ORIGINAL ARTICLE

Study of familial Parkinson's disease in Russia, Uzbekistan, and Zambia

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Objective: The aims of this study were (A) to determine inheritance patterns of familial Parkinson's disease in three different geographical areas (Russia, Uzbekistan, and Zambia); (B) compare clinical characteristics of familial with sporadic Parkinson's disease; and (C) assess whether there were ethnic differences in clinical manifestations of the disease.

Methods: Fifty two index cases of familial Parkinson's disease in Moscow, 55 in Tashkent, and 27 in Lusaka were selected on the basis of the typical clinical features of Parkinson's disease with a familial history. The sex ratio, transmission patterns, and segregation ratio were determined by pedigree analysis. **Results:** Familial Parkinson's disease was found in all three countries (30 families in Russia, 12 in Uzbekistan, and seven in Zambia), and appeared more common in Russia. Both autosomal dominant and autosomal recessive patterns of inheritance were seen, but autosomal dominance was more common in all countries.

Conclusions: In all three countries men have a higher risk of developing Parkinson's disease than women and there are ethnic differences in clinical manifestations of the disease. The onset of both familial and sporadic Parkinson's disease in Zambian patients occurs at a younger age and is associated with slow progression and a benign course, and generally responds well to levodopa treatment.

Most Parkinson's disease cases are sporadic. Since the second half of 19th century a number of articles regarding familial Parkinson's disease have been published,¹⁻⁶ but the role of genetic factors in the aetiology and pathogenesis of Parkinson's disease remains understudied.⁷⁻¹⁰ In the last few years hereditary factors have emerged as a major focus of Parkinson's disease research due to the discovery of two relevant genes: α -synuclein and the Parkin gene.¹¹⁻¹³ It has been established that α -synuclein is involved in the pathogenesis of the autosomal dominant form of Parkinson's disease, and mutations in the Parkin gene have been identified as the cause of autosomal recessive Parkinson's disease.¹⁴⁻¹⁷ Data regarding the molecular genetic analyses of familial Parkinson's disease confirm that Parkinson's disease is phenotypically and genotypically heterogeneous.¹¹⁻¹⁵ Hence, one cannot expect that mutations in one gene may be responsible for all types of familial and sporadic Parkinson's disease worldwide.

Two distinct mutations in the α -synuclein gene, which have been found in patients with familial Parkinson's disease in the Italian Contursi kindred and Greek families,¹¹ have not been found in those with white European ancestry¹⁸⁻²⁰ and Chinese²¹ patients with familial, younger onset, and sporadic Parkinson's disease. Heritability estimates based on quantitative genetic modelling or any other method does not take possible gene-environment interaction into account. Gene-environment interactions may be crucial in development of Parkinson's disease. There is no doubt both genetic and environmental factors contribute to the pathogenesis of Parkinson's disease.²²⁻²⁵ Different aetiological types of Parkinson's disease can be very closely linked clinically and metabolically.²⁶ Therefore, for understanding the mechanisms of clinical expression of Parkinson's disease both genetic classifications of the disease and determination of environment risk factors is required. The aetiological and genetic factors in Parkinson's disease may be different in Asians compared with the white population.²⁷⁻²⁹

The aims of this study were (A) to determine inheritance patterns of familial Parkinson's disease in three different geographical areas: Russia, Uzbekistan, and Zambia; (B) compare clinical characteristics of familial Parkinson's disease with sporadic Parkinson's disease; and (C) assess whether there were ethnic differences in clinical manifestations of the disease.

PATIENTS AND METHODS

Study sites and study period

Data were collected during the following periods:

- (A) January 1971 to July 1974 in the Department of Neurology, Postgraduate Training Institute for Physicians, Moscow, Russia.
- (B) January 1991 to September 1997 in the Department of Neurology, Postgraduate Training Institute for Physicians, Tashkent, Uzbekistan.
- (C) January 1999 to September 2001 in the Department of Medicine, University Teaching Hospital, University of Zambia, School of Medicine, Lusaka, Zambia.

