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Comparative study of clinical profile between familial and sporadic Parkinson's disease

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Abstract

The precise etiology of Parkinson's disease (PD) is unknown and the relative contributions of genetic and environmental factors may vary in different cases. So, the present study was conducted to compare clinical profile and medication dose in familial and sporadic PD. The patients in the present study were recruited from Movement disorders clinic of tertiary care centre after taking approval from the Institutional Ethics Committee and written informed consent from all patients. All patients underwent a detailed clinical examination and age of onset (in years), duration of motor symptom (in years), clinical subtype of PD (tremor vs bradykinesia dominant vs mixed), comorbid illness (diabetes, hypertension), L-dopa equivalent dose, individual PD medications with doses and other medications were noted. Modified Hoehn and Yahr staging was done in both the groups. Mean age of onset of disease was less than 50 years in both the groups. Majority of patients (85%) in both groups had tremor dominant PD. L-dopa dose for both the PD was found effective and there was non-significant difference in their doses. There was no significant difference in the demographic features, clinical characteristics and medication doses between familial and sporadic PD patients. To conclude, there was no significant difference between both the groups for clinical profile and medication used. This may be due the fact that frequency of genetic mutations in PD shows significant variation based on ethnicity which was not found in this Indian study.

Key words: Familial, L-dopa, Parkinson's disease, Sporadic

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Parkinson's disease (PD) is a common neurodegenerative disorder characterized by resting tremor, rigidity, bradykinesia and postural instability with good response to L-dopa. Dopamine loss is the main pathological feature of PD, and dopamine receptor agonists are the most effective symptomatic PD medication[1]. PD is unlikely to be a single disease entity; it represents a diversity of conditions resulting in a common clinical presentation[2]. The precise etiology of PD is unknown and the relative contributions of genetic and environmental factors may vary in different cases[2]. Those without a positive family history and classic late age of onset are sporadic forms whereas those patients with a positive family history and early age of onset (usually less than 40

years) are classified as familial PD. Approximately 10-15% of patients with the typical clinical picture of PD have a positive family history compatible with a Mendelian (autosomal dominant or autosomal recessive) inheritance[3]. Mutations within the genes at 6 loci (α-synuclein, LRRK2, Parkin, DJ1, PINK1 and ATP13A2) have conclusively been demonstrated to cause familial parkinsonism[4-7]. These genes are found in selective ethnic populations and a few of them have atypical clinical features like myoclonus and hypoventilation in α-synuclein[4], dementia with lewy bodies in E46K substitiution of α-synuclein gene[8] and progressive supranuclear gaze palsy like presentation in ATP13A2 related parkinsonism[7]. One study of specific gene mutations in PD has reinforced the relevance of oxidative stress and mitochondrial dysfunction in the familial and the sporadic forms of PD[9].

Braak proposed a staging model for the progression of pathological process in PD which starts in the brainstem and progresses in a topographically predictable sequence upto neocortex in last stage[10]. Drugs for PD can improve motor functions from their early stages[11]. On literature search very few studies were found which had compared clinical profile and medication dose for both the types of PD. So, the present study was conducted to compare clinical profile and medication dose in familial and sporadic PD in Indian population.

Material and methods

The present prospective study was conducted in a teaching hospital after taking approval from the Institutional Technical Advisory Committee and the Ethics Committee. The patients were recruited from Movement Disorders clinic of Sree Chitra Tirunal Institute of Medical Sciences and Technology (SCTIMST), Thiruvananthapuram, Kerala. Written informed consent was obtained from all patients prior to enrolment. Parkinson's disease was diagnosed by United Kingdom Parkinson's Disease (UKPD) Society Brain Bank diagnostic criteria[12].

One or more of the family members with a documented diagnosis were included in Familial PD group and no family member with a documented diagnosis of PD (other than proband) in preceding three generations or any successive generation were included in sporadic PD group. Patients with comorbid illness/condition likely to cause sleep dysfunction (like substance abuse, obstructive airway disease, cardiac failure) were excluded from the study.

Familial and sporadic PD patients who participated in the study were interviewed using the structured proforma during their routine clinic visits. All patients underwent a detailed clinical examination and the following parameters were recorded:

- age of onset (in years)
- duration of motor symptom (in years)
- clinical subtype of PD (tremor vs bradykinesia dominant vs mixed)
- comorbid illness (diabetes, hypertension)
- L-dopa equivalent dose, individual PD medications with doses
- other medications

Modified Hoehn and Yahr (H and Y) staging was done for Parkinson's disease in both the groups.

Table 1: Modified Hoehn and Yahr staging

Stage	Disease state
0	No signs of disease
1	Unilateral disease
1.5	Unilateral plus axial involvement
2	Bilateral disease, without impairment of balance
2.5	Mild bilateral disease with recovery on pull test
3	Mild to moderate bilateral disease; some postural instability; physically independent
4	Severe disability; still able to walk or stand unassisted
5	Wheelchair bound or bedridden unless aided

SPSS version 17 was used for data analysis. For categorical variables, percentages were compared by Fisher's exact test. For quantitative variables, Mann-Whitney test was used. p value < 0.05 was considered significant.

Results

A total of 20 cases of Familial and 20 cases of Sporadic PD were finally compared. In the Familial PD group, 12 (60%) patients had single effected family member, 7 (35%) patients had 2 effected family members and 1 (5%) patient had 3 effected family members (other than proband). Majority of patients in both groups had tremor dominant PD. Table 2 shows the classification of patients in both groups depending on clinical subtype.

