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MINI-SYMPOSIUM: Dementia in Parkinson's Disease

The Epidemiology of Dementia Associated with Parkinson's Disease

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative illness after Alzheimer's disease (AD). Cognitive impairment and dementia are common features in PD and characterized by a wide range of cognitive deficits distinct from those seen in AD. Mild cognitive impairment occurs even early in PD and is associated with shorter time to dementia. The purpose of this review is to present recent findings on clinical aspects of dementia in PD and to elucidate underlying clinical and neurobiological risk factors.

INTRODUCTION

The prevailing view in the 20th century was that Parkinson's disease (PD) did not affect mental functions, although several early reports noted that some patients with PD were cognitively impaired. Systematic studies until 30 years ago are very few, although some early longitudinal studies reported a considerable proportion with dementia. In an influential paper in 1988, Cummings reviewed 27 studies representing 4336 patients (21) and found a mean prevalence of 40%. During the following two decades, a large number of epidemiological studies have explored the frequency of dementia in PD (PD-D), and the most important findings will be reviewed in this paper.

These studies have used a variety of methods and designs, and this variation has most likely significantly affected the outcome. Important methodological differences include the tests used to assess cognition, the definition of dementia, the criteria for selecting patients, and whether cross-sectional or longitudinal design are used. For example, results vary according to whether attempts were made to identify all patients in a defined region or whether the study was based on convenience samples from hospital clinics. The use of a clinic-based sample rather than a population-based sample can potentially lead to over- or underdiagnosis of dementia. Clinic-based samples tend to be more complex, and thus, those with dementia may be overrepresented. On the other hand, these samples may be younger and have shorter duration, with lower risk for dementia than older and more advanced patients, which may have moved to nursing homes and may not be attending specialist clinics.

The optimal case identification method is door-to-door survey of a total population or a random sample, but few studies have used this method to investigate the prevalence or incidence of PD-D in the general population. Instead, studies have relied on identified PD patients known to the health-care system. This design may lead to an overestimate of dementia, as the mildest and undiagnosed cases have lower dementia risk. In addition, earlier studies did not account for dementia with Lewy bodies (DLB), which might therefore have been included in PD studies leading to an overestimate of PD-D. Until very recently, there were no consensus criteria for PD-D. The most widely used dementia criteria such as Diagnostic and Statistical Manual of Mental Disorders, third edition, revised, and fourth edition (DSM-IIIR and DSM-IV) require memory impairment, which is relatively less pronounced in PD-D compared to AD, whereas attention and executive dysfunction is relatively more impaired (16). Accordingly, some patients with PD-D may not have been detected. Consensus criteria are now available (25), and a diagnosis of probable PD-D requires: (i) a diagnosis of PD according to the Queen's Square Brain Bank criteria for Parkinson's disease (QSBB) criteria; and (ii) a dementia syndrome operationalized as decline from premorbid level in at least two cognitive domains which leads to impairment of daily functioning (occupational, social or personal care). The typical profile of cognitive deficits includes impairment in at least two of four cognitive domains: attention (which may fluctuate), executive function, visuospatial impairment and impaired free recall which usually improves with cueing. The presence of at least one behavioral symptom [apathy,

visual hallucinations (VH), delusions, depressed or anxious mood, excessive daytime sleepiness] supports the diagnosis of PD-D, but lack of behavioral symptoms does not exclude the diagnosis.

These criteria have, however, not yet been validated. Other diagnostic challenges remain. For example, there is yet no consensus regarding which methods to use to identify impairment of instrumental activities of daily living due to cognitive rather than motor dysfunction. This is a requirement for the Movement Disorders Society (MDS) PD-D diagnosis, and is the key feature distinguishing between PD-D and PD-mild cognitive impairment (MCI) (see below). Methods to address this have recently been reported, such as medical decision making, which is impaired even in PD patients with rather early cognitive impairment (57). Another potential measure is impairment in financial capacities, which has been shown to be affected in MCI in the general population (73), and which might also be useful in PD.

