Epidemiology of Parkinson disease in the city of Kolkata, India

A community-based study

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ABSTRACT

Objective: No well-designed longitudinal study on Parkinson disease (PD) has been conducted in India. Therefore, we planned to determine the prevalence, incidence, and mortality rates of PD in the city of Kolkata, India, on a stratified random sample through a door-to-door survey.

Method: This study was undertaken between 2003 to 2007 with a validated questionnaire by a team consisting of 4 trained field workers in 3 stages. Field workers screened the cases, later confirmed by a specialist doctor. In the third stage, a movement disorders specialist undertook home visits and reviewed all surviving cases after 1 year from last screening. Information on death was collected through verbal autopsy. A nested case-control study (1:3) was also undertaken to determine putative risk factors. The rates were age adjusted to the World Standard Population.

Result: A total population of 100,802 was screened. The age-adjusted prevalence rate (PR) and average annual incidence rate were 52.85/100,000 and 5.71/100,000 per year, respectively. The slum population showed significantly decreased PR with age compared with the nonslum population. The adjusted average annual mortality rate was 2.89/100,000 per year. The relative risk of death was 8.98. The case-control study showed that tobacco chewing protected and hypertension increased PD occurrence.

Conclusion: This study documented lower prevalence and incidence of PD as compared with Caucasian and a few Oriental populations. The mortality rates were comparable. The decreased age-specific PR among slum populations and higher relative risk of death need further probing. *Neurology*® 2010;75:1362-1369

GLOSSARY

AAIR = average annual incidence rate; **AAMR** = average annual mortality rate; **CI** = confidence interval; **FSQ** = family screening questionnaire; **ICC** = intraclass correlation coefficient; **IR** = incidence rate; **MD** = movement disorder; **NSSO** = National Sample Survey Organization; **OR** = odds ratio; **PD** = Parkinson disease; **PPS** = parkinsonism plus syndrome; **PR** = prevalence rate; **PRM** = Poisson regression modeling; **RR** = relative risk; **SP** = secondary parkinsonism; **VA** = verbal autopsy.

The epidemiology of Parkinson disease (PD) has important public health and social implications and also provides etiologic clues. India is a multiethnic country with genetic diversity. Recent cross-sectional studies from India, besides the Parsis study, have shown lower age-adjusted prevalence rates (PRs) of PD in comparison with predominantly Caucasian and a few Oriental populations (table 1).¹⁻¹¹ In India, with an aging population and increased life expectancy, it is expected that the disease burden due to PD will be enormous, but there is no prospective study to estimate its incidence and mortality. The incidence rates (IRs) in different countries vary from 1.5 to 20 per 100,000 per year.¹²⁻²⁰ The wide discrepancy in rates among different studies may stem from ethnicity, environmental factors, and varied methodology. Previous studies have shown that subjects with Parkinsonism have a higher relative risk of death compared with nonparkinsonian subjects in the same age range.^{14,21} The low PR in most of the Indian studies may be due to either lower incidence or higher mortality or a combination of the two.

Supplemental data at
www.neurology.org

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Table 1 Frequency of Parkinson disease as reported by studies from India and abroad

Country	Period of study	Method	Population surveyed	Cases detected	Crude prevalence rate (per 100,000)	Age-adjusted rate (per 100,000)
India (Parsis) ¹³	1988	DDS	14,010	46	328.3	148 ^a
India (South) ²	1993–1995	DDS	102,557 (Rural and urban)	34	33	76 ^f
India (East) ¹	1992–1993	DDS	20,842 (Rural)	11	53	68 ^b
India (East) ³	2003–2004	DDS	52,377 (Urban)	24	45.82	73.79 ^c
The Netherlands ⁴	1990–1993		6,969 (55+ y)	97	1,400	
Sicily ⁵	1987	DDS	24,496	63	257.2	194 ^b
Bulgaria ⁶	1997	DDS	Gypsies 6,163	1	16	
			Caucasians 87,025	119	137	
Argentina ⁷	1991	DDS	7,765 (40+ y)	51	656.8	206.9 ^d
China ⁸	1993–1994	DDS	26,105	23	119	127 ^d
Taiwan ⁹	1997–1998	DDS	75,579	37	367.9	130.1 ^b
			11,411 (40+ y)			
Japan ¹⁰	1996	CLS	132,315	156	117.9	99.5 ^e
Nigeria ¹¹	1987	DDS	20,000	2	10	

Abbreviations: CLS = case linkage study; DDS = door-to-door survey.

