CLINICS

CLINICAL SCIENCE

Clinical profile of Parkinson's disease in the Gumei community of Minhang district, Shanghai

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OBJECTIVE: We examined the demographic and clinical profiles of Parkinson's disease in Shanghai, China, to assist in disease management and provide comparative data on Parkinson's disease prevalence, phenotype, and progression among different regions and ethnic groups.

METHODS: A door-to-door survey and follow-up clinical examinations identified 180 community-dwelling Han-Chinese Parkinson's disease patients (104 males, 76 females).

RESULTS: The average age at onset was 65.16±9.60 years. The most common initial symptom was tremor (112 patients, 62.22%), followed by rigidity (38, 21.11%), bradykinesia (28, 15.56%) and tremor plus rigidity (2, 1.11%). Tremor as the initial symptom usually began in a single limb (83.04% of patients). The average duration from onset to mild Parkinson's disease (Hoehn-Yahr phase 1–2) was 52.74±45.64 months. Progression from mild to moderate/severe Parkinson's disease (phase≥3) was significantly slower (87.07±58.72 months; $p<0.001$), except for patients presenting initially with bradykinesia (53.83±24.49 months). Most patients (149/180, 82.78%) took levodopa with or without other drugs. The Hamilton Anxiety Scale revealed symptoms of clinical anxiety in 35 patients, and the Hamilton Depression Scale revealed depressive symptoms in 88 patients. The depressed or anxious subgroup (123 patients) demonstrated a significantly younger age at onset (55.54±7.68 years) compared with the overall mean ($p<0.05$).

CONCLUSION: Unilateral limb tremor was the most common initial symptom, and motor function deteriorated slowly over ≈4−9 years. Earlier-onset patients experience greater psychiatric dysfunction.

KEYWORDS: Parkinson's Disease; Depression; Anxiety; Motor Dysfunction; Dyskinesia; Han Chinese.

Liu K, Gu Z, Dong L, Shen L, Sun Y, Zhang T, et al. Clinical profile of Parkinson's disease in the Gumei community of Minhang district, Shanghai. Clinics. 2014;69(7):457-463.

Received for publication on November 15, 2013; **First completed revised on** January 7, 2014; **Accepted for publication on** January 7, 2014

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INTRODUCTION

Parkinson's disease (PD) results from the progressive degeneration of dopaminergic neurons in the substantia nigra (1). Although several gene mutations causing familial PD have been identified (2-4), the etiology of the more common idiopathic form remains unclear.

The first symptom of idiopathic PD may be a change in the sense of smell (4), but motor dysfunction (manifested as resting tremor, rigidity, or bradykinesia) is the first serious deficit, most often afflicting a single distal limb (1). Reduced dopaminergic activity in the substantia nigra in turn enhances cholinergic signaling (5). Therefore, pharmaceutical therapies aim to restore the balance between dopaminergic and cholinergic neurotransmission and include anti-cholinergics, dopamine replacement therapies, dopamine receptor agonists and inhibitors of dopamine degradation (5). Unfortunately, these therapies do not arrest or markedly slow the degeneration of dopaminergic neurons (6,7). However, medication, surgery and rehabilitation can provide motor symptom relief and improve patient quality of life (8-13). These treatments may be most effective when initiated in the earliest stages of the disease (4), but there is no consensus on this issue.

The prevalence of PD continues to increase in mainland China as the population ages. A recent epidemiological study (14) reported an incidence of 1.07% in Chinese citizens over 55 years old, 1.7% in those over 65 and 2.5% in individuals over 75, an age dependence similar to that reported in Europe and the United States (1). There are

No potential conflict of interest was reported.

DOI: 10.6061/clinics/2014(07)03

currently approximately six million Chinese PD patients and the annual rate of new case development is estimated at 100,000 (14). However, most patients and their families have limited knowledge of the disease and are unaware of its initial symptoms, delaying diagnosis and treatment initiation. In addition, regional prevalence varies widely (15).