Finally, most studies have been cross-sectional, providing an estimate of the proportion with dementia in a prevalence sample of PD patients. For several reasons, including the higher mortality rate in PD-D vs. nondemented PD subjects (53), which will lead to an underestimate of dementia frequency in cross-sectional studies, more accurate information regarding the true frequency of dementia in PD can be drawn from longitudinal studies. Such studies provide information on the incidence of PD-D, and if a healthy control group is included, the relative increase in the risk of developing dementia related to PD can be estimated. In addition, period prevalence, ie, the total proportion of people with dementia in a PD cohort during a specified time, by combining prevalence, incidence and mortality rates, provides important information concerning the total proportion of PD patients who will eventually develop dementia.

IMPACT OF DEMENTIA IN PD

Cognitive impairment and dementia in PD have important clinical impact. Several studies have convincingly demonstrated their negative effect on patient's quality of life (70) and carer burden. Cognitive impairment also signals a very high risk for the development of troublesome psychiatric symptoms, such as VH and apathy, as well as a more rapid motor decline and even higher mortality (4). In addition, dementia causes functional impairment, with an increased need for nursing home admission, which has important consequences both for the individual and for the society in terms of increased costs.

POINT PREVALENCE

In a systematic review employing strict methodological inclusion and exclusion criteria, 13 cross-sectional studies with a total of 1767 PD patients were included (6). Of these, 554 were diagnosed with dementia, yielding a prevalence of 31.3% (95% confidence interval 29.2–33.6). This review also included 24 studies which explored the prevalence of dementia in the general population and included patients with PD. This approach can address the question about the prevalence of PD-D in the community, and the proportion of the total dementia population which is due to PD-D. In this analysis, 3%–4% of patients with dementia in the general population were due to PD-D, and the estimated prevalence of PD-D in the general population aged 65 years and over was calculated to be 0.3%–0.5%.

The results of studies published after this review are in line with these findings, reporting rates of dementia in PD of 48% (38), 23% (10) and 22% (22). The Rotterdam study was a door-to-door survey of dementia, and these results support the finding in the systematic review that door-to-door surveys, including a larger proportion of mildly affected cases, result in a lower proportion of dementia than studies based on recognized PD patients.

INCIDENCE

Most studies of the "incidence" of dementia in PD have been based on longitudinal studies of community-based prevalence cohorts, ie, samples with a variety of disease duration. Thus, this method estimates the risk for developing dementia in PD patients, whereas a more strict design is to study a population-based cohort without dementia, and explore the risk for PD-D with time. These studies have found that the risk for dementia in PD is approximately 100 per 1000 patient years (2, 55), which means that in a prevalent PD population, approximately 10% will progress from nondemented to dementia per year. Compared to people without PD, the risk for developing dementia in PD was reported to vary between 1.7 and 5.9 (2, 22, 38, 55). As noted above, there are several reasons for this variation, including case selection procedures, definitions of dementia and the use of different estimates of risk.

In contrast to this design, the incidence of PD-D in the general population was recently reported in two studies. In the Medical Research Council (MRC) Cognitive Function and Ageing Study (81), all subjects 65 years or older in defined geographical regions of the UK were invited to participate, and more than 13 000 participants had a screening interview. Participants were assessed at baseline and two follow-up waves 2 and 6 years later. Consistent with the findings in the systematic review, the proportion with PD-D was 2%–3%. The Rotterdam study was a follow-up of the door-to-door survey reported above, with nearly 8000 subjects 55 years and older at baseline in 1990–1993 (22). Two follow-up visits were performed, and patients were diagnosed with prevalent PD at baseline (n = 99) and incident PD during follow-up (n = 67). The mean follow-up time was 6.9 years, and 4.3 years in the incident PD group. During follow-up, 15% of the prevalent PD group developed dementia compared to 4.9% of the control group, with a hazard ratio of 2.80 (1.79–4.38). In the incident cohort, the hazard ratio was 4.74 (2.49–9.02).

