Epidemiology of Parkinsonism

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Epidemiology is the study of large numbers of individuals to ascertain incidence, life expectancy, prevalence, time trends, preceding and associated illnesses, and other factors in a disease. Contrasted to laboratory studies in which the experimental conditions can be controlled, epidemiology examines natural events that may have been influenced by health care, economic, and social factors. Epidemiology is broadly divided into four categories—descriptive, analytic, clinical, and experimental—although there is considerable overlap (1).

Descriptive epidemiology deals with incidence, age and sex distribution, life expectancy, and prevalence rates. Analytic epidemiology is aimed at identifying factors that are positively or negatively associated with the illness and hence may be causally linked. Because the events that significantly influence the epidemiology of a disease cannot be controlled, it is important that any bias that may confound the observations be identified and avoided or adjusted for. Clinical epidemiology includes studies that require repeated clinical assessments and/or pathological studies to determine disease profile. Hypotheses generated by descriptive and analytic epidemiology may be tested with these studies. Experimental
epidemiology deals with planned large studies designed to determine the impact of intervention on the disease outcome (2,3).

No two epidemiological studies are identical. For many reasons, the methods utilized at one location or at one time may not be possible at another. Also, populations vary by time and place. Epidemiological studies are labor intensive. Patience and thoughtful planning are essential for proper studies, as is teamwork where clinicians work together with those who collect, enter, analyze, and interpret the data. Biostaticians are vital members of the team and should be involved early in the planning of a study. Team members should collectively consider the study design.

Parkinson syndrome (PS) is a clinical diagnosis, and different diagnostic criteria have been used in different studies, therefore, strict comparison of the literature is very difficult (4). A bias may be introduced at any stage—during data collection, analysis, or interpretations. In most studies, the familial PS cases are identified by direct or indirect history; this introduces a significant source of bias. One concordance study of Parkinson’s disease (PD) probands and the family members who had a movement disorder revealed that 74% of the secondary cases had PD while the remaining had a different disorder (5). In one family that had several autopsy-verified PD cases, family members were confident that a certain deceased sibling also had PD. He had died in an accident and an autopsy showed no PD pathology(5). Some PS cases may be misclassified as being “old” (5). Thus, it is essential that suspected cases be examined by a neurologist to verify the diagnosis.

It is not uncommon that seemingly similar epidemiological studies arrive at different conclusions. Any study may have only a certain portion that is scientifically valid. Epidemiological reports should be easily comprehensible to an average physician. The best guide is one’s own judgment. All analytic epidemiological observations where a certain factor/event is associated with PS or PD should not be interpreted as indication of a cause for the disease. The cause and effect always coexist, but definite causal linkage requires a considerably higher level of evidence than a mere association.

**INCLUSION CRITERIA FOR PARKINSON EPIDEMIOLOGY**

The two major considerations for inclusion in PS epidemiology are:

1. Does this individual have PS, normal aging, or another disorder?
2. Does this person have idiopathic PD (6,7) or another variant of PS?

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Aging and Parkinsonism

Primitive reflexes that are common in PD are also seen in normal elderly (8–10). Slowed motor functions characteristic of PD are part of normal aging as well (11,12). Paratonia (gegenhalten) in the elderly who cannot hear properly or are unable to follow instructions due to cognitive impairment may be mistaken as parkinsonian rigidity (8,13,14). Arthritis is common in the elderly, and pain during passive movement at the arthritic joint leads to involuntary resistance resembling rigidity. Flexed posture and impaired postural reflexes, the other major features of PS, are also seen in the normal elderly (10,13,15,16). In general, the age-related abnormalities are symmetrical, while PS is often asymmetrical. Rest tremor, a common early feature of PS (17), is not part of normal aging (18) and hence is the single most reliable feature of this disorder.

The most common tremor disorder that is mistaken as PD is essential tremor (ET) (19). Typically, ET is present on positioning a limb against gravity and during activity. ET is usually restricted to the upper limbs and/or head. By contrast, resting tremor is characteristic of PS/PD and may involve the upper and lower limbs. Evolution of ET with time is well known (20). Nearly one third of these patients develop rest tremor during late stages of the disease (19,20) and, therefore, may be mistaken as PS.