^a To US 1960 population.

^b To US 1990 population.

^c To US 2000 population.

^d To US 1970 population.

^e To Japan 1990 population.

^f Standard population not mentioned.

Therefore, we planned to undertake a door-to-door survey on a large heterogeneous population in the metropolitan city of Kolkata, India, to determine the prevalence, incidence, and mortality rates of PD. A nested case-control study was undertaken to determine putative risk factors.

METHODS A prospective community-based study was conducted to find subjects with PD through a 3-stage house-to-house survey. The institutional Ethics Committee cleared the proposal, and written informed consent was obtained before interview.

Sampling. The sampling strategy has been published elsewhere. The survey area was the municipal limits of the city of Kolkata (erstwhile Calcutta) with an area of 185 km² and population of 4.58 million.³

The sample was chosen from the whole city through selection of stratified random National Sample Survey Organization (NSSO, India) blocks based on geographical location and dwellings. The city population was initially divided into slum-dominant and non-slum-dominant areas. A total of 6 strata (1 from slum areas and 5 from non-slum areas) were formed. The slum population constitutes approximately one third of the Indian urban population. The slum dwellers are socioeconomically weaker and live in unhygienic, overcrowded conditions. Each stratum acted as a sampling frame (figure 1) from which a proportionate number of NSSO blocks were selected by using random number tables. From each block, 50% of alternating families were surveyed. For purposes of inclusion, we consid-

ered at least 1 year of residency in the area to avoid the floating population.

A validated family screening questionnaire (FSQ) was used to detect cases of major neurologic illnesses. This was administered to the head of the family by field workers.² In cases of confused PD patients as determined from history and examination, spouses or reliable family members were interviewed. This questionnaire also contained information on demography and questions to detect cases with movement disorders (MDs) including PD, such as tremulous movement of head, arms, and legs and speech and gait abnormalities. We added 3 more questions to capture subjects with MDs.

Survey. In the first stage, field workers screened the sample for the positive cases. The field doctor examined them, recorded the clinical details, and verified randomly chosen 10% of screened negative population in each block to detect the false-negative cases. The clinical details of all positive cases were scrutinized by a team of senior neurologists, including MD specialists, and a consensus diagnosis was reached. Few subjects were examined either in the institute or at home for resolving any confusion. In the third stage, 1 MD specialist revisited all houses of the diagnosed cases after 1 year of completion of the initial survey for follow up and recorded any change in the clinical and treatment profile, including death cases.

In the initial phase, a study was conducted to determine the sensitivity and specificity of the screening questionnaire for PD in the MD clinic, where the specialist acted as the gold standard. An initial cross-sectional survey was undertaken in 2003 to 2004, and subsequently annual screening was performed between 2004 and 2008 to find new cases and follow up with the old cases. Verbal autopsy (VA) was performed in death cases. This is a standard method of interview-based retrospective col-

Figure 1 Sample stratification

lection of information on death from a reliable family member or close associate in the absence of a routine autopsy.²² All data from VA cases were verified by the field doctor and subsequently by a senior doctor. The VA questionnaire was field tested to determine sensitivity and specificity under the supervision of a senior doctor, who acted as the gold standard. The period for prevalence was considered up to December 31, 2007, and incidence was calculated for the period between 2003 and 2007.