Table 2: Classification of patients based on predominant clinical manifestation

Subtype	Familial PD n (%)	Sporadic PD n (%)
Tremor dominant	17 (85)	17 (85)
Rigid-bradykinetic	2 (10)	2 (10)
Mixed	1 (5)	1 (5)

Diabetes was found in 25% patients of familial PD and 15% in sporadic PD; whereas hypertension was found in 20% cases of each type of PD. (Table 3)

Table 3: Number of patients with co-morbid illness in each group

Disease	Familial PD n (%)	Sporadic PD n (%)
Diabetes	5 (25)	3 (15)
Hypertension	4 (20)	4 (20)

There was no significant difference in the demographic features, clinical characteristics and medication doses between Familial and Sporadic PD patients. (Table 4)

Table 4: Comparison of demographic features, clinical characteristics and medication doses between Familial and Sporadic PD patients

Clinical feature and medications	Familial PD Mean ± SD (n=20)	Sporadic PD Mean ± SD(n=20)	p value
Age of onset (yrs)	46.8 ± 10	48.75 ± 7.9	0.41
Duration of motor symptom (yrs)	6.2 ± 3.2	7.7 ± 4	0.3
L-dopa equivalent dose (mg)	447.5 ± 216.1	589.5 ± 321.7	0.11
L-dopa daily dose (mg)	227.5 ± 172	374.7 ± 245.6	**0.035***
Dopamine in L-dopa equivalent dose (mg)	181.7 ± 172.7	190.5 ± 172.4	0.86
Rasagiline daily dose (mg)	0.15 ± 0.36	0 ± 0	0.42
Trihexyphenydyl daily dose (mg)	1.7 ± 2.6	1.05 ± 1.9	0.6
Amantadine daily dose (mg)	15 ± 67	65 ± 103.9	0.2
Escitalopram daily dose (mg)	2 ± 3.4	3.7 ± 4.8	0.38
Clonazepam daily dose (mg)	0.12 ± 0.3	0.05 ± 0.15	0.77
H and Y stage	2.12 ± 0.5	2.22 ± 0.44	0.56

*p value ≤ 0.05 (significant)

Discussion

Parkinson's disease (PD) is a progressive nervous system disease occurring most often after the age of 50 years and effecting all ethnic groups[13]. Genetic susceptibility plays a stronger role in early onset familial cases, whereas environmental factors play a stronger role for late onset sporadic cases[14]. But no other specific clinical signs or symptoms distinguish familial from sporadic cases. This study was conducted to compare the pattern of clinical features and medication dose used in two etiological subtypes of PD - Familial vs Sporadic.

In present study majority of patients (85%) in both groups had tremor dominant PD. Study conducted by Baba et al had also shown tremor dominant PD in both the groups in which 54% of the patients with familial PD and 48% of those with sporadic PD were reported tremor as initial motor symptoms[15]. In the present study no significant difference in initial motor symptoms were found in both the groups. Similar non-significant difference was also reported by Baba et al which explains that it may be due to the similar involvement of nigrostriatal lesion in either type of PD[15].

Diabetes and hypertension were the most common comorbid illnesses seen in both group of patients in present study. One study has shown that PD patients had diabetes mellitus (DM) and heart diseases as frequently as in the general population and these illnesses are common irrespective of gender or race[16]. Many studies suggest the asso-

ciation of DM with PD because both are age-related chronic diseases and share remarkably similar pathways of mitochondrial dysfunction[17,18].

Mean age of onset of disease was less than 50 years of age in both the groups and duration of disease was also less than 8 years in both the groups. H and Y stage also showed mean value around 2 in both groups. This shows that in present study; both the groups disease is in early stage because the peak age of onset of PD is in the early 60s (range 35-85 years), and the course of illness ranges from 10 to 25 years[19]. At the beginning of the illness or as the disease progresses, postural instability and falls manifest, which adds to the disability and severity of the illness[13,20]. L-dopa dose for both the PD was found effective and there was no difference in their doses. Similar L-dopa responsive Familial PD as compared to Sporadic PD was also found in other studies[15,21,22]. Drugs are most widely used treatment for insomnia in clinical practice for PD and these sleep disturbances may be related to factors such as depression[23]. In a survey of patients with PD living in the community, 40% were found to be using sleeping pills, compared to 23% of the non-PD controls[24]. Similarly in our study clonazepam and escitoparm were given to both the groups. There was no significant difference between the two groups with respect to age of onset, disease duration, clinical subtype, disease severity, comorbid illness, levodopa equivalent dose and other non-PD medications. Previous studies highlighted the importance of all above mentioned factors in motor disturbances[25]. Though the mean L-dopa daily dose was lower in Familial PD patients, there was no significant difference in L-dopa equivalent dose between the two groups indicating no significant difference in the total dose of dopaminergic medications.

Madegowda et al reported Parkin gene mutations in 2 out of 20 cases of familial early onset PD from South India[26]. Punia et al did LRRK2 mutation testing in 1012 Indian PD patients and found a heterozygous G2019S mutation in a single young PD patient[27]. Another recent study from South India testing for LRRK2 G2019S mutation in 86 familial PD cases did not find even a single case positive for the mutation. These studies suggest that the frequency of genetic mutations in PD shows significant variation based on ethnicity[28]. This could be the reason that we could not find significant difference for clinical features and treatment between both the groups in our study. Similar results were found in Papapetropoulos et study which was conducted in Greece[29].

Conclusion

We conclude that we could not find significant difference between both the groups for clinical profile or motor symptoms and dose of medications used. This may be due to the fact that frequency of genetic mutations in PD shows significant variation based on ethnicity which was not found in this Indian study. In our study we compare mainly motor symptoms of PD. However larger studies are needed to compare both motor as well as non-motor symptoms of both the types of PD.

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Conflict of interest: None

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