Here, we utilized integrated medical resources and a complete medical service platform to conduct a door-to-door survey in the Gumei community of Shanghai's Minhang district. The survey and follow-up medical examinations ultimately identified 180 PD patients. The data accrued from these patients were retrospectively reviewed to identify the earliest symptoms and disease progression. These results may facilitate earlier diagnosis and improve clinical management in this community.

MATERIALS AND METHODS

Population

This was a single-center study based in a single community. The sampling population comprised Han residents living in the Gumei community of Minhang district, Shanghai, who had medical records archived in the local health service center. Gumei is located in southwest Shanghai between the suburbs and the city. The residents originate from various regions of the Yangtze River delta region of China and thus constitute a convenient sample population for studying the characteristics of PD in this region. The study was approved by the local ethics committee and each enrolled PD patient provided written informed consent.

The standard diagnostic criteria for PD (16) include a slow disease onset with at least two of the following manifestations: (1) resting tremor or bradykinesia responsive to levodopa, (2) rigidity, or (3) abnormal gait/posture.

Physical examination, auxiliary tests, questionnaire assessment and documentation of disease history were all conducted by physicians with neurology training. We referred to the standard PD diagnostic criteria (16) to develop the questionnaire. None of the subjects had a history of contact with the specific dopaminergic neurotoxin MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine) and patients with Parkinson's syndrome or Parkinson's overlap syndrome were excluded. None of the enrolled PD patients had cerebellar signs, pyramidal signs, or orthostatic hypotension. The demographic characteristics recorded were age, gender, marital status and occupation. Medical history included the presence of hypertension, diabetes, hyperlipidemia, coronary heart disease, blood hyperviscosity syndrome, smoking and drinking habits, cerebrovascular diseases (including hemorrhagic and ischemic lesions), drug poisoning and head trauma. Clinical information on PD included age at onset, major symptoms and signs, and detailed disease course.

METHODS

Community medical practitioners were specifically trained to identify PD symptoms. Individuals with at least one PD symptom (resting tremor, bradykinesia, rigidity, or abnormal gait/posture) were registered in the first phase. These potential PD patients were then recruited for physical examinations and detailed assessment of medical history at the Gumei Health Center by neurologists who confirmed PD and determined the clinical stage. The PD stage was determined according to the revised Hoehn-Yahr scale, which considers multiple PD parameters, including age at onset, initial symptoms, progression and effects of medication (16). The PD stage was further assessed using the unified PD Rating Scale (UPDRS) (17), while associated depression and anxiety were assessed by the Hamilton Depression Scale (HAMD) (18) and the Hamilton Anxiety Scale (HAMA) (19).

We classified 180 PD patients into three groups according to their initial symptom: tremor, bradykinesia, or rigidity.

Statistical analysis

Data are expressed as the mean $\pm$ standard error of the mean (SEM). SAS11.0 software (SAS Institute Inc., Cary, NC) was used for all statistical analyses. Unpaired t tests were performed to compare continuous variables between two groups. Chi-square (χ^2) tests were used to compare categorical results among multiple groups, and the means of multiple groups were compared using Kruskal-Wallis one-way analysis of variance (ANOVA) followed by Dunn's post hoc test. $P<0.05$ was considered statistically significant.

RESULTS

General survey information

We interviewed 36,981 residents of Gumei during a door-to-door survey conducted between June 2008 and December 2011. We identified 180 PD patients (104 males, 76 females) ranging from 35 to 94 years of age (mean age, 65.16$\pm$9.60 years). Among the participants, 126 were local residents (with medical insurance cards issued by Shanghai) and 54 were non-locals (including migrant workers and elderly individuals living with their children who did not have Shanghai citizen medical insurance cards but who had legally lived in Shanghai for at least 2 years). Only one female patient had a family history of PD (her mother).

Parkinson's disease prevalence by age

The patient population was divided into five groups by age range (years): 15−49, 50−59, 60−69, 70−79, and ≥80. The prevalence of PD was positively correlated with age in patients 50−79 years of age and was highest in the 70−79 year group (62/4143, 1.496%) (Table 1).

