Original Article

The Natural Progression of Parkinson's Disease in a Small Cohort with 15 Drug-naïve Patients

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Abstract

Background: The studies of the natural progression of Parkinson's disease (PD) in Chinese populations have been lacking. To address this issue and obtain a preliminary data, we conducted a PD progression assessment in 15 adults with *de novo* PD from a nutritional intervention trial (NIT) cohort in Lin County China.

Methods: Using the Copiah County screening questionnaire and United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria, we surveyed the available NIT cohort members in 2000 and diagnosed 86 patients as PD. In 2010, we resurveyed all PD patients and confirmed definite PD diagnosis in 15 cases with the rest of them being dead (54); having probable (10) PD or vascular Parkinsonism (3); refusing to participate (2); or being away (2). In both surveys, we used Hoehn and Yahr (HY) scale and assessed the disease progression. Unified Parkinson's Disease Rating Scale (UPDRS) was added to the second survey.

Results: In 2010, the average disease duration for 15 definite PD patients was 13.6 ± 7.3 years. Over a 10-year time span, 9 out of 15 patients remained at the same HY stage while the remaining 6 progressed. Rigidity (47% vs. 100%; $P = 0.002$) and postural instability (7% vs. 47%; $P = 0.005$) worsened significantly. The mean UPDRS motor scores in 2010 were 39.4 ± 23.7.

Conclusions: Overall worsening of motor function in PD seems to be the rule in this untreated cohort, and their rate of progression seemed to be slower than those reported in the western populations.

Key words: Drug-naïve; Epidemiology; Parkinson's Disease; Progression

Introduction

It has been well-documented that the neuropathologic process in Parkinson's disease (PD) involves the loss of the nigral dopaminergic neurons and dopaminergic nerve terminals in the striatum.[1] The duration of the PD prodrome has been estimated ranging from 2 to 50 years depending on the clinical feature in question, duration of follow-up, accuracy of diagnosis, age of onset, and gender.[2] Although the first appearance of motor signs requires the loss of at least 50% dopamine neurons in substantia nigra,[1,3,4] studies of the prelevodopa era were not able to provide details on the rate of progression of motor impairment using validated scores or rating scales.[5,6] More recent studies, however, showed that latencies to Hoehn and Yahr (HY) Stage IV and V could last for up to 40 years[6,7] attributing to the advent of effective symptomatic therapies with dopaminergic agents, seemingly delaying the progression of disabilities in PD.

Whereas studies from the west provided limited guidelines to characterize the natural progression of PD in population residing in countries of eastern hemisphere, researchers in this field have dealt with the lack of population-based measurements in *de novo* cohorts in China for the past several decades. To explore the natural progression of PD in Chinese people, we conducted a preliminary study among a small cohort from a well-defined nutritional intervention trial (NIT) in Lin County China.[8-11]

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Methods

Study population

In 2000, we screened and diagnosed PD cases among NIT cohort members who were available in the follow-up studies.[10,11] NIT was a randomized, double-blind,

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placebo-controlled study that evaluated the benefits of multiple antioxidants in the primary prevention of gastrointestinal cancers in Lin County from 1986 to 1991.[8,9] The initial participants were adults aged between 40 and 69 with no history of malignancy or other debilitating disease or taking any vitamin, mineral supplements regularly, or were taking specific medications when entered the NIT study. For the current study, additionally, the subjects had to reside in one of the four communes of Lin County 4 days/week or 6 months/year. In 2010, we conducted a second survey among the participants who were identified in 2000 as PD cases to verify their diagnosis and evaluate disease progression.

Informed consent was obtained from all participants during the two surveys. The Human Subjects Review Board of the Chinese Cancer Institute Chinese Academy of Medical Sciences approved this substudy.

The first survey

Ascertainment of PD cases in the NIT was reported elsewhere.[10] Briefly, potential PD cases were identified using a PD symptom screener, (Copiah County Questionnaire),[12,13] and subsequently examined by a study neurologist. For those who were either screened positive or suspected having Parkinsonism at the end of the neurological examination were further evaluated and diagnosed with the United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) diagnostic criteria.[14] At the end of the first survey, 86 participants were diagnosed as PD and were visited by a senior neurologist for further treatment and prevention at the local health stations or in their homes. The age groups, gender, and the cardinal features are illustrated in Table 1.

