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EPIDEMIOLOGY OF PARKINSON'S DISEASE

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This article reviews the epidemiology of Parkinson's disease, with particular attention to disease frequency and risk factors for disease. Some areas that might appropriately be considered in an epidemiologic work, such as natural history, etiologic theories resulting from epidemiologic investigations, and the population effects of pharmacologic intervention, are covered in detail in other articles in this issue and thus considered only briefly or not at all here. Before beginning, however, the working definition of Parkinson's disease for this article, epidemiologic terms, and specific problems encountered in the epidemiologic study of Parkinson's disease are considered.

DEFINITIONS

This discussion considers *Parkinson's disease* to be a distinct clinical and neuropathologic entity, characterized clinically by bradykinesia, resting tremor, cogwheel rigidity, and postural reflex impairment and pathologically by the loss of pigmented neurons, most prominently in the substantia nigra, with associated characteristic eosinophilic cytoplasmic inclusions (Lewy bodies). This definition excludes all parkinsonism of known etiology and any disorder with multiple system involvement or significant lesions of the striatum, such as progressive supranuclear palsy, olivopontocerebellar atrophy, Shy-Drager syndrome, multiple system atrophy, or striatonigral degeneration.[40]

Epidemiologic Terms

Prevalence refers to the total number of persons with a disorder within a given population at a fixed point in time. In contrast, *incidence* is the number

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of new cases of a disorder first developed or diagnosed during a specific time interval. Ideally incidence and prevalence are determined by screening entire populations defined by specific geographic or political boundaries (*community-based studies*).[65] Estimates of prevalence based on populations identified by other methods (such as participants in a hospital clinic) do not accurately reflect the general population of an area, since cultural, economic, or other factors may influence case selection.

Risk factors for disease may be explored in three general types of epidemiologic studies.[65] Prospective cohort or follow-up studies identify unaffected persons who differ with respect to a specific factor proposed to be related to the disease (an *exposure*), then observe these individuals over time, and measure the frequency of new disease in exposed and unexposed persons. For relatively rare chronic diseases beginning in late life, such as Parkinson's disease, prospective cohort studies are difficult to perform, since a large number of unaffected individuals must be followed for decades. A faster and more economical approach is provided by the case-control study. In case-control studies, individuals already affected with the disease of interest are compared with individuals without the illness, and exposures proposed to relate to the illness are compared. Finally in some cases (such as MPTP-induced parkinsonism), identification and intensive investigation of an unusually high incidence of disease, either in space or in time (a *cluster*), may provide important clues to disease etiology.

PROBLEMS ENCOUNTERED IN EPIDEMIOLOGIC STUDIES

Diagnostic accuracy poses a major problem in epidemiologic studies of Parkinson's disease because there is no definitive diagnostic test. As yet no epidemiologic study has included autopsy confirmation of cases. Epidemiologic studies should be reviewed with an awareness of the methods used to identify and diagnose cases and potential problems that might result from methodologic differences. For example, variations in the experience of diagnosticians can affect diagnostic accuracy. In some communities, essential tremor accounted for 10% to 40% of the false-positive diagnoses of Parkinson's disease.[50, 53] Conversely bona fide Parkinson's disease may be misdiagnosed as depression or, in the very elderly, "normal" aging. Disorders such as progressive supranuclear palsy or multiple system atrophy may not be easily distinguished from Parkinson's disease early in the course of illness.[40]

Varying definitions of diagnostic criteria make it difficult to compare studies performed at different times or in different areas. Many of the atypical parkinsonian syndromes were widely recognized only in the last several decades, and these may have been classified as Parkinson's disease in earlier reports. In some older studies, many cases are classified as *arteriosclerotic parkinsonism* that today might be considered typical Parkinson's disease.[8, 43, 47] Other reports grouped drug-induced parkinsonism and postencephalitic parkinsonism along with Parkinson's disease in determining incidence or prevalence rates, although these disorders are etiologically and pathologically distinct.[8, 43, 61]