Statistical analysis. PRs are expressed as per 100,000 population. Average annual incidence rates (AAIRs) and average annual mortality rates (AAMRs) are expressed as per 100,000 population per year. Age-adjusted rates were calculated by adjustment directly to World Standard Population.²³ The 95% confidence intervals (CIs) of all the rates were calculated based on Poisson distribution. The χ^2 test was used to assess significance of differences in unpaired proportions; $p < 0.05$ was considered significant. A nested case-control study was undertaken with age (± 5 years)-matched and sex-matched controls to assess the risk factors of PD. Controls were selected randomly from the case neighborhood in a 1:3 (case-to-control) ratio, and 92% agreed to participate (table e-1 on the *Neurology*[®] Web site at www.neurology.org). Multivariate analysis of the case-control data was performed through conditional logistic regression. Poisson regression modeling (PRM) was applied on prevalence and IR data to assess their relation with age and sex. Kaplan-Meier survival analysis was conducted with the prevalent cases of PD, the surviving cases being censored at the time of study closure. Statistica versions 6 [StatSoft Inc., Tulsa, OK; 2001] and 17 [SPSS Inc., Chicago, IL; 2008] were used for statistical analysis.

Operational definition. To minimize the number of cases missed, the presence of at least 2 of the following features was considered for parkinsonism: rest tremor, bradykinesia, rigidity, and postural instability.²⁴ We excluded those cases with features

of parkinsonism plus syndrome (PPS) and secondary parkinsonism (SP) for diagnosis of PD. PPS was considered per defined criteria.⁵ SP included those who had obvious causes leading to features of parkinsonism, such as neuroleptic use in the past 6 months preceding the onset of symptoms, infection, trauma, stroke, and hydrocephalus.

RESULTS The screened population was 100,802 individuals from 21,398 families out of 282 randomly selected blocks. The literacy rate was 83.23%, and the sex ratio (men to women) was 1:1.12. A total of 89 families refused or could not be contacted for participation in the study. The total population was exclusive of refusal cases.

The screening instrument for capturing PD cases showed a sensitivity of 88.23% (lower limit of 95% CI 63.09) and specificity of 100% (lower limit of 95% CI 71.40) based on 40 clinic cases, and sensitivity and specificity of VA were 97.5% and 57.14% based on 61 randomly selected community death cases.

The intrarater validation of individual questions on the FSQ showed perfect agreement among the 3 raters for all except 2 questions, which had an intra-class correlation coefficient (ICC) value of 0.794, indicating strong agreement. In interrater validation, there was perfect agreement between raters in all but 3 questions. For 2 of these questions, agreement was strong (ICC 0.794), and for 1, it was fair (ICC 0.310) (details in table e-2).

Table 2 Prevalence, incidence, mortality rates of Parkinson disease in Kolkata, India, and the corresponding age-adjusted and sex-specific rates^a

Measurement	No. of cases	Crude rate (/100,000)	Age-adjusted rate (/100,000)	Sex-specific rate ^b (/100,000)
Prevalence	41	40.67 [29.04–55.40]	52.85 [37.74–71.98]	M: 45.15 [26.77–71.38], F: 60.34 [37.95–91.15]
Average annual incidence (2003–2007)	23	4.56 [2.87–7.51]	5.71 [3.59–9.40]	M: 5.01 [2.50–8.96], F: 6.20 [3.21–10.84]
Average annual mortality (2003–2008)	13	2.28 [1.21–3.80]	2.89 [1.54–4.94]	M: 2.65 [1.14–5.22], F: 1.89 [0.60–4.34]

^a Figures in brackets denote corresponding 95% confidence intervals.^b Age-adjusted rate to Worlds Standard Population.

Table 2 shows the PR, AAIR, and AAMR of PD. Tables 3 and 4 depict age and sex distribution of the sample, which matched with the city population (Census India, 2001).

Prevalence. Of 52 cases with parkinsonism, PD was detected in 41 cases (the rest were PPS [6] or SP [5]). Table 3 shows overall, age- and sex-specific, and age-adjusted PRs. By applying PRM, the PR rate showed a significant, but nonlinear increase with age ($p < 0.001$) in comparison with sex ($p = 0.01$). The mean age of the subjects was 62.03 years (range 28–82 years). Prior diagnosis was made in 23 cases (56.09%), and only 18 cases (43.90%) received treatment. By applying PRM, the PR of the nonslum population showed a significant increasing rate with advancing age above 62.5 years compared with the slum population.