Table 1: Characteristics of the PD cases identified during the first survey and the second survey (*n* (%))

Characteristics	The first survey (*n* = 86)	The second survey (*n* = 15)
Age (years)		
50–59	6 (7)	3 (20)
60–69	42 (49)	8 (53)
70–79	32 (37)	4 (27)
≥80	6 (7)	0 (0)
Gender		
Female	45 (52)	6 (40)
Male	41 (48)	9 (60)
Cardinal features		
Bradykinesia	86 (100)	15 (100)
Resting tremor	83 (97)	13 (87)
Rigidity	49 (57)	7 (47)
Postural instability	26 (30)	1 (7)
HY stage		
1	14 (16)	4 (27)
2	54 (63)	10 (67)
3	18 (21)	1 (7)

Among PD patients during the first survey, none of them had HY Stage VI or V; the cardinal features are representative of classic PD clinical features as are defined in UPDRS motor scale. PD: Parkinson's disease; UPDRS: Unified Parkinson's Disease Rating Scale; HY: Hoehn and Yahr.

The second survey

In 2010, we revisited all available PD patients in their homes. In this survey, we confirmed PD diagnosis and assessed their disease progression. To confirm PD diagnosis, individuals who were diagnosed in 2000 underwent a detailed neurological examination by study neurologists according to a standardized diagnostic protocol which was used in the previous survey.[10] The protocol was comprised of a neurological history and a detailed examination. To establish the diagnosis of idiopathic PD, in addition to the accurate history, examination and medical records, UKPDSBB clinical diagnostic criteria was still applied. Those participants who did not meet the full clinical diagnostic criteria or was clearly due to some other causes were given the diagnoses of probable PD, vascular Parkinsonism (VPD) or drug-induced Parkinsonism.[15]

We assessed PD progression using HY scale, which was also applied in the first survey. Unified Parkinson's Disease Rating Scale (UPDRS)[16] part III, motor score was added in this section to further characterize the Parkinsonian features of these treatment-naïve patients.

Among 86 PD patients diagnosed during the first survey, only 28 were available for reexamination with 15 (9 men and 6 women) confirmed of PD diagnosis, and 10 probable PD, 3 VPD in 2010. For the rest 58 patients, 54 deceased at the time of second survey (22 died of stroke, 10 cancer, 17 cardiovascular disease, and 5 nonspecified illnesses), 2 refused to participate, and 2 were out of the county.

We provided health care information and dispatched medicine (including artane and carbidopa/levodopa/entacapone) to the patients diagnosed as PD or probable PD in the two surveys. Due to economic limitations, these 15 patients refused to take any anti-Parkinsonism medication, and we have confirmed this with the patients, their relatives, and the village doctors.

Statistical analysis

Data were analyzed using SPSS 17.0 statistical software (SPSS Inc., USA). Continuous data were expressed as mean ± standard deviation (SD), or median (ranges). Mean values were compared using the paired *t*-test. The Chi-square test was used to compare categorical variables which were presented as proportions (frequency %). $P < 0.05$ was considered as statistically significant.

Results

The mean age of the 15 study patients was 61.1 ± 10.3 years at the symptom onset and 75.2 ± 6.6 years in 2010. Their mean disease duration was 13.6 ± 7.3 years in 2010. The mean mini-mental state examination and activities of daily living scales were 23 ± 3 and 13 ± 4 in 2000 and 21 ± 5 and 15 ± 3 in 2010 respectively.

The clinical features of the 15 patients are summarized in Table 2. Thirteen patients (87%, 13/15) were tremor dominant. As to the motor functions, all patients presented with bradykinesias at study entry whereas only fewer than half of

them had rigidity (47% vs. 100%; $P = 0.002$;). Resting tremor, on the other hand, was present in the majority of the patients initially with some noticeable increase in prevalence ten years later (87% vs. 93%; $P = 0.960$). These discrepancies were primarily technical as the result of the way UKPDSBB was set up. Postural instability was only present in one patient at the initial assessment and became much more prevalent 10 years later (7% vs. 47%; $P = 0.005$; Table 2). The mean UPDRS motor scores in 2010 were 39.4 ± 23.7 for total and 10.1 ± 7.4 for tremor scores (item 20 and 21); 5.8 ± 5.2 for rigidity (item 22); 16.8 ± 9.0 for bradykinesia (item 23–27; and 31).

As to the HY staging, over a 10-year time span, 9 patients remained at the same stages while 6 progressed (1.5 in 2000 vs. 3 in 2010, $t = 2.278$, $P = 0.039$). At the beginning of the study, most of the patients were at a lower stage, averaging 1.8. Ten years later, they deteriorated to 2.4, giving an overall slow progression ($P = 0.088$). It took the 15 patients 13.6 ± 5.9 years to reach the HY stages 2.4 and UPDRS motor scores 39.4 ± 23.7.

Discussion

This study represents one of the first attempts in understanding the natural progression of PD in treatment-naïve Chinese patients, underpinning the importance of addressing the disease progression without being confounded by dopaminergic interventions. In contrast, most of previous work on PD progression in other parts of the world involved patients having received levodopa therapy,[17-23] potentially biasing objective interpretation.

