we found that individuals of TD type were significantly more than those of PIGD type in PDOH. That means Patients with TD had significantly better olfactory function than those with PIGD. Our results were in line with Stern's [20] and Iijima's [7] foundings. However, other studies have found no significant difference in tremor between patients with PDOH and PDH [21,22]. This apparent discrepancy might be related to the limited sample size and other coexisting genetic or environmental confounders. The mechanisms of the correlation between tremor and olfactory impairment is unclear. Though cerebellum is not part of the olfactory center [23], it might be involved in the transportation of smell. In other studies, smell could activated part of cerebellum [24], while olfactory dysfunction could be observed in patients with cerebellar atrophy or partly impairment in cerebellar [25,26]. Olfactory dysfunction might be correlated with cerebellar lesion in PD patients.

Conclusion

In conclusion, our study suggests that tremor-dominant type and constipation may be involved in Chinese han PD patients with hyposmia, not depression and level of serum uric acid. This study has several limitations that, a relative small sample size and all the patients were from one center. In the future, multi-center's prospective longitudinal studies in larger populations will be required to replicate and verify our findings.

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***Correspondance to:**

Yi-Ming Liu

Department of Neurology

Qilu Hospital of Shandong University

PR. China