For epidemiological surveys, the diagnostic criteria should be simple, consistent through the study interval, and easy to apply. After careful consideration of different diagnostic criteria utilized in epidemiological studies, de Rijk et al. (4) concluded that the most suitable is the presence of two of the three cardinal signs—bradykinesia, rigidity, and tremor. In individuals with preexisting ET, the additional diagnosis of PS should be made only when all three signs are present (19).

Parkinson Variants

The second major consideration is to classify PS cases into different variants. Most neurologists use the term PD for Lewy body disease (6,7). Distinction between different PS variants is difficult, especially during the early stages of the disease. Even in a clinical setting where patients are repeatedly evaluated by experts, accurate clinical diagnosis may not be possible because the telltale features that distinguish other variants from PD may evolve much later or never (7,21,22). Diagnostic criteria applied retrospectively to autopsied cases (23,24) are not practical in epidemiological studies, which are as a rule based on clinical assessment. Classification into possible, probable, and definite PD (25) has limited value in epidemiological studies, which are primarily aimed at measuring the magnitude of the
disorder in the population. Some drug-induced PS patients have underlying idiopathic PD (26), and response to levodopa (LD), though valuable, does not always distinguish between different Parkinson syndromes (27). In one study, when the initial clinical diagnosis of PD was made, only 65% of those cases had PD at autopsy (7).

PD is the most common PS variant in clinical (28,29) and pathological series (17). All variants of PS produce significant functional handicap and may improve on the same drugs. Classification into different PS variants is valuable, but it should be recognized that such an exercise would only provide approximate estimates. Autopsy studies to confirm the diagnosis are not possible in epidemiological surveys. Therefore, for descriptive epidemiological studies, all PS variants should be considered. Further classification may then be made based on the best clinical evidence.

DESCRIPTIVE EPIDEMIOLOGY

Incidence of Parkinsonism

Incidence is defined as the number of new cases per year and is usually described per $10^5$ population. Incidence can be determined for various categories including gender and age. Incidence studies are difficult because all of the new-onset patients who need to be included may not be recognized until sometime later. In addition, the number of new cases in a community may vary from one year to the next. Consequently, incidence studies require a long period of observation in the same community.

The reported incidence rates of PS vary widely. The lowest incidence in Western countries is reported from Sardinia at 4.9/$10^5$ (30). The latest crude annual incidence in Finland is 17.2/$10^5$ (31). Based on six general practices in the Netherlands (32), annual incidence was 12/$10^5$ for women and 11/$10^5$ for men.

In the Western countries, the most reliable incidence studies are from Rochester, Minnesota. Health care in Olmstead County, including Rochester, is provided mainly by the Mayo Clinic–affiliated staff, and the medical records have been carefully compiled since the 1930s. The record linkage system (33) allows the tracking of all Olmstead County residents evaluated at the Mayo Clinic and affiliated hospitals, community physician offices, a community hospital, chronic care institutions, and veterans hospitals where these patients may be seen. In most PS cases, the diagnosis is confirmed by a qualified neurologist affiliated with the Mayo Clinic (29). Four different incidence reports based on the Rochester, Minnesota, population have been published (28,29,34,35). Drug-induced parkinsonism (DIP) was not known until the early 1960s (36). For the purpose of
Table 1 shows a summary of incidence rates reported in those studies. There was no significant change in incidence over 55 years. The latest study (29) revealed a PS incidence of 25.6 per 10^5. The PS incidence was 0.8/10^5 in those 0–29 years of age, 25.6/10^5 in those 50–59 years, and was more than 11 times higher (304.8/10^5) in the 80- to 99-year age group (29). There has been no significant change in age-specific incidence rates during the 55-year interval of these studies (37). However, there is a trend to higher incidence between age 70 and 90 in the most recent study, which is attributed to neuroleptic usage (37). The slightly higher overall incidence of PS in the latest report (29) likely reflects longer life expectancy in the general population, more frequent use of neuroleptics, and improved diagnosis among the demented (29).

An Italian study of persons 65–84 years of age noted an annual incidence of 529.5/10^5 for PS and 326/10^5 for PD (38). Some studies have reported a decline in PD incidence after age 79. A northern Manhattan study (39) indicates that the incidence rates of PD consistently increase through age 85. Baldereschi et al. (38) found a continued increase in incidence after age 75, and no decline was noted up to 100 years of age in another study (37). Pathological studies show a progressive increase in the rate of incidental Lewy body (LB) inclusions with advancing age (40,41). These cases are regarded as having preclinical PD. The decline of PS and PD in the very old that has been observed in some studies is attributed to difficulty in ascertaining cases in the presence of comorbid disorders (29). Thus, age remains the single most important risk factor for PS.