Table 2: Disease progression among the 15 PD patients (2000–2010)

Clinical features	2000	2010	χ^2/t value	*P*
Resting tremor, %	87	93	0.003	0.960
Rigidity %	47	100	9.886	0.002
Bradykinesia, %	100	100	NA	NA
Postural instability, %	7	47	8.612	0.005
UPDRS III total	–	39.4 ± 23.7	–	–
UPDRS–tremor	–	10.1 ± 7.4	–	–
UPDRS–rigidity	–	5.8 ± 5.2	–	–
UPDRS–bradykinesia	–	16.8 ± 9.0	–	–
HY stage	1.8 ± 0.8	2.4 ± 1.1	1.835	0.088

UPDRS: Unified Parkinson's Disease Rating Scale; HY: Hoehn and Yahr; PD: Parkinson's disease. NA: Not applicable. "-": data not collected.

The impact of levodopa on PD progression remains controversial. While some argue that levodopa may slow down its progression;[17-19] some do not believe that dopaminergic intervention can alter the course of progression over the long run;[22,23] and others insist that levodopa hasten the overall deterioration.[18,19] For instance, Maier-Hoehn back in 1983 reported that levodopa reduced the number of patients in HY Stage IV or V (or death) per 5-year period of disease duration by 30–50%[24] as opposed to the more recent report suggesting that rapid progression was positively associated with levodopa use.[20,21] While it was not our intention to draw head to head comparison with these contributions, we believe the current study could re-fuel the debate on the long-term outcome of levodopa therapy, and provide a useful reference to study PD progression and to understand the role of levodopa in this process.

The current study measured the mean disease duration, which, when calculated against the change of HY scales, provides an effective way of gauging the rate of progression. When compared with other cohorts in other parts of the world [Table 3], the patients in the current study showed a slower progression. In addition, patients' HY stage in our study deteriorated < 1 stage in 10 years, which was much slower than that were described by Hoehn and Yahr.[25] who reported that without treatment, the median time taken to progress from Stage I to Stages IV and V is 9.0 ± 7.2 and 14.0 ± 3.4 years, respectively, and Marttila and Rinne reported that progression to Stage V occurred 10 years after disease onset.[26] As shown in Table 3, our patients seemed to have similar HY stages[27-29] with longer duration or similar disease duration but lower HY stages.[30]

As to the UPDRS measurements, in the current cohort of 15 cases, the mean motor score reached 39.4 ± 23.7 at the end of the 13-year duration [Table 3]. In comparison, it took only 6 years to reach the same range of UPDRS score for Japanese cohort.[31] These observations provided additional support to the notion that our cohort may have progressed at a slower pace. While the potential reasons for this discrepancy remain uncertain, variability among Asian population from different countries may reflect the impact of other epidemiological factors such as diet, environment, or other population-based differences.

The limitations of this study were as follows: 1. Due to the fact that only a few patients refused to take medicine, this study was a small cohort with just 15 patients. If possible, we should

Table 3: Comparison of UPDRS motor scores and HY stage scores among current study and other selected studies published

Regions	Case size (*n*)	UPDRS motor score	HY stages	Disease duration (years)	Studies
Lin County, China	15	39.4 ± 23.7	2.4 ± 1.1	13.6 ± 7.3	Zhang *et al.*
Kobe, Japan[27]	153	34 ± 16	3.0 ± 0.7	5.9 ± 2.4	Abe *et al.*
Miami, Florida[28]	44	21.7 ± 9.8	2.3 ± 0.7	9.0 ± 5.4	Papapetropoulos *et al.*
London, UK[30]	76	N	4.3	12.8	Hughes *et al.*
Fukushima, Japan[31]	13	39.1 ± 14.2	N	6.1 ± 5.7	Saito *et al.*
Tyne Wear, UK[32]	109	34.1 ± 11.2	2.0 ± 0.7	6.9 ± 6.1	Graham and Sagar

N: No data reported; UPDRS: Unified Parkinson's Disease Rating Scale; HY: Hoehn and Yahr.

observe the natural progression of PD in a larger cohort; 2. Only individuals from the NIT cohort were surveyed in the current study. This makes it difficult to directly compare our results to other studies. Ideally, we should have conducted simultaneous assessments of PD progression in non-NIT participating Lin County residents and in one of the nutritionally adequate counties in the same geographical region.

The current report represents the first step in addressing the natural progression of PD in rural China. Future studies in this direction will undoubtedly expand on our initial investigation, leading to more extensive studies in both rural and urban population in China, ideally prospectively.

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