Incidence. A total of 23 cases of PD had onset of illness over the 5-year study period, and the AAIRs, age-adjusted rates, and sex-specific IRs are provided

in table 4. PRM analysis of these results showed IR increasing with age ($p < 0.001$), but sex had no effect ($p = 0.052$).

Follow-up and mortality. In the third stage (follow-up visit), there were 13 deaths (8 men, 5 women) of 41 cases over a period of 6 years, and a total of 3 cases could not be examined because of refusal (1) and migration (2). Of the remaining 25 cases, 1 case had multiple system atrophy, and another had features of essential tremor. Thirteen subjects were taking levodopa preparation and 9 other anticholinergics. Most of the subjects had shown a therapeutic response. None showed dyskinesia, but they received relatively low doses of levodopa. Additionally, 3 subjects were taking antipsychotics, 3 were taking antidepressants, and 4 were taking antihypertensives for comorbid disorders.

Overall AAMR and sex-specific mortality are provided in table 2. The difference of AAMR between slum (2.02) and nonslum (2.39) populations was in-

Table 3 Age- and sex-specific prevalence of Parkinson disease in Kolkata, India

Age band, y	Men			Women			Total		
	Population	No. of cases	PR	Population	No. of cases	PR	Population	No. of cases	PR
<40	36,624	0	0	32,792	1	3.05	69,416	1	1.44
40–44	3,336	2	59.95	3,436	1	29.10	6,772	3	44.30
45–49	3,853	0	0	3,177	2	62.95	7,030	2	28.45
50–54	2,716	3	110.46	2,191	1	45.64	4,907	4	81.52
55–59	2,400	1	41.67	1,735	0	0	4,135	1	24.18
60–64	1,393	2	143.58	1,391	4	287.56	2,784	6	215.52
65–69	1,074	3	279.33	986	4	405.68	2,060	7	339.81
70–74	917	4	436.21	961	5	520.29	1,878	9	479.23
75–79	426	1	234.74	428	1	233.64	854	2	234.19
80+	470	2	425.53	496	4	806.45	966	6	621.11
Total (95% CI)	53,209	18	33.83 (20.06–53.49)	47,593	23	46.23 (30.40–70.30)	100,802	41	40.67 (29.04–55.40)
AAR (95% CI)	45.15 (26.59–70.91)			60.34 (37.95–91.15)			52.85 (37.74–71.98)		

Abbreviations: AAR = age-adjusted rate; CI = confidence interval; PR = prevalence rate.

Table 4 Age- and sex-specific incidence of Parkinson disease in Kolkata, India

Age band, y	Men			Women			Total		
	Population	No. of cases	AAIR	Population	No. of cases	AAIR	Population	No. of cases	AAIR
<35	31,960	0	0.00	28,350	0	0	60,490	0	0
35-39	4,664	1	4.29	4,262	1	4.69	8,926	2	4.48
40-44	3,336	1	6.00	3,436	2	11.64	6,772	3	8.86
45-49	3,853	0	0	3,177	0	0	7,030	0	0
50-54	2,716	2	14.7	2,191	0	0	4,907	2	8.15
55-59	2,400	1	8.33	1,735	0	0	4,135	1	4.84
60-64	1,393	2	28.72	1,391	4	57.51	2,784	6	43.10
65-69	1,074	2	37.24	986	0	0	2,060	2	19.43
70-74	917	2	43.62	961	2	41.62	1,878	4	42.60
75-79	426	0	0	428	2	93.45	854	2	46.84
80+	470	0	0	496	1	40.32	966	1	20.7
Total (95% CI)	53,209	11	4.13 (2.06-7.39)	47,593	12	5.04 (2.61-8.80)	100,802	23	4.56 (2.87-7.51)
AAR (95% CI)	5.01 (2.50-8.96)			6.21 (3.21-10.49)			5.71 (3.59-9.40)		

