Population-based Studies on the Clinical Progression of Motor and Non-motor Features in Parkinson's Disease

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Abstract

Although Parkinson's disease (PD) is a movement disorder in which tremor, rigidity and bradykinesia constitute the cardinal signs of the disease, it is increasingly recognised to be associated with a wide range of motor and non-motor features. Population-based studies demonstrate that the motor course in PD is generally slowly progressive, with average annual progression rates of ≤3%. However, there is remarkable inter-individual variation in the clinical course of PD, with advanced age and predominant postural instability and gait difficulties being major risk factors for more rapid motor and cognitive decline. Around 20–40% of patients exhibit subtle cognitive deficits at diagnosis. These usually worsen over time and progress into dementia, which approximately 80% of PD subjects develop during the course of their disease. Population-based studies indicate rather high frequencies of other non-motor symptoms in moderate to advanced stages, such as depression, fatigue, apathy, sleep disorders and autonomic dysfunction, although prevalence rates often are lower than those observed in clinic-based studies. However, as several population-based studies were cross-sectional, uncontrolled and did not use currently accepted rating scales or diagnostic criteria, the relative risk and clinical course of many disease-related features remain unclear in the general PD population. Further population-based studies are warranted in order to extend current knowledge on the clinical course in representative PD cohorts.

Keywords

Parkinson's disease (PD), progression, course, decline, population-based, community-based, epidemiology

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Parkinson's disease (PD) is the most common neurodegenerative movement disorder, affecting more than one million people in Europe. The cardinal features of the disease include resting tremor, bradykinesia, rigidity and postural abnormalities. Long understood as a solely movement disorder caused by progressive neuronal cell loss and dopamine depletion in the nigrostriatal system, PD is today recognised as a multisystem brain disorder that causes a wide range of motor and non-motor symptoms. Given that the first description of PD was published almost 200 years ago[1] and the disease is recognised to be frequent, disabling and costly,[2] one might presume that its clinical characteristics and course are well described. However, although numerous epidemiological studies have been conducted during recent decades to assess the phenomenology and pattern of PD, the number of studies providing longitudinal data on its clinical course is rather limited.

Even fewer studies have been performed to prospectively assess the progression of motor or non-motor features in population-based cohorts, despite the fact that such information is probably best suited to give a correct description on how the disease progresses in the general PD population. Such information is important for patients, care-givers and healthcare planning. In this article we provide an overview of current knowledge of the clinical course of motor and non-motor features of PD derived from population-based studies.

Methodological Considerations

Most studies conducted to assess the clinical course of PD are clinic-based. A major drawback of such studies is that the populations investigated may be skewed and their data thus difficult to generalise. This article therefore mainly refers to population-based studies. Such studies are also referred to as being 'community-based', 'unselected' or 'representative'. However, even data derived from population-based cohorts may vary in quality. Information on the longitudinal course may be extrapolated from independent cross-sectional studies that include samples with different disease duration or stage. However, such data have to be interpreted carefully as study design and methods of assessments of clinical features often vary between studies. Repeated assessments within one cohort are a more appropriate way to describe clinical disease progression. Finally, the demographics of incident cohorts are less affected by mortality than those of prevalence cohorts. Thus, prospective longitudinal studies conducted in population-based incident cohorts may be considered the gold standard in order to provide information representative for disease progression in the general PD population.

Motor Symptoms

Clinical Rating Scales

There are numerous measurements to assess the clinical course of PD. However, the Unified Parkinson's Disease Rating Scale (UPDRS) is the most widely used and accepted rating tool in PD.[3] It was designed

to follow the longitudinal course of the disease and has been shown to be both reliable and valid.[4] It is divided into four subscales, covering symptoms of mentation, behaviour and mood (subcsale I), activities of daily living (subscale II), motor symptoms (subscale III) and complications of therapy (subscale IV). Each item in subscales I and III is quantitatively scored on a five-point scale (from 0 to 4). A modified version of the UPDRS has recently been published.[5]

The Hoehn and Yahr scale[6] is the other main scale in PD and measures the stage of the disease by including both impairment and disability of movements, balance and gait. The scale allocates stages from 0 (no signs of disease) to 5 (wheelchair bound or bedridden unless assisted). Non-motor features are not captured by the Hoehn and Yahr scale.

Rate of Functional Decline

The rate of motor decline in drug-naïve patients has not been assessed longitudinally in representative cohorts. In patients on regular antiparkinsonian treatment, population-based longitudinal cohort studies found annual progression rates between 1.5 and 3.1%, as measured by the UPDRS motor score, underlining the generally slowly progressive nature of PD.[7,8] However, there is remarkable inter-individual heterogeneity in the motor course of PD. Population-based studies suggest that higher age at motor onset is an important denominator of more rapid motor progression in PD.[7] The annual increase in UPDRS motor score was found to be 50% more rapid in patients 70 years of age at disease onset than in subjects 50 years of age at onset.[7] The predicted time for progressing one Hoehn and Yahr stage for patients 70 years of age and 50 years of age at motor onset was 5.1 and 9.3 years, respectively.[7] In addition, some representative studies report a non-linear progression of motor symptoms, with more rapid functional decline during the early stages of the disease.[8,9]