Patients and selection criteria

Patients with an established diagnosis of parkinsonism or suspected Parkinson's disease were referred to each of the centres in Tashkent and Moscow from neurological clinics and hospitals. In Zambia all patients attending the specialist clinic at the University Teaching Hospital (Lusaka) (a single neurological referral clinic in Zambia) were screened prospectively for Parkinson's disease. Informed consent was given by each individual participating (in Uzbekistan and Zambia) in the study.

In Russia Parkinson's disease was diagnosed using the Webster scale; in Uzbekistan and Zambia the diagnosis was based on the Unified Parkinson's Disease Rating Scale (UPDRS). Parkinson's disease was diagnosed either when at

Table 1 Genetic characteristics of the families: inheritance patterns of familial Parkinson's disease

Countries	Familial		
	Total	SG/MG	Sporadic
Russia	30	7/23	22
Uzbekistan	12	5/7	43
Zambia	7	2/5	20
Total	49	14/35	85

SG/MG, single generation/multigenerational.

least two of the following four cardinal signs were present in an individual not receiving antiparkinsonian medication: (1) resting tremor, (2) bradykinesia, (3) rigidity, (4) impaired postural reflexes or if one of the cardinal signs was improved by antiparkinsonian treatment (generally with levodopa). Other patients with symptoms of parkinsonism were excluded for the following reasons:

- (1) Parkinsonism in dementia.
- (2) Parkinsonism with associated neurological features (for example, multiple system atrophy or progressive supranuclear palsy).
- (3) Drug induced parkinsonism.
- (4) Cerebrovascular parkinsonism.
- (5) Unspecified parkinsonism: no clear time relation with possible causes (for example, dementia or antidopaminergic drugs or more than one possible cause). Patients fulfilling the criteria for Parkinson's disease who showed no progression of the disease over years or who were not responsive to antiparkinsonian drugs were also considered "unspecified".

Evaluation of patients included a standardised questionnaire (in three languages: Russian, Uzbek, English) and detailed neurological examination by a neurologist experienced in movement disorders (one of authors, MA) in all three countries. Each patient had the following information recorded: geographical and ethnic origin, sex, age, place of birth, age at onset and duration of the disease, disease course from onset, medical history, dose and duration of antiparkinsonian treatment. All probands were hospitalised and their response to levodopa was evaluated by comparing untreated (that is, after 24 hours levodopa withdrawal) and treated (that is, after giving the patient a single dose of levodopa). UPDRS scores "on" and "off" and Hoehn and Yahr scores were determined for patients in Uzbekistan and Zambia. Brain computed tomography or magnetic resonance imaging were performed in 36 patients from Uzbekistan and Zambia, and all were normal. Slit lamp examination and copper metabolism studies were normal in all patients with young onset Parkinson's disease (below the age of 40).

Family history

In all three countries data on familial aggregation were collected, during the screening phase of the survey, before any diagnostic procedure was performed. Information about the presence of Parkinson's disease or similar symptoms among first degree and other relatives were obtained according to a structured questionnaire. Family history of Parkinson's disease was considered positive if it was reported for at least one parent or sibling. Extensive pedigrees were constructed for all familial and sporadic cases. The sporadic cases made up a control group for familial cases. The sex ratio, transmission pattern, and ancestral secondary cases, and segregation ratio were determined by pedigree analysis. Families were classified as single generation families when all affected members belonged to only one generation and multigenerational when affected members spanned more than one generation.

Patients in Russia include Russians, Ukrainians, Jews, and Belorussians; patients in Uzbekistan include Uzbeks, Tadjiks, Tartars, and Kazakhs; and in Zambia patients include black adult Zambians from four major tribes: Bemba, Lozi, Nyanja, and Tonga. The following ethnic groups were excluded: Asians in Russia, Slavs and Jews in Uzbekistan, and non-indigenous Zambians in Zambia.

Data analysis

A segregation ratio was estimated for each family corresponding to the ratio of affected to total number of offspring descending from an obligate carrier, affected or not. Total segregation ratio was considered as the sum of the ratio found in each family. In the case of an autosomal dominant model, one would expect a value of 0.5 for segregation ratio. The segregation ratio was also estimated in each single generation and multigenerational families. The χ^2 test was used to test difference between single and multigenerational families for sex ratio, categories of age at onset, and initial symptom. The non-parametric Wilcoxon test was used to calculate differences in age, age at onset, disease duration, Hoehn and Yahr stages and UPDRS scores.