Prevalence of depression and anxiety by age

The youngest two groups exhibited the highest scores on the HAMA and HAMD scales, indicating higher rates of anxiety and depression in younger PD patients, whereas the scores were negatively correlated with age in patients older than 60 years (Table 1).

Initial symptoms

Tremor was the most common initial symptom (112 of 180 patients, 62.22%), followed by rigidity (38/180, 21.11%) and bradykinesia (28/180, 15.56%). Two male patients had both tremor and rigidity at disease onset (2/180, 1.11%). The sex ratio (male:female) did not differ significantly among groups defined by initial symptom (tremor: 1.18:1.00, rigidity: 1.11:1.00, bradykinesia: 1.33:1.00; $p=0.796$).

Age at onset

The average age at onset was 65.16$\pm$9.60 years of age, with the majority of patients exhibiting initial symptoms

Table 1 - Parkinson's disease prevalence and psychiatric status by age range (years).

Group	Number, n (%)					
	Total	15–49	50–59	60–69	70–79	≥80
Parkinson's disease patients	180	5	31	69	64	11
Registered population	36,981	17,210	6028	5512	4143	4088
Parkinson's disease prevalence	0.480%	0.041%	0.513%	1.252%	1.496%	0.268%
HAMA		16.4±3.1*	14.4±2.8*	10.4±3.3	11.2±2.9	8.7±3.4
HAMD		7.4±3.4*	7.1±3.3*	5.2±3.2	4.7±3.4	4.5±3.6

HAMA: Hamilton anxiety scale (18). Mild: 0–17, Mild/Moderate: 18–25, Moderate/Severe: 26–30, Very Severe: >30.
HAMD: Hamilton depression scale (19). Normal: 0–7, Clinical: >20.
PD: Parkinson's disease.
*$p<0.001$ *vs.* 60–69 years.

between 60 and 79 years of age (131/178, 73.60%). The age at onset in the tremor group was older than that in either of the other two groups and significantly older than that in the rigidity group ($p=0.014$). Tremor was the most common initial symptom in every age group (Table 2) but was particularly frequent in patients with older age at onset (≥60 years).

Initially affected body part

The body part or parts first affected are presented in Table 3. The two patients who experienced two initial symptoms (tremor and rigidity) were excluded from the analysis. In the remaining 178 patients, the PD initial symptom usually afflicted only a single limb (131/178, 73.60%) and was most frequently tremor (93/131, 70.99%). Thus, the vast majority of patients first presenting with tremor (112) exhibited tremor in only one limb (93/112, 83.04%) and this unilateral tremor started most often in a right limb (68/93, 73.12%). Similarly, rigidity usually first presented in a single limb (28/38, 73.68%). In contrast, bilateral limb onset was relatively more common when bradykinesia was the first symptom (39.28% *vs.* 10.71% bilateral tremor and 10.53% bilateral rigidity).

Disease progression

There were 101 patients classified as mild and 77 classified as moderate/severe according to the revised Hoehn-Yahr scale (12,17). The average delay from the initial symptom to mild PD (stages 1–2) was 52.74±45.64 months. Progression from mild to moderate/severe PD (stages 3–5) required 87.07±58.72 months, significantly longer than the delay from the initial symptom to mild PD ($p<0.001$). Disease severity differed significantly among groups classified according to the initial symptom ($p=0.025$). The duration from the initial symptom to mild PD was similar among groups ($p>0.05$), but the duration from mild to moderate/severe was significantly shorter in the bradykinesia group compared with the tremor and rigidity groups ($p=0.012$ and 0.006, respectively) (Table 4). We did not observe a significant difference between the tremor and rigidity groups ($p=0.448$), suggesting that PD with first-onset bradykinesia is a more rapidly progressing variant.

Pharmaceutical and non-pharmaceutical treatments

The majority of patients were treated with either levodopa (83/180, 46.11%) or a combination of levodopa and at least one additional drug (66/180, 36.67%), including amantadine (5/180, 2.78%), artane (trihexyphenidyl hydrochloride) (6/180, 3.33%), a monoamine oxidase B inhibitor (MAO-B) or dopamine agonists (6/180, 3.33%), or coenzyme Q10 (2/180, 1.11%). Twelve patients (6.67%) did not take any type of medication.