### Lifetime Risk of Parkinsonism

The current lifetime risk of PS from birth is estimated at 4.4% for men and 3.7% for women (42). Lifetime risk for men 60 years of age is estimated at...
4.6% and for women 3.7% (42). This report (42) proposes that at any age, future risk of PD can be calculated (42). The risk of PS in the elderly in an Italian longitudinal study (38) was even higher than that reported from Rochester (42), and men had a higher risk than women (38). Thus far, the highest incidence and risk of PS in the elderly are reported from Italy (38).

**Parkinson Variants in the General Population**

As noted above, this classification in epidemiological surveys can only be approximate as the final diagnosis may not be possible until after autopsy (7). PS classification has been evolving with time even within the same community (28,29,34,35). Following the first description in 1817 by James Parkinson (43) and the discovery of substantia nigra neuronal loss and LB inclusions, parkinsonism was regarded as a single clinicopathological entity. That concept changed in the 1920s and 1930s. After von Economo encephalitis, an estimated 60% of the victims developed PS, which was classified as postencephalitic parkinsonism (PEP) (44,45). At one time, these patients constituted a large proportion of the PS cases in the general population. No new PEP cases have been reported since the mid-1950s (Table 1). Arteriosclerosis was once reported as a common cause of PS (34,35), but that is a very rare diagnosis now (28,29). This apparent reduction in arteriosclerosis as a cause of PS is due to increased diagnostic accuracy of PS, rather than a dramatic decline in arteriosclerosis in the general population.

Neuroleptic-induced parkinsonism (DIP) was first recognized in the late 1950s and is now a common PS variant (28,29,38) accounting for between 7% (28) and 20% of all PS cases (29). DIP is now the second most common PS variant and is more common in women than men (29).

Large clinicopathological studies of Shy-Drager syndrome (SDS) (46), striatonigral degeneration (SND) (47), and progressive supranuclear palsy (PSP) (48) were first reported in the 1960s, though clinical description of PSP was documented in the nineteenth century (49). Olivopontocerebellar atrophy (OPCA), which often includes some features of PS, has been known since 1900. The current classification includes SND, SDS, and OPCA under the common heading of multiple system atrophy (MSA). Prominent dysautonomia in SDS and akinetic rigid PS features in SND were not fully recognized until 1960 and 1964, respectively, and in all likelihood such cases prior to that were classified as PEP or atypical parkinsonism because they occurred at a relatively young age and had widespread nervous system involvement. In spite of the improved understanding of these uncommon PS variants, the diagnosis is not always possible clinically (7,21,22,50). Autopsy series may be biased because the families of those suffering from the unusual
PS variants may have heightened interest in finding out the nature of the disease and, therefore, be more likely to consent to an autopsy. The true frequency of these variants in the general population is, therefore, not possible to determine. In one epidemiological study, 2.5% of all PS patients were classified as MSA and 4.3% as PSP (29). A previous study from the same community reported PSP diagnosis in 1.4% and MSA diagnosis in 2.1% of PS cases (28). Thus, MSA and PSP each represent less than 5% of the contemporary PS cases in North America.

The most common PS variant in epidemiological studies (28,38,51) is idiopathic PD (6). The proportion of those with PD, however, varies widely in different studies—e.g., 42% (29), 62% (38), and 85% (28). Preponderance of PD is also noted in autopsy studies of unselected PS cases (27,52,53). Dementia with Lewy bodies (DLB) is now a well-recognized entity (54), and extrapyramidal features may also be seen in Alzheimer’s disease (AD) (55). One recent PS study (29) noted that 14% of all PS cases had dementia manifesting within one year of PS onset and classified these as “Parkinsonism in dementia.” Most of these cases likely had DLB (55). The clinical and pathological classification of PS variants continues to evolve, but the most common variant is still PD (6,7).