Abbreviations: AAIR = average annual incidence rate; AAR = age-adjusted rate (to World Standard Population); CI = confidence interval.

significant. Maximum mortality was observed in the 70- to 74-year age band. The mean age of death cases was 71.31 years (men: 70.38, women: 72.8). The standardized mortality ratio was 3.79 (95% CI 2.01–6.48; men: 5.23, women: 2.53). Thirteen cases of 31 with PD and age greater than 55 years died, and over the same period, 590 subjects of 12,683 nonparkinsonian population died of other causes. So the relative risk (RR) stood at 8.98 (95% CI 5.89–13.70). The most probable causes of death were prolonged bedridden state in 3 (23.07%), ischemic heart disease in 3 (23.07%), cerebrovascular accident in 2 (15.38%), asthma in 2 (15.38%), train accident in 1 (7.6%), sunstroke in 1 (7.6%), and cancer in 1 (7.6%). The median survival time based on Kaplan-Meier survival analysis was 13.5 years (figure e-1).

Case-control analysis. Both univariate and multivariate analysis were conducted to detect the association of risk factors of PD. Among controls, the prevalences of smoking and tobacco chewing were 33.3% and 26.08% among men and 0% and 20.37% among women. In univariate analysis, history of regular tobacco use (besides smoking) showed a lower risk for development of PD (odds ratio [OR] 0.15, 95% CI 0.04–0.70), whereas hypertension increased the risk (OR 2.45, 95% CI 1.03–5.84). The other putative risk factors did not show appreciable increase or decrease in odds. In conditional logistic regression analysis, only nonsmoking tobacco use showed up as a significant factor decreasing risk (adjusted OR 0.16, 95% CI 0.03–0.75). The overall

predictability was modest, with a Nagelkerke R^2 value at 0.137.

DISCUSSION One concern about diagnosis of PD is the lack of biomarkers and dependence on clinical evidence. Epidemiologic ascertainment of cases is commonly based on the administration of interview-based questionnaires. Sensitivity and specificity of such questionnaires depends on the number of questions, and various studies have shown that a minimum number of questions (as low as 2) improves sensitivity but decreases specificity.²⁵ Conversely, by increasing the number of questions, specificity may be increased, but sensitivity is reduced. However, the lower limit of sensitivity and specificity of the PD screening instrument indicates that a few cases might have been misdiagnosed or early cases might have been missed.

The adjusted PR of PD in this study and those of other recently conducted studies from India¹⁻³ have documented lower values as compared with Caucasian populations. A lower prevalence of PD has been shown among Bulgarian gypsies of presumably Indian origin in comparison with Caucasians living in the same environment.⁶ Similarly, an Anglo-Indian study from Southern India recorded a very low prevalence of PD.²⁶ These 2 studies suggest a possible role of genetic influence. Only the study among Parsis from India observed high prevalence of PD, which can be explained by a distinct ethnicity and higher aging population.¹³ Hence, lower prevalence among Indian studies may be true and may be related to

either low incidence or increased mortality. The higher prevalence of PD among women has been documented in Finland, Japan, and India.^{1,27,28} This may be related to environmental factors rather than genetic factors. Lack of estrogenic support was shown to induce nigral cellular degeneration in animals.²⁹ Because tobacco smoking was infrequent among women in this study, the prevalence of PD may be higher because of lack of its protective effect.³⁰ However, the lack of simultaneous increase of PR of PD among the slum population compared with the non-slum population might indicate a protective effect due to some environmental factor, which needs to be probed further.

This study documented a lower AAIR of PD as compared with North American (20),¹⁴ many European (19),^{15,16} Japanese (15),¹⁰ Australian (7),¹⁸ and Chinese in Taiwan (10)⁹ populations, but similar to 1 Italian (10)¹⁶ and Libyan population (4.5)¹⁸ and higher than in the Chinese population (1.5).⁸ Age-specific AAIRs were also lower in comparison with similar studies in the above populations.^{9,10,13–18} A meta-analysis by Zhang et al. showed that there was no change in IRs over the past 50 years, signifying that adjusted IR in this study is possibly stable.¹² This study has shown no significant difference in sex-specific incidence and, hence, suggests that the chance of developing PD is almost equal in both sexes. Conversely, evidence of 2-fold higher incidence among Italian men over women may indicate a probable influence of sex in the occurrence of PD.³¹ The role of ethnic influence is revealed from different IRs among different racial populations, and the lowest rate is noted among Asians.³² This is in accordance with our finding.