RESULTS

Fifty two index cases in Moscow, 55 cases in Tashkent, and 27 cases of familial Parkinson's disease in Lusaka were selected on the basis of the typical clinical features of Parkinson's disease and a familial history. A total of 49 families and 85 sporadic cases were enrolled in the study. All were of urban origin. Table 1 shows the inheritance patterns of familial Parkinson's disease in patients studied.

In multigenerational families the pedigrees spanned two to four generations in Russia and two to three generations in Uzbekistan and Zambia. Parental consanguinity was noted only in single generation families: three in Russia, two in Uzbekistan families, and none in Zambia. The distribution of affected relatives is shown in table 2. In Russia all modes of transmission were observed: male-to-male, male-to-female,

Table 2 Distribution of the number of affected relatives with Parkinson's disease in multicase families

Country	No of relatives					
	Unexamined			Examined		
	Total	Affected	%	Total	Affected	%
Russia	558	74	13.2	153	14	9.1
Uzbekistan	216	25	11.5	132	11	8.3
Zambia	240	24	10.0	84	5	5.9

Table 3 Clinical characteristics of patients with familial Parkinson's disease compared with sporadic Parkinson's disease

Characteristics	Russia		Uzbekistan		Zambia	
	Familial (n = 118)	Sporadic (n = 22)	Familial (n = 48)	Sporadic (n = 43)	Familial (n = 36)	Sporadic (n = 20)
Mean age at onset (range)	60.4 (39–75)	64.7 (44–73)	63.2 (18–78)	65.1 (46–81)	37.6 (24–43)	54.1 (37–75)
Mean (SD) duration of disease in years	10.3 (4.9)	9.6 (5.2)	9.6 (3.8)	11.4 (4.7)	11.2 (4.7)	9.3 (3.6)
Male (%)	63 (53)	12 (54.5)	27 (56)	23 (54)	21 (58)	13 (64)
Female (%)	55 (47)	10 (45.5)	21 (44)	20 (46)	15 (42)	7 (35)
Class of age at onset (%)						
Juvenile (<21 years)	–	–	2 (4.1)	–	–	–
Young (21–40 years)	3 (2.5)	–	4 (8.2)	–	5 (14)	6 (30)
Common (>40 years)	15 (97.5)	22 (100)	42 (87.5)	43 (100)	31 (86)	14 (70)
Initial symptom (%)						
Tremor	54 (45)	11 (50)	17 (35)	23 (53)	7 (19)	4 (20)
Bradykinesia	41 (34)	7 (32)	22 (46)	14 (32)	18 (50)	8 (40)
Both	23 (21)	4 (18)	9 (19)	6 (15)	11 (31)	8 (40)
Predominant feature (%)						
Tremorous	53 (45)	9 (41)	14 (29.2)	18 (42)	7 (20)	5 (25)
Akinetic-rigid	29 (25)	6 (27)	20 (41.6)	10 (23)	20 (55)	11 (55)
Mixed	36 (30)	7 (32)	14 (29.2)	15 (35)	9 (25)	4 (20)

female-to-female, and female-to-male transmission. In Uzbekistan and Zambia male-to-female and female-to-male transmission were found. In Russian families the mean (SD) age at onset of Parkinson's disease was earlier (63 (2.8); $p < 0.05$) than their affected parents and grandparents (68 (2.5)). Sibship size was larger in multicase families than in sporadic in all three countries, but significantly larger in Zambia.

Clinical characteristics of the families

Clinical data of all unexamined and examined are summarised in table 3. The mean age at onset was younger in familial than sporadic Parkinson's disease in all three countries and the most striking difference was found in Zambian patients. Moreover, age at onset of both familial and sporadic cases in Zambia was younger than Russia and Uzbekistan. Age at onset of familial Parkinson's disease in Uzbekistan was older than Russia. Juvenile onset (<21 years old) was observed only in two patients with familial Parkinson's disease in Uzbekistan and young onset (21–40 years) was found more often in Zambia than in Russia and Uzbekistan.