Deep brain stimulation (DBS) is a relatively new therapy in China, and only 4/180 patients (2.22%) in this population had undergone DBS.

DISCUSSION

The initial manifestations of PD differ among patients both with regard to severity and the afflicted region (20). Many patients do not recognize these early symptoms and the rate of early diagnosis is therefore low (21), greatly reducing the potential efficacy of current therapies for improving quality of life. A more detailed description of the earliest symptoms, combined with greater awareness among at-risk populations, may facilitate earlier PD diagnosis and improve QOL.

Aging

Epidemiological studies have shown that PD prevalence and incidence correlate strongly with age; therefore, age is one of the strongest risk factors for PD (1). The case-controlled design is most commonly used in PD studies due to the limited number of cases within a given sampling population and the variability in clinical profile (22). In the

Table 2 - Initial Parkinson's disease symptoms and age at onset (years).

Initial Symptom	Total (%)	M/F	15–49	50–59	60–69	70–79	≥80	Avg	Range
Tremor	112 (62.92%)	66/46	2 (40.00%)	19 (61.29%)	45 (65.22%)	42 (65.61%)	4 (36.36%)	61.19±9.74*	34–94
Rigidity	38 (21.34%)	20/18	1 (20.00%)	7 (22.58%)	13 (18.84%)	12 (18.78%)	5 (45.46%)	56.32±9.62	31–86
Bradykinesia	28 (15.73%)	16/12	2 (40.00%)	5 (16.13%)	11 (15.94%)	10 (15.61%)	2 (18.18%)	59.39±7.35	45–87

Note: M/F: male/female; Avg: average age at onset of symptom; Range: range of ages for specific symptom onset, *$p<0.05$ tremor group *vs.* rigidity group. Two patients with at least two initial symptoms were excluded from the table.

Table 3 - Initial symptoms and first affected body parts.

Initial symptom		Bilateral limb				Unilateral limb								Trunk	
						Single arm			Single leg						
	n (%)		Both arms	Both legs	Arms and legs	n (%)	Left	Right	n (%)	Left	Right	n (%)	Left limbs	Right limbs	n (%)
Tremor	112	12 (10.71%)	5	3	4	64 (57.14%)	22	42	29 (25.89%)	3	26	7 (6.25%)	3	4	0
Rigidity	38	4 (10.53%)	0	3	1	11 (28.95%)	3	8	17 (44.74%)	6	11	3 (7.89%)	2	1	3 (7.89%)
Bradykinesia	28	11 (39.28%)	1	6	4	4 (14.29%)	2	2	6 (21.42%)	4	2	4 (14.29%)	1	3	3 (10.71%)
Total	178	27 (15.17%)	6	12	9	79 (44.38%)	27	52	52 (29.21%)	13	39	14 (7.87%)	6	8	6 (3.37%)

Note: Two patients with at least two initial symptoms were excluded from the table.

present study, we interviewed 36,981 people using a door-to-door survey and identified only 180 confirmed PD patients. Similarly, a study by Harvard University and the University of Pennsylvania (23) identified only 160 PD patients out of 50,000 interviewees. The higher PD prevalence observed in our study may reflect differences in population demographics and inclusion/exclusion criteria, such as updated PD diagnostic criteria (16) and the exclusion of potential patients younger than 14 years, the minimum age for registration at local health centers. Nonetheless, both surveys indicate that very large sample sizes are required to gather sufficient information on PD patients to establish specific clinical subgroups.