The AAMR of this study is comparable with those of studies worldwide, varying between 0.5 and 3.8 per 100,000.²⁷ The higher mortality rate among men can explain the higher prevalence among women. However, the median survival time in this study is close to that of Taiwan.⁹ The causes of death in this study differ from another Asian study where pneumonia was a commonly recognized cause of death among patients with PD. Also, a higher RR as compared with the United States (2.2)²¹ and Taiwan (3.8)⁹ and standardized mortality ratio in this study (8.98) indicate either more severe disease or a deficiency of health care in the community.⁸ Lack of a social support system and paucity of trained manpower, rather than socioeconomic factors, are the main constraints, because there was no significant difference in mortality between slum and non-slum cases. The earlier age at death is possibly a reflection of the general pattern of mortality in individual countries, depending on life expectancy.

The case-control study revealed that the only risk factor was hypertension and a protective factor was

tobacco chewing, similar to another report from India.³² The effect of tobacco chewing is prolonged because of persistent contact with buccal mucosa and provides higher potency than smoking cigarettes.³³ The role of vascular pathology and that of hypertension have been emphasized in vascular parkinsonism.³⁴ However, hypertension is now considered as a risk factor in neurodegenerative disorders such as Alzheimer disease.³⁵ Therefore, it is possible that hypertension may accelerate neurodegeneration. Conversely, a few cases of vascular parkinsonism also respond to levodopa.³⁶ It is noteworthy that the incidences of hypertension and stroke are increasing in India,³⁷ and some of the PD cases may be truly vascular in origin and probably misdiagnosed because of levodopa responsiveness and lack of biomarkers emphasizing further study.

Therefore, the lower prevalence of PD is explainable by lower IR, which may be related to either genetic or environmental factors. The studies from India have documented a genetic contribution in up to 8.5% of cases of familial and sporadic PD.³⁸ Thus, in the absence of a genetic contribution, environmental factors may confer protection. Various phenolic compounds, such as curcumin from turmeric, have shown antioxidative and anti-inflammatory effects.³⁹ Interestingly, Indians consume curcumin daily in their diet from early childhood. Curcumin prevents aggregation of α -synuclein in experimental animals and possibly cell death.⁴⁰ It is possible that long-term consumption of curcumin might confer protection against development of PD. This issue merits exploration.

There are some limitations in this study. Because the method of case ascertainment is interview based, early cases may be missed. The lower 95% confidence limit of sensitivity and specificity of the screening instrument might indicate that a few early cases may have been missed. Thus, the estimate could be higher. Many elderly persons could not tell the exact date of birth, and so lack of uniformity of age-specific IRs and PRs may be related to misgrouping of the subjects in different age bands. The diagnosis of PD is clinical, and some of the PD cases might be variants of PPS, if autopsy could be performed in death cases. The case-control study has limitations, such as recall bias and improper quantification of the exposure of interest. The specificity of VA is usually low because there is no way to validate the diagnosis in the absence of autopsy verification.²²

Nevertheless, we have documented lower PRs and IRs of PD. Mortality is comparable. In view of the close age and sex matching of our sample to the Kolkata population, the results are generalizable. The case-control study shows that PD increases with systemic hyperten-

sion and decreases with tobacco chewing. The lower IR may be related to environmental factors. The higher RR of death of subjects with PD demands greater attention, better care, and social support. Lack of a parallel increase of PD prevalence among the slum population might indicate the existence of a protective factor and needs probing.

AUTHOR CONTRIBUTIONS

Statistical calculations were performed by Dr. A. Hazra.

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