The risk for developing dementia may vary according to the duration of PD (see below), and thus, variations in the mean disease duration among the cohorts may affect the observed incidence of dementia. Thus, following patients from onset of disease provides a more accurate estimate of the incidence of dementia in PD. In the CamPaign study, the first study of dementia in PD based on an incident PD cohort, 180 PD patients were reexamined 3 and 5 years after baseline. Seventeen percent had developed dementia after 5 years of disease, with an incidence of 38.7 (23.9–59.3) per 1000 person-years (78, 79). Thus, this finding suggests that the incidence of dementia is lower early in the disease course. The lower dementia incidence may also be related to the lower age at baseline in this cohort compared to most prevalence studies, or to the method of diagnosing dementia. Unfortunately, a control group was not included, precluding an estimate of the risk of dementia in early incident PD.

PERIOD (CUMULATIVE) PREVALENCE

The cumulative proportion of PD patients who develop dementia with time is an important clinical feature in PD, and requires a prospective, longitudinal design. However, several longitudinal studies did not control for the selected attrition due to death, and have merely added up the number of patients who become demented before death. This will underestimate the true proportion with dementia. Another important methodological feature is the interval between assessments, as it is impossible to know whether a nondemented individual who drops out more than 1 year after the final assessment has developed dementia or not between last assessment and withdrawal.

Only one study to date has prospectively followed newly diagnosed PD patients to assess the frequency of dementia over more than 10 years. In the Sydney study, 136 patients with carefully diagnosed PD were recruited from neurologists for inclusion in a clinical trial. Patients were assessed at baseline with a comprehensive neuropsychological assessment (65). After 3 and 5 years, 26% and 28% were demented (65); after 15 years, 48% of the evaluated patients had dementia, a further 36% evidence of cognitive impairment and only 15% remained without evidence of cognitive impairment (36). Recently, data from 20-year follow-up were presented (37), reporting that 83% of the 30 survivors had dementia after 20 years, and that 75% of the total cohort had developed dementia prior to death. As no attempt to control for selective attrition due to death was made, the 75% prevalence rate is probably an underestimate.

The Stavanger study was based on a prevalence cohort of people with PD in southwestern Norway, after a careful extensive search in the community. At baseline, the average duration of PD was 9 years, and 28% had dementia. After 8 years, after adjustment for mortality, the cumulative prevalence of dementia was calculated to be 78% (1). Based on the 12-year follow-up period, Markov analysis was performed to enable a more precise estimate of the risk of developing dementia for an individual patient based on age, sex and duration of PD (18). Without correcting for attrition due to death, the proportion that developed dementia has been stable at approximately 60%, but the cumulative prevalence steadily increased to 80%–90% by age 90 years. More specifically, at age 70 years, a man with PD but no dementia has a life expectancy of 8 years, of which 3 years would be expected to be with dementia. At any age, the life expectancy after onset of dementia was substantially reduced. At 12-year follow-up, only 10% of the population were alive and without dementia, after having suffered from PD for an average of 19 years.

The majority of studies report that the mean duration from onset of PD to development of dementia is approximately 10 years (37, 41). There are, however, wide variations. In a study combining two relatively large and community-based cohorts of patients with PD, we found a linear relationship between time from onset of PD and diagnosis of dementia. Whereas some patients develop cognitive impairment and subsequent dementia within few years after onset of PD, others remain free from dementia for 20 or more years before developing dementia (5). Thus, because as reported above the vast majority of surviving PD patients will eventually develop dementia, a key clinical feature is to estimate the time from onset PD to dementia. This time interval is related to the type and extent of brain pathology (11, 32) (see also chapter accompanying paper). In addition, it is a priority to identify clinical or biomarkers which can predict the time to dementia (see below).

The long-term studies demonstrate that although the majority of surviving PD patients develop dementia, a small subgroup remain free of dementia even after decades with PD. Thus, another key research question is to identify factors which may *protect* against dementia in long-standing PD, as this might provide clues to preventive therapies.

RISK FACTORS FOR DEMENTIA IN PD

Many demographic and clinical features have been assessed as potential risk factors for dementia in PD, with inconsistent results. The most established risk factors emerging from longitudinal studies are more severe parkinsonism, particularly nondopaminergic symptoms, higher age and MCI at baseline.