FREQUENCY OF PARKINSON'S DISEASE

Community-based studies of Parkinson's disease incidence and prevalence were not performed until a century and a half after James Parkinson's 1817

report of six cases.[58] In 1958, Kurland[43] reported an estimated combined prevalence of 187 per 100,000 for postencephalitic, arteriosclerotic, and nonarteriosclerotic parkinsonism in the population of Rochester, Minnesota. Annual disease incidence was estimated to be 20 per 100,000 persons. Case identification was performed through the records linkage system of the Mayo Clinic, assuring both that the majority of affected residents were identified and that the medical information available was of uniformly high quality. In 1967 Gudmundsson[29] identified cases of Parkinson's disease in Iceland by physician's reports and personal examination, estimating a combined annual incidence of 16 per 100,000 cases for arteriosclerotic and nonarteriosclerotic parkinsonism. Estimated prevalence for these two disorders was 162 per 100,000, similar to the estimate for Rochester, Minnesota. Numerous subsequent surveys attempted to estimate disease prevalence in a community by using all available health care records (national health registries; pharmacy rosters; hospital and chronic care facility rosters; questionnaires directed to physicians, nurses, and social workers) to identify patients.[2, 8, 14, 31, 34, 38, 50, 53, 55, 61, 64, 70] These studies would have missed early cases and cases not receiving medical care. Diagnostic errors could have caused increased or decreased inclusion of actual cases. Results from many of these are shown in Table 1.

A different approach to estimating disease prevalence in a community involves a door to door survey of all households, usually screening specific age groups. Persons identified as possibly suffering from a specific disorder are then referred for neurologic evaluation. Apart from differences in diagnostic criteria and diagnostic skill, these surveys should provide the most accurate estimates of disease prevalence for the age group screened. Door to door surveys are costly, but a number of such surveys have been successfully performed, often in association with a national census.[6, 45, 63, 66, 67] Results of these surveys are presented in Table 2.

Despite the method used, estimates of disease prevalence vary widely, from 31 per 100,000 in Libya[2] to 328 per 100,000 in the Parsi community in

Table 1. ESTIMATED INCIDENCE AND PREVALENCE OF PARKINSON'S DISEASE IN REPRESENTATIVE COMMUNITY-BASED STUDIES

Location (Authors)	Publication Year	Prevalence (per 100,000)	Annual Incidence (per 100,000)
Rochester, MN (Kurland[43])	1958	187	20
Carlisle, England (Brewis et al[8])	1966	113	12
Victoria, Australia (Jenkins[34])	1966	85	—
Iceland (Gudmundsson[29])	1967	162	16
Baltimore, MD (Kessler[38])	1972	128*	—
Turku, Finland (Marttila and Rinne[50])	1976	120.1	15
Aberdeen, Scotland (Mutch et al[53])	1986	164.2	
San Marino (D'Alessandro et al[14])	1987	152	—
Yonago, Japan (Harada et al[31])	1983	80.6	—
Sardinia, Italy (Rosati et al[64])	1980	65.6	10
Northampton, United Kingdom (Sutcliffe et al[70])	1985	108.4	4.9
Benghazi, Libya (Ashok et al[2])	1986	31.4	—
Rochester, MN (Rajput et al[61])	1984	—	4.5
Izumo City, Japan (Okada et al[55])	1990	82	20.5
			—

*Males.

Table 2. ESTIMATED PREVALENCE OF PARKINSON'S DISEASE IN DOOR TO DOOR SURVEYS

Location (Authors)	Publication Date	Ages Screened	Prevalence (per 100,000)
Chinese cities (Li et al[45])	1985	age >50	44
Copiah Co, MS (Schoenberg et al[67])	1985	age >39	347
Igbo-ora, Nigeria (Schoenberg et al[66])	1988	age >39	58.6
Parsi community, Bombay, India (Bharucha et al[6])	1988	all ages	328.3
Terrasini & Santa Teresa di Riva, Sicily, Italy (Rocca et al[63])	1990	all ages	243

Bombay, India.[6] Although methodologic differences may account for some variation, it is possible that different distributions of factors related to Parkinson's disease etiology across populations may contribute to geographic differences in disease frequency. These factors could include genetic differences in susceptibility to disease, differences in exposure to causative factors, and differences in exposure to protective factors.

RISK FACTORS FOR PARKINSON'S DISEASE

Age

Parkinson's disease is rare before the age of 30, and incidence rises with increasing age thereafter.[61] This is true in all community-based studies, regardless of the absolute prevalence of disease in the population.[31, 43, 50, 53, 64, 70] Some examples of age-specific prevalence in different communities are shown in Table 3. The reasons for this relationship are not known. Possible explanations for the correlation between increasing age and prevalence of Parkinson's disease include age-related neuronal vulnerability or an etiologic mechanism dependent on the passage of time.