Life Expectancy in Parkinsonism

All the PS variants limit mobility. Increased tendency to falls and dysphagia predispose these patients to life-threatening complications (56,57). Life expectancy prior to the widespread use of LD was significantly reduced. In one hospital-based PS series during the 1950s and 1960s, the mean survival after onset was 10.8 years (58). A large proportion of these patients had PEP. The PEP cases had longer survival than other PD cases (58,59). When the PEP cases were excluded, the mean survival in the remaining cases was 9.42 years (58). That study is frequently cited as the yardstick for the pre-LD era life expectancy. Mean survival in the contemporary PS cases cannot be compared with that study. There have been significant social and health care advances leading to longer life in the general population. One would expect that PS patients would share these survival gains. Comparison for PS patients’ survival should be made matching for year of birth, gender, and region/country.

Kurtzke et al. (60) noted that patients in the 1980s were, on average, 5 years older at death than those who died in the 1970s, implying that life expectancy since the widespread use of LD has increased by 5 years. Several other studies have also reported longer life expectancy (61,62,63,64), though it remains reduced compared to the general population (64). Some observers, however, remain unconvinced (65,66). At the other extreme are
studies that suggest that current PS cases survive longer than the general population (67,68). It is difficult to reconcile that individuals suffering from a progressively disabling disorder would live longer than the matched general population. The most common error in the better-than-expected survival studies is measuring survival from the date of onset assigned several years retrospectively. During that period, the general population would have suffered some death. That gives the PS group an artificial advantage, since they survived at least to diagnosis (67). When we assessed our patients using the date of onset, the PS patients survived longer than the general population (64). The other reason for this error is inclusion of only LD-treated cases (68). For any number of reasons, some patients may not be treated with LD and those destined for longer survival may be treated with LD, which introduces a significant bias. Longer survival has been noted by others if only the LD-treated cases were considered (28). Restricting a study to only clinically diagnosed PD and excluding other variants introduces another source of bias, as the inaccuracy of clinical diagnosis is well known (7,21).

A blinded study withholding modern drugs from one group of matched patients is not possible. In a clinic-based study of 934 PS cases seen between 1968 and 1990 (64,69), survival measured from the date of first assessment was significantly reduced ($p < 0.0001$) in PS (64,69). This study (64,69) also considered the impact of widespread and easy access to LD (regardless of cost) on the survival. The survival remained shorter ($p = 0.029$) than expected for the general population (Fig. 1). Prior to January 1, 1974, LD was available almost exclusively to patients seen at the Movement Disorder Clinic Saskatoon (MDCS). When survival in patients assessed before this date was compared to the expected survival, reduction was even more pronounced ($p < 0.0001$). (Fig. 2) Taken together, these indicate that widespread use of LD has improved survival in PS (64,69). There was no difference in the use of other drugs, which may explain the survival differences (64,69). The survival is negatively impacted in patients with dementia (61,69,70) and in those with a PS diagnosis other than PD. The most favorable prognosis was in the patients diagnosed as PD who had no dementia at initial assessment (64,69).

The timing of treatment with LD indicates that survival benefit is achieved only when patients are treated prior to the loss of postural reflexes (58,64,71). Similar observations of longer survival in patients with early LD treatment have been reported by others (62).

When Figs 1 and 2 are considered together, it is evident that the survival gap between current PS cases and the general population has narrowed ($p = 0.029$ vs. $p < 0.0001$). This gain in life expectancy is attributable exclusively to the better symptomatic control on LD, which
FIGURE 1 Comparison of survival in parkinsonian patients with unrestricted levodopa availability (Obs.) to a sex- and year of birth–matched regional population (Exp.).

FIGURE 2 Comparison of survival in parkinsonian patients who had severely restricted access to levodopa (Obs.) to a sex- and year of birth–matched regional population (Exp.).
prevents disability and life-threatening complications (56,57). We estimate that an average patient with PD onset at age 62 now lives for approximately 20 years. The survival is shorter in other degenerative diseases associated with PS (17,22). Average survival from onset of PSP is approximately 9 years (72), although rare cases may live for 24 years after onset (22).

**Prevalence of Parkinsonism**

The prevalence rate is defined as the number of PS patients in the population at a given time and is usually described as cases per 10^5. The term point prevalence implies prevalence rate on a particular date. The two main factors that determine the prevalence rate are the incidence of new cases and the life expectancy. Those issues have been discussed above. If the number of new cases emerged at a constant rate but the life expectancy increased, the prevalence rate would rise.