Psychiatric symptoms

Psychiatric symptoms such as anxiety and depression are more common in PD patients than in the general population (1), although the rate varies across sample populations. In the current study, 16 patients with anxiety symptoms were taking appropriate anti-anxiety medication and receiving psychiatric therapy, but 29 patients with anxiety symptoms were not receiving any treatment. Similarly, according to the HAMD, 88 patients exhibited signs of depression, but only 17 were treated. This is consistent with other PD patient populations (24) in which the psychiatric symptoms are often regarded as secondary to the motor symptoms. The average age at PD onset in the 45 patients with anxiety and 88 patients with depression was 55.54 ± 7.68 years, significantly younger than the overall mean PD age at onset (65.16 ± 9.60 years). Whether this association reflects greater anxiety due to early onset (a situational factor), a common neurocellular etiology (25), or whether these psychiatric disorders can in fact exacerbate core PD symptoms or accelerate progression is a matter of current debate. It is clear that depression and anxiety interfere with memory and executive function, suggesting that they may exacerbate the cognitive symptoms of PD (26,27).

Correlation between initial symptom and age of onset

The most common initial symptom in our study was tremor (62.22% overall), which was within the range of 55%−74% reported in previous studies (28). It should be noted, however, that the reported incidence of tremor as the first symptom may be inflated, as tremor is more noticeable than mild rigidity and bradykinesia. Uitti et al. (29) reported tremor as the initial symptom in only 47% of a large PD population (585/1244). This same study also reported a higher rate of bradykinesia as the initial symptom (29%, 361/1244) when compared with the 15.56% (28/180) in our study. The average age at onset was older in patients with tremor as the principal onset symptom compared with patients reporting rigidity or bradykinesia as the onset symptom (the combined group), suggesting that ''tremor-first'' PD is a milder clinical variant. PD occurring after age 50 is considered late onset (30,31). By this definition, 62.86% (110/175) of all late-onset cases in our study presented first with tremor, indicating that tremor is a more common initial symptom in late-onset patients, in agreement with a report by Helmich et al. (32). Bostantjopoulou et al. (33) also found that tremor was the most common onset symptom in patients over 68 years old, whereas rigidity and bradykinesia were relatively more common onset symptoms in middle-aged (early onset) patients. We found that tremor

Table 4 - Parkinson's disease progression among patients with different onset symptoms.

Severity	Number	Tremor	Rigidity	Bradykinesia
			Average duration (months)	
Mild stage	101	53.18±47.91 (n = 64)	53.57±40.63 (n = 21)	49.38±41.87 (n = 16)
Moderate/severe stage	77	90.41±62.17* (n = 41)	105.24±62.94* (n = 26)	52.14±24.10 (n = 10)

Note: Mild PD: Hoehn-Yahr phase 1–2; Moderate/severe PD: Hoehn-Yahr ≥ phase 3.
*$p<0.01$ *vs.* Bradykinesia patients. Two patients with at least two initial symptoms were excluded from the table.

patients were older than rigidity patients ($p<0.05$), but age at onset was not different between tremor and bradykinesia patients or rigidity and bradykinesia patients (both $p>0.05$). Larger sample sizes are required to assess whether rigidity-first PD and bradykinesia-first PD follow distinct courses.

It was reported that the prevalence of tremor as the onset symptom was negatively correlated with age, whereas rigidity as the first symptom was positively correlated with age (34). However, tremor was the most common onset symptom in every age group in our study and all symptoms had a similar age at onset (between 50 and 69 years old). Thus, our results suggest that tremor-first PD is a less-aggressive variant, but larger-scale studies including greater numbers of rigidity-first and bradykinesia-first patients are needed to clarify this issue.

Initially affected body part

The majority of patients exhibited their first noticeable symptom in a unilateral limb and this proportion was highest in tremor-first patients. A previous study also reported unilateral limb onset in a majority of PD patients, with the highest prevalence in tremor-first patients (34). The right limb was the first affected body part in the majority of tremor-first and rigidity-first PD patients, whereas another study reported that tremor more often started in a left limb and bradykinesia generally afflicted both limbs at onset (1). These differences are of significant interest because they reflect differences in progression at the neurocellular level and may therefore provide insight into the etiology of sporadic PD. The sample population came from different regions of the Yangtze River delta, but all were of Han ethnicity. Whether these discrepancies with previous studies reflect the influence of region or ethnicity warrants further study.