Parkinsonism

Several longitudinal studies have confirmed that patients with more severe and advanced parkinsonism have a higher risk for dementia than those with less advanced PD. More interestingly, an association between specific motor symptoms and dementia has been reported in several studies. Symptoms such as rigidity, postural instability and gait disturbance predict more rapid cognitive decline and shorter time to dementia. In one study, speech and axial impairment, indicative of predominantly nondopaminergic deficiency, were found to predict incident dementia, whereas dopaminergic symptoms such as rigidity and akinesia were not (51). Several studies have found an association between postural instability and gait disorder (PIGD) motor subtype to be associated with dementia. Of note, the motor profile differs with time, the most common change being from tremor dominant to PIGD type. We recently showed that in nearly all dementia cases, dementia was preceded by PIGD-dominant PD, or by a transition from tremor dominant to PIGD-type PD. Dementia was very rare in patients with tremor-dominant PD (9). Similar findings were reported in another study (17). Similarly, in the CamPaign study of incident PD, severity of nontremor type (ie, mixed or PIGD type) motor symptom severity was associated with a higher risk for dementia independent of age (79). The mechanism underlying this association between motor subtype and risk for dementia is unknown.

Age

Age and age at onset are both associated with a higher risk of dementia. This is not surprising, given that age is the most prominent risk factor for dementia in the general population. Interestingly, age and severity of motor symptoms seem to have a combined rather than additive effects on the risk of dementia (50). Age, duration of disease and age at onset are highly correlated in PD cohorts, and thus, it can be difficult to disentangle their relative importance, ie, whether it is age, duration of disease or rather age of onset of PD that is driving the age-associated risk for dementia, although in one study exploring this question, age, but not age at onset or duration of disease, was significantly associated with the risk for dementia (5). Based on such evidence, a model of the relationship between age and disease-related processes in PD was proposed, suggesting that, on the background of the pathological

process inherent to PD, aging plays a substantial role in the pathogenesis through an interaction with the disease process in non-dopaminergic structures (50).

MCI

A considerable proportion, between 20% and 30%, of nondemented PD patients have cognitive impairment, even early in the disease (27, 58). At a group level, impairment on neuropsychological tests, in particular tests of memory and executive functioning (44, 49), was found to predict a shorter time to develop dementia. More recently, several studies have demonstrated that PD patients with MCI have a higher risk for developing dementia over time than those with normal cognitive performance. First, in a cohort with advanced PD, Janvin *et al* showed that after 4 years, more than 60% of PD patients with cognitive impairment had developed dementia compared to only 20% of those with normal cognition (45). Similarly, in the CamPaign study reported above, based on an incidence cohort, those with cognitive impairment at disease onset had a higher risk of dementia (78, 79). This and other cohorts have demonstrated a marked heterogeneity in the pattern of cognitive performance in PD. Some patients have a more frontal-executive pattern of impairment, whereas others have a more temporal-amnestic impairment. Importantly, the CamPaign study suggested a dissociation in the risk for dementia based on different cognitive profiles: deficits of posterior cortical cognitive functions, such as semantic fluency and visuoconstructional abilities, were associated with a higher dementia risk, whereas executive impairment was not. The findings in this study was backed by specific genetic variations related to this clinical pattern, with tau H1 haplotype associated with posterior deficit and increased dementia risk, whereas the Catechol-O-methyltransferase (COMT) genotype was associated with executive impairment but not dementia risk (see below).

Consensus regarding the definition and classification of MCI-PD has not yet been established, but is a priority. However, the validity of the concept of PD-MCI is further supported by imaging studies reporting cortical atrophy in PD-MCI (14), and Positron emission tomography (PET) studies have revealed a characteristic pattern of reduced metabolic activity (39). These studies strongly suggest that the early cognitive deficits in PD, particularly those related to posterior dysfunction, represent the earliest phase of a dementia process, representing a potential for prevention of dementia. This is a key priority for future research.