Several different methods have been used to determine PS prevalence rate. These include review of all the health records in a given community, consumption of antiparkinson drugs (73,74), direct survey of population, and indirect measurement by multiplying incidence rate with mean survival. Although labor intensive, the most reliable method is the door-to-door survey of a community population. The usual procedure involves two steps, an initial survey questionnaire followed by a neurological examination of those whose response is suggestive of PS (75–79). In spite of the considerable efforts, 6–18% of the eligible population cannot be assessed (77,78). The distinction of PS from normal age-related changes and from other systemic and neurological diseases are important considerations for inclusion/exclusion in such surveys. Door-to-door surveys show that between 35% (78) and 42% (75) of the PS cases identified during the survey were not previously diagnosed. These cases would have been missed in a record review. An undiagnosed PS case would not be receiving antiparkinson drugs, hence the studies based on drug consumption would significantly underestimate the prevalence rate.

Some prevalence studies include only clinically diagnosed PD (31), while others include all PS variants (78). While some studies include all residents of a community and adjust for the age distribution of the population, known as age-adjusted prevalence rate, others restrict the surveys to only persons above a certain age (e.g., 40 years) (75) and describe a crude rate.

In the Caucasian population, the crude prevalence ratios vary from 84/10^5 to 775/10^5 population (80,81). The prevalence rates based on door-to-
door surveys are 57/10^5 in China (79), 371.5/10^5 in Sicily (78), and 775/10^5 in Australia (83). In a Parsi community from Bombay, India, the prevalence rate was 328/10^5 (76). In a U.S. community-based study of Copiah County residents, which included only persons over the age of 40 years, the prevalence rate was 347/10^5 (75). A Dutch study in the early 1990s found a prevalence rate of 1.4% in those aged 55–64 years and 4.3% in an 85- to 95-year age group (82).

In a representative sample of community residents 65 years and older from Canada (83), the prevalence rate was 3% (3000/10^5), while in institutionalized persons (84) the rate was 9% (9000/10^5). Somewhat comparable figures were reported from Australia (81). They included only PD cases in persons 55 years and older. The prevalence rate of PD was 3600/10^5 in the community and 4900/10^5 in the institutionalized persons (81). They estimated that the crude prevalence rate of PD in the entire community was 775/10^5.

Bennett et al. (10) performed a random sample survey in Boston area residents ≥65 years (10) for PS signs. They classified PS as having two of four signs: tremor, bradykinesia, rigidity, and gait abnormality. The prevalence of PS in this study was 14.9% (14,900/10^5) in age 65–74 years, 29.5% (29,500/10^5) in 75–84 years, and 52.4% (52,400/10^5) in those ≥85 years (10). This observation represents the highest reported prevalence. It is not clear in this report (10) how many patients were evaluated by a neurologist, and the study has been criticized (29). The age-adjusted (31) 1991 Finnish population PD prevalence rate was 139/10^5. In a European collaborative study (85) restricted to 65 years and older, the PD overall rate was 1800/10^5, and in the 85- to 89-year age group, it was 2600/10^5.

Prevalence rate can also be estimated by multiplying the incidence rate and the mean survival. Most researchers regard Rochester, Minnesota, incidence rates as representative for North America. The latest annual incidence of PS in Rochester is 25.6/10^5. The survival in PS has increased substantially during the last 3 decades. A conservative estimate of mean survival in contemporary PS is 15 years, though an average PD case would survive longer. Thus, the minimum prevalence rate in the North American general population is estimated at 384/10^5.

The literature indicates that (1) the age-specific incidence (in Rochester) was unchanged between 1935 and 1990 (37); (2) there is an increase in PS in persons 70–99 years, primarily due to increase in DIP (37); (3) there is large pool of at-risk population, as the general population is living longer; (4) there has been a substantial increase in life expectancy in PS on the current treatment (64,69,86), and (5) the lifetime risk of parkinsonism, which in the 1950s was estimated at 2.4% (34), is now estimated at 3.7% in women and 4.4% in men (42).
Gender and Parkinsonism

A higher incidence of PS in men has been reported in several studies (29,31,38,39,42,87,88), though some reviews conclude that this difference may be artifactual (80). The available evidence indicates that men have a slightly higher risk of parkinsonism than women, with the exception of DIP (29).