Disease progression

We graded PD as mild or moderate/severe according to the revised Hoehn-Yahr system (16). The duration from first symptom onset to mild PD (52.74±45.64 months) was significantly shorter than the time to progress from mild to moderate/severe PD (87.07±58.72 months). The disease was the most severe and progression the fastest in patients with bradykinesia as the onset symptom. Alternatively, there was no difference between the rigidity and tremor groups in terms of PD progression, but patients who reported tremor as the first symptom were typically older and experienced slower disease development. It has been postulated that the rate of dopaminergic neuron degeneration is slower in patients presenting first with tremor compared with other PD subtypes (35). However, Jankovic and Kapadia (36) found that later-onset patients, which may include a greater proportion of tremor-first patients, had more rapidly progressing disease according to the UPDRS and ADL scoring systems.

We conducted a survey of PD prevalence, phenotype and progression in an ethnically homogenous population of community-dwelling Han Chinese to provide additional comparative data for more effective clinical management. Whereas this study surveyed almost 37,000 residents, only 180 confirmed PD cases were identified. Thus, our data concerning unusual phenotypes are limited and it appears that a very large-scale multicenter study will be necessary to accurately assess the initial characteristics and progression of patients presenting first with bilateral bradykinesia or bradykinesia in all limbs. Furthermore, non-drug therapies are still rare in China, as are certain specific drug combinations.

Our retrospective analysis of 180 PD patients in the Gumei community of Shanghai revealed that tremor was the most common onset symptom in this community. Most tremor patients had late-onset PD with a right limb affected first and this disease variant progressed relatively slowly compared with PD with bradykinesia as the first symptom. Symptoms of anxiety and depression were associated with lower age of onset, implying that psychiatric treatment may be an integral aspect of therapy for early-onset PD.

Comparative Epidemiology

A recent meta-analysis of 13 epidemiological studies from China reported a pooled peak prevalence of 1.663% (in patients ≥80 years old) and an overall incidence of 797 per 100,000 person-years with a male predominance (37). Moreover, the prevalence was said to be lower in China than in most developed countries but the incidence higher than in some developing countries. From a survey of urban and rural communities around the large cities of Beijing, Xian and Shanghai, Zhang et al. (14) reported a PD prevalence of 1.7% for those older than 65. Both prevalence estimates are slightly higher than the peak value of 1.496% (in patients 70−79 years old) reported in the current study. However, all these estimates are consistent with the lower PD prevalence in Asian countries compared with North America and Europe (38). Moreover, non-motor symptom expression may also differ between Asian and Western countries (39), underscoring potential differences in PD presentation among ethnic groups. Differences in PD prevalence between countries or ethnic groups may be influenced by differences in life expectancy or the availability of diagnostic facilities, but incidence estimates tend to confirm a lower incidence of PD in Asians and Africans (including African Americans) compared with Europeans (37,40). These differences have been attributed to genetic variations, such as differences in single nucleotide polymorphism (SNP) patterns in PD-associated genes, including

LRRK2, across populations (41) and to lifestyle and environmental differences. Lifestyle factors include smoking (42), coffee consumption (43), medical compliance (44), nutrition (45) and exercise (46), whereas well-studied environmental factors include toxins such as pesticides (47). Any of these factors may account for the differences across studies of Han Chinese populations. However, many of these associations between environmental factors and PD have not been replicated consistently (48), suggesting methodological flaws or more complex gene-environment interactions.

ACKNOWLEDGMENTS

This work was supported by grants from the project of National Natural Science Foundation of China (No. 31171014 and 30970869), the project of Science and Technology Commission of Shanghai Municipality (No. 09DZ1950400), the Board of Health of Shanghai, China (No.2008086), the youth projects of the National Natural Science Foundation of China (No. 31100783) and the Youth Key Project in Shanghai College of Medicine of Fudan University (No. 09-L37).

AUTHOR CONTRIBUTIONS

Liu K was responsible for study design and execution. Gu Z, Zhang T and Shi N were responsible for the diagnose. Dong L, Shen L, Zhang Q and Zhang W were responsible for the survey. Sun Y was responsible for the records. Zhao M analyzed data. Sun X provided study guidance.

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