VH and other neuropsychiatric symptoms

Psychiatric symptoms are common in PD, and are particularly common in PD-D (4). VH are among the most characteristic neuropsychiatric features of PD, and may even aid in the differentiation of PD from other parkinsonian disorders (77). VH are common in PD (26), particularly in patients with dementia. In a longitudinal, community-based study, we found VH to be associated both with a higher rate of cognitive decline (3) as well as a higher risk for development of dementia (1). The association of VH with dementia is probably related to VH being associated both with Lewy body pathology in the temporal lobe, particularly in amygdala (33) as well as with cholinergic deficits (61).

Psychiatric symptoms other than hallucinations may also be associated with dementia risk. Apathy, which is a common and characteristic symptom in PD (20), was found to be associated with dementia risk in a recent 4-year prospective study (60). Rapid Eye Movement (REM)-sleep behavior disorder (RBD) is another very characteristic feature of Lewy body diseases (15), and has been shown both to be a risk factor for developing PD and is also commonly found in PD. There is evidence that the development of RBD in patients with PD is associated with both MCI (28) and dementia in PD (56, 74), although longitudinal studies have not yet been reported.

Other factors

There is convincing evidence of an association between smoking and reduced risk for PD (8), possibly mediated by an effect upon nicotinic receptors. Nicotinic receptors are involved in learning and memory, and smoking may therefore theoretically protect against cognitive decline and dementia in PD. However, smoking also increases inflammation and oxidative stress and is associated with cardiovascular disease. Two longitudinal studies have supported the hypothesis that smoking may reduce the risk for dementia (52) and cognitive decline (76) in PD. However, another longitudinal study did not find an association between smoking and cognitive impairment (8).

A significant relationship between anti-Parkinson drug use and risk for dementia has not been convincingly demonstrated. However, an inverse relationship between use of amantadine and risk for dementia was found in a naturalistic study (42). Consistent with this finding, a recent study showed that memantin, which has a similar mechanism of action as amantatin, had a positive effect on cognition in a sample of PD-D and DLB. In contrast, anticholinergic drugs may have a negative effect on cognition, as recently observed in a longitudinal study where PD patients who had used drugs with anticholinergic activity had a much more rapid cognitive decline than those who had not (24). Naturalistic studies like this are subject to a range of potential bias. These findings are nevertheless consistent with pathologic studies showing that treatment with anticholinergic drugs are associated with the density of amyloid plaques in patients with PD (62).

Estrogen replacement therapy has been found to be associated with a decreased risk for dementia in PD in one study (54), whereas risk factors for Alzheimer's disease and vascular dementia such as high cholesterol (46), head trauma, diabetes mellitus and hypertension were not associated with the risk for PD-D (34, 52). There is also conflicting evidence regarding whether hyperhomocysteinemia, which is a well-known risk factor for cognitive decline in the general population, is associated with an increased risk for dementia in PD. Some studies have demonstrated such an effect (66), whereas other studies do not find such an association (59). However, cerebrovascular disease, although less common in PD than in the total population, seems to have a significant, but small, effect on the risk for dementia in PD (13). Such associations may provide a strategy for dementia prevention in PD, and indeed, one large registry-based study found a strong association between use of simvastatin and more than 50% reduction of the incidence of dementia in PD (80).

Biomarkers

There are currently no established biomarkers to predict the rate of cognitive decline and risk for dementia in PD. As the established clinical risk factors such as age, MCI and severity of nondopaminergic symptoms are nonspecific, biomarkers are potentially useful both in order to predict the clinical course as well as serving as potential markers of disease progression to be used in clinical trials. Several potentially interesting biomarkers have been found to be associated with cognitive impairment in Lewy body diseases, such as cerebrospinal fluid proteins (abeta 42, p-tau, alpha-synuclein), Electroencephalography (EEG) and structural and functional imaging. However, there are as yet no longitudinal studies which have shown that these markers can predict the risk for dementia in PD, but such studies are ongoing and promise to provide important diagnostic and prognostic information.