Gender

In most studies, Parkinson's disease prevalence does not differ significantly between men and women.[2, 14, 31, 50, 64, 70] Examples of prevalence by gender are

Table 3. AGE-SPECIFIC PREVALENCE OF PARKINSON'S DISEASE IN SELECTED STUDIES

Location (Authors)	Prevalence Per 100,000 by Age Group					
	0–39	40–49	50–59	60–69	70–79	80–89
Rochester, MN (Kurland[43])	—	50:5	239	758	70–84:1407	>84:2646
Northampton, United Kingdom (Sutcliffe et al[70])	—	50:3	64	277	702	>79:1136
Sardinia, Italy (Rosati et al[64])	3.3	38.6	204.5	342.1	311.3	82.6
Yonago, Japan (Harada et al[31])	4.7	39.9	85.8	245.1	698.4	752.7
Finland (Marttila and Rinne[50])	0.8	27.8	136.2	503.5	736.1	>79:464.8
Aberdeen, Scotland (Mutch et al[53])	0	46.6	77.9	254	839.6	>79:1924.5

shown in Table 4. A notable exception is the result of the door to door study in China, where Li et al[45] found men to be 3.7 times more likely to have Parkinson's disease than women. Even with adjustment for differences in men and women in the population, this figure is remarkable. Identification of the reason for this difference in the Chinese population may provide an important clue to the etiology of Parkinson's disease.

Race

The community-based studies of Parkinson's disease prevalence shown in Tables 1 and 2 generally show the highest rates of Parkinson's disease in Europe and North America, whereas rates in Japan, China, and Africa are markedly lower. These data have been interpreted to indicate a greater risk for Parkinson's disease among whites. Hospital-based series in the United States and Africa similarly found Parkinson's disease to be much lower in blacks.[37, 56, 57] Exceptions to this observation are two door to door studies—one performed in Copiah County, Mississippi,[67] and the other in a Parsi colony in Bombay, India.[6] Prevalence in Copiah County was similar between whites and blacks, if cases were chosen using the least stringent diagnostic criteria (*possible Parkinson's disease*), although whites continued to have higher prevalence if more rigorous criteria (*probable Parkinson's disease*) were used to identify cases. In the Parsi community in Bombay, prevalence was similar to that found in Europe and North America. The Parsis are relatively recent immigrants to India and form a closed community into which conversion is impossible. Although socioeconomic or environmental factors may explain the prevalence differences cited here, a still to be refuted possibility is that Parkinson's disease is more common in whites, most likely as the result of a common genetic characteristic.

Genetic Predisposition

A number of studies have suggested that Parkinson's disease is a genetic disorder. Most convincing is the large Italian kindred described by Golbe et al.[27] This family, stemming from common ancestors in an Italian village, appears to have autosomal dominantly inherited, typical Parkinson's disease. One cousin-cousin marriage, however, is present in the published kindred, and similar intermarriage may have occurred in prior generations. Thus although clearly this family is important to the clarification of genetic mechanisms in

Table 4. CRUDE PREVALENCE OF PARKINSON'S DISEASE BY GENDER IN SELECTED STUDIES

Location (Authors)	Prevalence Per 100,000	
	Men	Women
San Marino (D'Alessandro et al[14])	154	150
Yonago, Japan (Harada et al[31])	63.3	96.6
Sardinia, Italy (Rosati et al[64])	57.5	73.9
Northampton, United Kingdom (Sutcliffe et al[70])	102	114
Finland (Marttila and Rinne[50])	97.7	140.4
Benghazi, Libya (Ashok et al[2])	32.5	30.3

Parkinson's disease and particularly for molecular genetic research, the pattern of inheritance may only appear to be autosomal dominant as the result of intermarriage.

Most other studies support a less prominent role for genetic factors, suggesting that heredity is important only in some families or postulating multifactorial inheritance with symptoms dependent on environmental factors.[3, 42, 47, 52] Interpretation of these studies is difficult, however, because diagnosis was typically made using only historical information. Twin studies further support a less prominent contribution of genetic factors in Parkinson's disease, since concordance rates between monozygotic and dizygotic twins are similar.[46, 49, 78, 79, 82] In classic autosomal dominant disorders, monozygotic twins show much higher concordance than do dizygotic twins. Parkinson's disease, however, is a disorder of late life. If age at onset differs significantly between twins and one twin dies before symptoms are apparent, genetically concordant twins may appear to be discordant.