Several studies have reported no difference between males and females while other studies have reported a higher prevalence in women (78,89). More recent studies have noted higher incidence and prevalence rates in the males than in females (29,38,76,90,91). The cumulative evidence so far favors a slight male preponderance of PS and PD.

Race, Ethnicity, Skin Color, and Risk of Parkinsonism

Parkinsonism has been reported in all races. Several studies have suggested that those with darker skin have a reduced risk of PD compared to lighter complected individuals (30,92,93,94). However, these differences were attributed to the source of the study—U.S. private hospitals—which at that time African Americans had limited access to (95,96). Studies that included communities with a mixed population did not observe any racial differences (39,75). The risk of parkinsonism is best measured by incidence rates and not by prevalence rates, which are affected by survival rates. In a mixed community, Mayeux et al. (39) observed that the incidence was highest in African American males, but there was higher mortality in this group. There is no evidence that darker skinned persons have a larger number of substantia nigra pigmented neurons or that the vulnerability of these neurons differs in different races. In one dopa-responsive dystonia autopsied case, we discovered markedly hypopigmented substantia nigra, but her skin color and tendency to tan were similar to her other siblings (97). Thus, skin color by itself is not related to the risk of PS or PD.

Geography and Parkinsonism

In most countries, geography and ethnicity are intertwined. In relatively newly settled countries (e.g., the United States and Canada), all racial and ethnic groups live in the same geographic location, which permits better assessment of the role of geographic background in parkinsonism.

The Parkinson-dementia-ALS complex of Guam is unique (98). There are no other large geographic clusters of well-documented PS or PD. The lowest reported prevalence rate is 57/10^5 population in China (79), followed by 65.6/10^5 in Sardinia (30), 67/10^5 in Nigeria (77), 80.6/10^5 in Japan (99); the highest reported rate is from Australia (81) at 775/10^5. African
Americans and Caucasians living in the same U.S. communities have similar incidence (39) and prevalence rates (75). The prevalence rate in U.S. African Americans was five times higher than in Nigerians, who presumably share a common genetic background. (77). This difference remained significant when the life expectancy in the general population in the two countries was taken into account (77). It is of note that the same investigator conducted those two studies (75,77) using the same methodology.

Geographic differences among different western Canadian provinces have been reported (100), and a north-south gradient in the United States has been suggested in one study (101) but not confirmed by others (102). Difference in incidence of PS based on the population density in Saskatchewan revealed that those born and raised in smaller communities (population \( \leq 200 \)) had an increased risk of parkinsonism (103,104). This study included only those cases that had onset before age 40 years (103). Several other North American and European reports noted a higher risk of PD with rural residence during early age (105–109), but others failed to substantiate this finding (110,111). One Canadian study noted no increase in the risk of PD in those who had previously lived in rural areas or had worked on a farm (112).

In summary, there are geographic differences for the risk of PD, but the risk is not linked to racial or ethnic background. It is attributable to shared geography, which points to a shared environmental exposure.

**ANALYTIC AND EXPERIMENTAL EPIDEMIOLOGY OF PD**

Epidemiological studies for the causes of PD are difficult to pursue. PD is a clinical diagnosis, and therefore there is significant misclassification bias (5). In addition, reporting of exposure history can be subject to recall bias. A genetic basis for PD has been identified in only a small proportion of cases (see Chapter 14).

**Premorbid/Comorbid Disorders and Lifestyle**

Clues to PS etiology maybe found in premorbid and comorbid disorders. Several studies have reported that a history of psychoneurosis and psychosomatic illness is more common in PS cases than in matched controls (113,114). A distinctive PD personality—introspective, frugal, stoic, well organized, and adverse to risk—has been suggested (115,116). The significance of these findings is unknown. It may indicate a common pathophysiology or that the individuals with these premorbid disorders have an increased risk of PS.
**Lifestyle and Parkinsonism**

Several lifestyle issues, including smoking, consumption of coffee, alcohol, and different diets, have been studied in an effort to determine their relationship to PD. Smoking has been the focus of many studies. Some reports indicate that smoking has a protective effect against PD, while others found no relationship. Current smoking and past smoking were noted to have a protective effect in some studies, and only the male smokers had reduced risk in another study. No difference in PD risk related to smoking was observed by others. The cumulative tobacco exposure is reported to reduce PD risk by some, but no dose effect was found by others. One recent report of monozygotic PD twins noted that the twins without PD had smoked more than the co-twins with PD.