Duration of disease was longer in familial (11.2 (4.7); $p < 0.01$) than in sporadic cases (9.3 (3.6)) in Zambian patients; it was longer in sporadic cases (11.4 (4.7); $p < 0.05$) than in familial Parkinson's disease (9.6 (3.8)) in Uzbekistan.

In all three countries males were more predominant than females.

Differences in clinical symptoms are shown in table 3. Clinical manifestations of Parkinson's disease in probands and their affected relatives were similar in each multigenerational family. There was some differences in clinical manifestations of Parkinson's disease in multigenerational and sporadic families between countries. In Russia in multigenerational families tremor predominated, among siblings in sporadic families all clinical forms of Parkinson's disease were found. In the multigenerational families of Uzbekistan and Zambia a higher prevalence of akinetic-rigid syndrome of Parkinson's disease was observed.

Severity of the disease and degree of response to levodopa treatment was similar in familial and sporadic cases in Russia and Uzbekistan. Severity of Parkinson's disease in Zambian patients was less prominent than in the Russian and Uzbekistan patients. But responsiveness to levodopa treatment in Zambian patients was significantly better than in the patients from Russia and Uzbekistan. In addition, significantly slower progression of the disease was found in Zambian patients suggesting that the course of Parkinson's disease in Zambian patients is more benign than in the patients of Russia and Uzbekistan.

Associated diseases in Russian families with familial and sporadic disease are shown in table 4. In addition, the clinical course of Parkinson's disease was more benign in probands who had type 2 diabetes and these showed good response to treatment with levodopa. Associated diseases in Uzbekistan are shown in table 5. Unlike the Russian patients, the number of disease and affected relatives was significantly lower, except that goitre was more common. Similarly,

Table 4 Associated diseases in families with familial and sporadic Parkinson's disease in Russia; values are numbers

Disease	Familial (n = 30)		Sporadic (n = 22)	
	Families	Cases	Families	Cases
Diabetes, type 2	8	32*	5	11
Glaucoma	4	12†	3	7
Schizophrenia	6	8	–	–
Essential tremor	3	6	4	6
Migraine	3	5	2	3
Epilepsy	3	3	–	–
Goitre	–	–	3	6
Amyotrophic lateral sclerosis	–	–	5	5
Hereditary spastic paraplegia	2	2	–	–
Torsion dystonia	2	2	–	–

*15 also had Parkinson's disease; †eight also had Parkinson's disease.

Table 5 Associated diseases in families with familial and sporadic Parkinson's disease in Uzbekistan; values are numbers

Disease	Familial (n = 12)		Sporadic (n = 43)	
	Families	Cases	Families	Cases
Goitre	4	7	5	9
Diabetes, type 2	2	5	2	3
Glaucoma	2	3	3	1
Essential tremor	2	4	2	5

Table 6 Associated diseases in families with familial and sporadic Parkinson's disease in Zambia; values are numbers

Disease	Familial (n = 7)		Sporadic (n = 20)	
	Families	Cases	Families	Cases
Epilepsy	2	4	4	7
Diabetes, type 2	2	3	3	5
Goitre	1	1	2	3
Essential tremor	1	1	3	3
Migraine	2	2	3	4
Hereditary spastic paraplegia	1	4	–	–

associated diseases in Zambian families are shown in table 6. Among affected relatives epilepsy and diabetes type 2 were relatively common.

DISCUSSION

Over the last century familial aggregation studies have shown an increased risk for Parkinson's disease in relatives of probands with different clinical form of Parkinson's disease.^{30–32} This is the first study comparing familial and sporadic Parkinson's disease in three ethnic and geographically different countries. Comparison of baseline characteristics of familial Parkinson's disease in our three countries with some of the literature data are shown in table 7, and support the presence of familial cases of Parkinson's disease in Russia, Uzbekistan, and Zambia.