It is hoped that the role of genetic factors in Parkinson's disease etiology may soon be clarified because the rapid development of molecular genetic technology has focused much attention on this question.

Toxicant Exposure

A cluster of toxicant-induced parkinsonism in young narcotics addicts, caused by the intravenous injection of the compound MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), suggested that exposure to an exogenous agent might cause Parkinson's disease in some cases.[44] Parkinsonism is known to result from numerous chemical injuries,[22] but MPTP-induced parkinsonism is remarkable in that it strictly mimics the anatomic and clinical features of Parkinson's disease, rather than causing more widespread central nervous system injury (see other articles in this issue).

Comparisons of international differences in prevalence of Parkinson's disease and industrialization suggest that Parkinson's disease is less common in countries more recently industrialized. Studies using antiparkinsonian drug sales to estimate prevalence found vegetable farming, wood pulp mills, and steel alloy industries in areas with the highest disease prevalence.[1, 3] Rajput[72] found an association between young age at onset of Parkinson's disease and residence in rural Saskatchewan. Tanner[72] found a similar association between young-onset parkinsonism and rural residence in a Chicago-based clinical series.

These early observations have been tested in numerous case-control studies.[10, 15, 16, 32, 33, 35, 40, 73, 75] Many of these are summarized in Table 5. Although both the methods used and the locations of these studies have differed, all show an association between at least one of the proposed exposures—rural residence, farming, well-water drinking, or herbicide/pesticide exposure—and an increased risk for developing Parkinson's disease. The significance of this association should be weighed cautiously, however. All of these studies are limited by small size, and differing methods prevent direct comparisons. Although reproducibility of the associations over many different studies lends strength to the observations, a cause and effect relationship cannot be assumed. Much further collaborative work between clinicians, epidemiologists, and laboratory scientists is necessary to clarify the import of the association between rural residence or its associated factors and Parkinson's disease.

Table 5. CASE-CONTROL STUDIES TESTING ASSOCIATION BETWEEN RURAL LIFE, AGRICULTURAL CHEMICALS, OR WELL-WATER DRINKING AND PARKINSON'S DISEASE

Location (Authors)	No. Cases/ No. Controls	Associations			
		Rural Home	Farming	Well-Water Drinking	Herbicides/Pesticides
China (Tanner et al[73])	100/200	−	−	−	+
Quebec (Zayed et al[81])	42/84	NA	−	+	+
Madrid (Jimenez-Jimenez et al[35])	81/162	NA	NA	+	+
Kansas (Koller[41])	150/150	+	−	+	−
Hong Kong (Ho et al[33])	35/105	+	+	NA	+
Chicago, IL* (Tanner et al[75])	78/78	−	+	−	−
British Columbia (Hertzman et al[32])	57/122	NA	NA	NS	+
New Jersey/Pennsylvania* (Dulaney et al[16])	154/154	+†	NA	NS	NS
Campania, Italy (Campanella et al[10])	83/83	NA	NA	+	NA
California, members 7th Day Adventist church (Davanipour et al[15])	49/>34,000	+	NA	NA	NA
Kansas (Wong et al[80])	38/38	+	+	−	−

NA = not assessed; NS = not significantly different.
*Parkinson's disease onset <51.
† $P = 0.06$.

Infection

Following the pandemic of encephalitis lethargica, Poskanzer et al[59] proposed that all cases of parkinsonism were the result of exposure to that infectious agent and that Parkinson's disease would ultimately disappear as survivors of that epoch died. The latter prediction proved incorrect, and few cases of parkinsonism today are believed to be postencephalitic. One recent study[51] suggested in utero exposure to influenza virus may cause a loss of nigral neurons and consequent increased vulnerability to Parkinson's disease, but this observation was not confirmed.[17]

Many attempts to identify an infectious agent in Parkinson's disease failed.[18, 48] Fazzini, Fleming, and Fahn[19] found increased cerebrospinal fluid antibody titers to coronaviruses in persons with Parkinson's disease. Specific coronaviruses have an affinity for basal ganglia in some animals, and members of this species commonly affect agricultural animals such as pigs. Rather than reflecting an exposure to an environmental chemical, the increased risk of developing Parkinson's disease associated with rural residence may reflect environmental exposure to an infectious agent.