Lewy body inclusions and marked substantia nigra pigmented neuron loss is the hallmark of PD, and presence of LB observed incidentally at autopsy has been regarded as an indication of preclinical PD. In one autopsy series of 220 brains, incidental LB inclusions had no relation to ever smoking or current smoking, nor was there any association between presence of LB and the pack-years of smoking. The risk of LB inclusion correlated with the age of the patient. If smoking was protective against PD, one would expect that smokers would have a lower frequency of incidental LB. Smoking benefit to PD risk would also be evident in age of onset and rate of progression. Smokers, in fact, have a younger onset age, and the progression is not influenced by continued smoking.

In summary, the literature on smoking and risk of PD remains controversial. In spite of several epidemiological studies suggesting a protective effect, as noted above, several critical pieces of evidence do not support this hypothesis. The reported negative association notwithstanding, it is likely that smoking is a marker of the underlying personality trait.

Studies of the association between PD and the consumption of alcohol have also produced controversial results. Lower frequency of PD has been reported in coffee drinkers. A recent report on diet in twins, on the other hand, indicates that chocolate consumption increases the risk of PD. In Western cultures where coffee and alcohol use is common, the incidence of PD is higher than in cultures that do not utilize these substances. The evidence for coffee, alcohol, or other foods having a protective effect on PD remains weak.
Comorbid Psychiatric Disorders

Depression

Prior to the onset of motor symptoms, depression is more common in PD than in the matched control subjects (114,136–141). Between 30 and 90% of PD patients (142) have been reported to have depression. Depression is frequently unrecognized by patients and caregivers. The available evidence indicates that depression in PD has an endogenous basis in addition to being in reaction to the severity of physical disability (143–146).

Dementia and Parkinsonism

The reported frequency of dementia in PS ranges from 2% (147) to 81% (148), although most were minimally affected in this study. Some cognitive impairment has been reported even in mild early parkinsonian patients (149,150) and is more likely in depressed patients (146). The reported frequency of dementia varies depending on the patient population and the intensity of the search. (151). Several other studies have reported that approximately one third of PS patients at any given time have dementia (147,152–154). Late age of PD onset is associated with increased dementia risk. Dementia was more common in those with onset after age 60 years than the earlier onset (25% vs. 2%) in one study (147) and in those with onset after age 70 years compared to the younger individuals in another study (155).

Dementia evolves at a higher rate in PD than in the matched population. In one case-control study, dementia evolved 3.8 times more often in the patients than in the controls at 5 years (113). In a community-based study, nondemented PD patients (156) were compared with the age-, sex-, and educational level–matched general population. At the end of 4.2 years, the dementia was 5.9 times more common in PD than in the controls (156). One study concluded that by age 85 years, 65% of the surviving cohort had dementia (155). Diagnosis of dementia is associated with significantly reduced survival (60,64,70,157–162).

Other Comorbid Disorders

Literature has produced contradictory evidence on the risk of cancer in PS (58,113,163). Based on available evidence, it is concluded that risk of cancer in PD is not different from the general population. The reported risk of stroke varies considerably. At one time, cerebral ischemia was regarded as a common cause of PD (34,35). Pathological studies indicate that stroke is an extremely rare cause of PS (17). Two recent studies concluded that stroke is less common in parkinsonian patients than in the general population (164,165). One study (165) speculated that dopamine deficiency has a protective effect against ischemic brain damage.
Essential Tremor and Parkinsonism

Several studies found an increased risk of PS in ET patients (166–168), while others could not substantiate this finding (169–172). One reason for the differences is the different patterns of referrals—the most complicated cases attend highly specialized centers. The pathological findings in PD and ET are remarkably different (6,173). In our clinic-based, autopsy-verified ET cases, nearly one third of patients had resting tremor as a natural evolution of the ET (19,20). Of the 21 ET cases, 6 (29%) had clinical evidence of parkinsonism—resting tremor, bradykinesia, and rigidity (19). Only one of those 6 cases had LB pathology. Two had PSP, 2 had DIP, and one had basal ganglia ischemic lesion (20). If the risk of PD were significantly higher in ET patients, we would have expected to see more cases with PD pathology. It is concluded that the risk of PD in ET is not different from that in the general population.

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