Familial Parkinson's disease appears to occur more often in Russia than in Uzbekistan and Zambia. This may be due to different circumstances for gene-environment interaction between countries. Our preliminary data comparing the frequency of Parkinson's disease between the residents of the capital of Uzbekistan (Tashkent) and provinces showed that Parkinson's disease is rarer in the regions of Uzbekistan where people drink only green tea. This fact may be important because in Uzbekistan about 70% of people live in rural areas where, for many decades, pesticides were used

in the cultivation of cotton plants. Exposure to pesticides is one of the risk factors for development of Parkinson's disease.³⁵ Moreover, recently it was reported that a phenolic compound in green tea exerted a neuroprotective influence in models of experimental parkinsonism.³⁶

In each country inheritance of Parkinson's disease was found, most commonly autosomal dominant. There are three major findings from our study. Firstly, the younger age at onset in both familial and sporadic Parkinson's disease in Zambian patients, which is similar to that reported in Tunisian patients.³⁴ Secondly, in all countries men have a higher risk of development of Parkinson's disease than women; and thirdly, the course of Parkinson's disease in Zambian patients was more slowly progressive and benign compared with the others. Zambian patients also responded better to levodopa treatment than other groups.

Although the reasons for the male predominance of Parkinson's disease remain unknown, the female steroid hormones may be responsible for protection from Parkinson's disease.^{37–40} It has been established that in the central nervous system oestrogen can provide a neuroprotective effect and have a role in the process of oxidative stress, which is considered as a potential cause of nigral degeneration in Parkinson's disease.³⁷

We consider that the concomitant presence of type 2 diabetes in two to three generations of Russian and Zambian patients is not coincidental, as it has also been reported by others.^{41–42} The relation between brain dopamine and insulin seems important, probably in the degree of interaction of the corresponding genes or mutations. A recent study showed the presence of the 3397 ND1 mutation in maternally inherited diabetic patients and their maternal relatives, which was previously associated with Parkinson's disease.⁴³

This study had limitations. Firstly, as this is a descriptive clinical study with no gene testing, it is not possible to decide whether the findings are applicable to all familial cases or only to some subgroups. Secondly, data collection spanned over 30 years, which could introduce a time effect. Thirdly, this is a hospital based study, not population based, and we recognise that our analyses were limited to participants referring or attending our centres. Different proportions of familial cases in different countries may be supported by population data.

Table 7 Comparison of baseline characteristics of familial Parkinson's disease in three countries with literature data

Characteristics	Maraganore <i>et al</i> ¹ 1991	Plante-Bordeneuve <i>et al</i> ² 1995	Gouider-Khouja <i>et al</i> ³ 2000	Russia	Uzbekistan	Zambia
No of families	20	14	21	52	55	27
Single generation	5	6	10	7	5	2
Multigenerational	15	8	11	23	7	5
No of secondary cases	20	17	67	88	36	29
No affected	40	31	88	118	48	36
Men (%)	16 (40)	14 (45.6)	44 (50)	63 (53)	27 (56)	21 (58)
Women (%)	24 (60)	17 (54.8)	44 (50)	55 (47)	21 (44)	15 (42)
Age at onset (years)	58	59.6	39 ± 14.4	60.4	63.2	37.6
Disease duration (years)	8	9.0 ± 4.3	12.6 ± 9.8	10.3	9.6	11.2
No (%) of symptoms at onset						
Tremor	25 (62.5)	18 (58.0)	37 (63.8)	54 (45)	17 (35)	7 (19)
Bradykinesia	13 (32.5)	13 (42.0)	13 (22.4)	41 (34)	22 (46)	15 (50)
Both	–	–	8 (13.8)	23 (21)	9 (19)	11 (31)
No (%) with symptomatic form						
Tremorous	5 (13.5)	1 (3.0)	14 (24.1)	53 (45)	14 (29.2)	7 (20)
Akinetic-rigid	3 (7.5)	8 (26.0)	21 (36.2)	29 (25)	20 (41.6)	20 (55)
Mixed	32 (8.0)	22 (71.0)	23 (39.7)	36 (30)	14 (29.2)	9 (25)

Our study suggests that there are ethnic differences in the clinical expression of Parkinson's disease. Ethnic differences in the clinical characteristics of Parkinson's disease probably reflect underlying genotypic differences. It is very likely that the different clinical forms of Parkinson's disease in the same family and between families in each country may have resulted from interactions of genetic or environmental modifiers, or both. At present it is obvious that familial aggregation patterns cannot be explained by segregation of a single autosomal gene. The next step would be to elucidate ethnic differences in disease pattern and the molecular basis of the genetic susceptibility to Parkinson's disease to understand gene-environment interactions.

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