Genetics

Although the main risk factor for PD is age, the importance of genetic factors has been increasingly highlighted. In most cases, it is assumed that an interaction of genetic susceptibilities and environmental factors in the aging brain influences disease development and progression (68). There is some evidence of an association between genes and risk of dementia in PD (48), but little evidence exists. Longitudinal-based studies failed to find an increased risk for dementia among the relatives of patients with PD compared to relatives of normal control subjects, although dementia in PD was associated with a family history of PD (47). In contrast, in a recent large historical cohort study, a higher risk for cognitive impairment and dementia was found in relatives of PD patients compared to relatives of control subjects, particularly for PD patients with early age at onset (67), supporting the association between genetic factors and dementia in PD.

Missense mutations of the *alpha-synuclein* gene (*SNCA*) have been found in PD families with autosomal dominant inheritance (63). Patients with *SNCA* mutations exhibit L-dopa responsive parkinsonism with early age of onset, rapid progression and a high prevalence of dementia and other psychiatric manifestations. However, SNCA point mutations have so far been found in large PD families only but never in the sporadic disease and remain a very rare cause of PD (12). Multiplications rather than point mutations in *SNCA* have been shown to be one of the most prominent risk factors in familial PD (72) and can be found even in the sporadic disease (7). A dose dependency of this effect is demonstrated as patients with *SNCA* triplications show an early disease onset with a high rate of dementia, while patients with *SNCA* duplications have a later onset and exhibit a more typical pattern of PD (19).

Mutations in the *leucine-rich repeat kinase 2* gene (*LRRK2*) are the most common cause of Mendelian PD identified so far (23). PD patients carrying *LRRK2* mutations show a clinical pattern similar to sporadic disease but with a somewhat more benign progression and a lower rate of dementia, despite showing a wide range of pathologic patterns including diffuse Lewy body disease and sometimes tau-protein aggregations.

Mutations in three genes, in *parkin*, *PINK1* and *DJ-1*, cause autosomal recessive PD. Typically affected patients present with an early age at onset with a somewhat slower progression and lower rate of dementia in the case of PINK1 and DJ-1 and a picture indistinguishable from the sporadic disease in the case of Parkin. Parkin has been postulated to be essential in Lewy body formation (69), yet only two of the *Parkin* mutant PD brains that have come to autopsy so far showed typical Lewy bodies (64).

The *Apolipoprotein E (APOE) ε4* allele is associated with a higher risk and earlier onset of AD. Thus, an association with dementia in PD has been hypothesized. Associations between the *ε4* allele type and Lewy body pathology (75) and advancing neuropathological changes according to the Braak staging (29) support this hypothesis. Although a current meta-analysis concluded that the *ε4* allele is associated with a higher prevalence of dementia in PD (40), this association was not confirmed when PD-D was defined using more strict criteria (46). Thus, further studies are needed to clarify the role of *APOE* in PD-D.

The *H1* haplotype of the *microtubule associated protein (MAP) gene*-encoding tau protein, has been implicated in PD by linkage analysis (71). Although equivocal results exist, a meta-analysis found a positive association of PD and PD-D with the *H1* haplotype (35). Interestingly, a gene–gene interaction between *MAPT* and *SNCA* (31), co-localization of alpha-synuclein and tau protein within the Lewy bodies in PD (43) and synergistic fibrillization observed *in vitro* (30) were also reported. Not surprisingly therefore, a recent study identified the *MAPT* genotype as a strong independent predictor of dementia in PD (78).

CONCLUSIONS

The point prevalence of dementia in PD is close to 30% and the incidence rate is increased 4–6 times as compared to controls, although it may be lower during the first 3–5 years after onset of PD. The cumulative prevalence is very high; at least 75% of PD patients who survive for more than 10 years will develop dementia. In addition, MCI is common even at disease onset, and is associated with a shorter time to dementia. Other risk factors for dementia are old age, severity of motor symptoms, in particular PIGD, and presence of VH. The genetic contributions to dementia in PD have not yet been established. Future studies should explore biomarkers of dementia in PD, and carefully explore the association between specific cognitive deficits, biomarkers and time to dementia. Such information is a key factor in the search for treatments which can prevent the development of dementia in patients with PD.

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