Trauma

Trauma is often listed as a risk factor for Parkinson's disease because retrospective case-control studies often reported an association between head trauma and Parkinson's disease.[7, 16, 72] Studies comparing prospectively collected information (that is, information collected before an individual developed Parkinson's disease), however, do not find this association.[60] Subjects with a chronic illness typically seek explanations for their disease in prior experiences, and those with central nervous system injuries might be particularly thoughtful about head injuries. A similar pattern of recall is seen in other neurologic diseases, such as Alzheimer's disease, in which prospectively collected information shows no association between head injury and disease but retrospectively collected information typically suggests that head trauma is associated with Alzheimer's disease.[11] It is most likely that the reported association between head trauma and Parkinson's disease reflects biased recall, rather than a cause and effect association. Unless prospectively collected information shows such an association, trauma should not be considered to increase the risk of Parkinson's disease.

Emotional Stress

Stress was among the earliest proposed causes of Parkinson's disease.[12, 28] Laboratory studies suggest that stress-produced changes in central dopamine systems could theoretically contribute to the development of parkinsonism.[68, 69] Similarly persons already affected with Parkinson's disease experience transient worsening of their symptoms during stressful periods.[23] Two reports linked the extreme emotional and physical hardship of concentration camp imprisonment with the subsequent development of Parkinson's disease.[20, 77] Whether these observations reflect an accelerated nigral injury as the result of stress-related increase in dopamine turnover with resultant increased oxidative injury, nutritional deficiencies of dietary protective agents, or other factors cannot be determined. Evaluation of the relationship of less severe emotional or physical

stress to the development of Parkinson's disease poses a methodologic challenge.

PROTECTIVE FACTORS FOR PARKINSON'S DISEASE

Dietary intake of factors that interfere with the pathogenetic mechanisms underlying Parkinson's disease might prevent disease development. For example, if oxidative mechanisms are involved in the pathogenesis of Parkinson's disease, intake of antioxidant vitamins may be protective.[13] Consumption of foods rich in tocopherol decreased the risk of developing Parkinson's disease in two case-control studies, one comparing patients with Parkinson's disease to same-sex siblings and one comparing patients to spouses.[24, 25] The use of supplemental multivitamins, vitamin E, or cod liver oil was similarly associated with a decreased risk for Parkinson's disease.[74] No significant differences between cases and controls in dietary intake of vitamins E, C, beta-carotene, protein calories, or total calories were found in a Chinese population,[71] but the tocopherol content of many of the foods commonly eaten in China was not available, so this negative result could simply reflect inadequate information.

Although the numbers studied to date are small, these studies suggest that eating foods rich in tocopherol or some associated behavioral or dietary factors may protect against the development of Parkinson's disease in some cases. These observations allow the suggestion that areas with a low prevalence of Parkinson's disease may not be those with a lesser concentration of environmental toxins but rather those in which there is higher dietary intake of protective substances.

Cigarette Smoking

Smoking was first observed to have an inverse association with Parkinson's disease in a study of US military veterans in the late 1960s.[36] The inverse association of cigarette smoking and Parkinson's disease was confirmed in numerous subsequent case-control studies in the United States and Europe.[5, 7, 9, 16, 21, 30, 39, 54, 76] Only three studies found no association between smoking and Parkinson's disease.[33, 62, 73] Two of the negative studies were performed in China or Hong Kong. Smoking is extremely rare in Chinese women but relatively common in men, whereas Parkinson's disease occurs in Chinese men nearly four times more often than in Chinese women.[45, 72] If smoking exerted a true biologic protective effect, a much higher prevalence of Parkinson's disease would be expected in the nonsmoking Chinese women than in men. Rather than reflect an actual biologic action, decreased smoking in Parkinson's disease could simply reflect the more conservative personality that may accompany Parkinson's disease.[7, 24]

SUMMARY

Additional epidemiologic studies may provide important insights into the etiology of Parkinson's disease. Moreover as the elderly population of Europe and the United States grows, accurate public health planning requires accurate incidence and prevalence estimates. The recent development of a therapy that may slow disease progression (see article by Tetrud elsewhere in this issue)

makes early identification and treatment of Parkinson's disease particularly important. Investigations of early markers of Parkinson's disease or markers of disease susceptibility are critical areas of future research, requiring careful collaboration between epidemiologists and laboratory scientists.

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