Clinical Phenotype

Evidence suggests a change in clinical phenotype during the disease course in most patients with PD. Whereas tremor severity usually does not worsen over time, severity of bradykinesia, rigidity and gait and balance tends to progress at similar rates, possibly indicating different underlying pathophysiological processes.[8] Although postural abnormalities are considered one of the cardinal features of the disease, postural instability is uncommon in early PD. In a community-based study of 128 patients with PD, only 1% reported unsteadiness as their initial symptom. However, at an average of six years of disease duration, 64% had postural instability with falls and 49% had speech difficulties.[10] Furthermore, in a population-based longitudinal study of patients who were non-demented after on average nine years of disease duration, most of those with initial tremor-dominant parkinsonism developed a clinical phenotype characterised by predominant postural instability and gait difficulties (PIGD). The proportion of patients with PIGD phenotype increased from 54 to 88% during eight years of follow-up.[11] PIGD, as well as freezing of gait, are important risk factors for falls, which are considerably more frequent in PD than in the general population and often associated with injuries.[12,13]

Motor Complications

Clinic-based studies report that about 10% of subjects develop motor problems each year.[14] However, data derived from population-based studies indicate that this may be an overestimate. In a community-based prevalence study, 78% of the patients did not experience motor fluctuations after over six years of levodopa treatment.[15] In another population-based prevalence study, 28% of levodopa-treated patients suffered from dyskinesias and 40% from response fluctuations after about seven years of disease duration.[16] In a four-year longitudinal community-based study, the proportion of self-reported involuntary movements and motor fluctuations increased from 10 to 43% and 31 to 46%, respectively.[9] Risk factors for the development of motor complications in population-based studies are largely consistent with those found in clinic-based studies and include younger age at onset, higher disease severity, longer duration of disease and treatment and higher levodopa doses.[15,16]

Non-motor Symptoms

Cognitive Decline and Dementia

The risk of developing dementia is two- to six-fold increased in PD compared with the general population.[17–19] Increasing evidence from representative studies suggests that cognitive impairment may be present even in early stages of PD. In a recent community-based study of incident untreated subjects, 19% were classified as having mild cognitive impairment (MCI),[20] which was two-fold more frequent than in a group of age- and sex-matched normal controls. In another population-based uncontrolled study in early PD, 36% of patients had evidence of cognitive impairment at diagnosis,[21] 10% had developed dementia and a further 57% showed evidence of cognitive impairment after 3.5 years of follow-up.[22] This is in keeping with a community-based prevalence study in which more than half of non-demented patients had some form of cognitive impairment after about 12 years of disease duration.[23]

The cognitive impairment in PD is slowly progressive. In a population-based prevalence sample, the observed mean annual change in mini-mental state examination (MMSE) was approximately one point.[24]

Severity and range of cognitive impairment increase with advance in Parkinson's disease, which probably reflects the spread of underlying pathology to relevant subcortical and cortical brain areas.

However, while the change in score for non-demented patients was similar to that in normal control subjects, patients with dementia declined with more than two MMSE points per year,[24] suggesting a non-linear progression of cognitive deficits in PD.

Severity and range of cognitive impairment increase with advance in PD, which probably reflects the spread of underlying pathology to relevant subcortical and cortical brain areas. Prevalence rates of dementia in large community-based studies using standardised cognitive assessment and Diagnostic and Statistical Manual of Mental Disorders (DSM-IIIR) criteria range from 23 to 41%.[25] However, since dementia in PD is associated with two-fold increased mortality,[26] cross-sectional studies probably underestimate the true frequency of PD with dementia (PDD). In a large prospective population-based study, the cumulative prevalence of PDD after 17 years of disease duration was as high as 78%,[27] similar to another long-term study.[12] The cumulative incidence of PDD increases with age and disease duration and, conditional on survival, increases to 80–90% by 90 years of age.[28]

Independent risk factors for PDD found in population-based studies include advanced age,[29] neuropsychological deficits and MCI[30,31] and severity of parkinsonism,[32] particularly axial symptoms such as postural instability and speech problems.[11] During an eight-year prospective follow-up study of a community-based sample of non-demented patients with PD, development of PIGD parkinsonism was associated with accelerated cognitive decline and an approximate 50% risk of dementia within the following four years.[11] Interestingly, none with tremor-dominant parkinsonism at study end had developed dementia, in line with another clinic-based study.[33]

Depression

Depression is an important predictor of reduced quality of life in PD.[34,35] In a recent systematic review of prevalence studies of depression in PD, frequency rates ranged from 2.7 to 35% in population-based studies fulfilling quality criteria for inclusion, compared with 12.7 to ~90% in clinic-based studies.[36] In studies from the general PD population, the mean prevalence of major depression was 8.1%, and the mean prevalence of clinically relevant depressive symptoms (major depression, minor depression or dysthymia) was 10.8%.[36] A four-year longitudinal community-based study reported an increase in the proportion of patients with self-reported depression from 27 to 56%.[9] The profile of depressive symptoms in non-demented PD is different from that in non-PD subjects, with more concentration difficulties but significantly less sadness, anhedonia and feelings of guilt.[37] This pattern may explain why suicide, despite the higher prevalence of depression in the disease, is not more common in PD than in the general population.[38,39]

Fatigue in Parkinson's disease may occur as a physical or mental problem, and both dimensions of fatigue are more prominent in Parkinson's disease than in the general population.

Psychosis

Psychotic symptoms in PD include minor phenomena such as illusions and senses of presence or passage, simple and complex hallucinations, with and without insight, and delusions. Visual hallucinations are found to be the most common form in PD. While provisional diagnostic criteria for psychosis associated with PD have been proposed recently,[40] they have not yet been taken into account in most published studies. Few population-based studies of psychosis have been conducted in PD. In a cross-sectional population-based prevalent sample of patients with a mean disease duration of 12 years, 10% had hallucinations with insight retained and 6% had more severe hallucinations or delusions.[41] However, among patients who lived in nursing homes, the corresponding figures were significantly higher, at 23 and 19%, respectively.[41] In another community-based study of patients with six years of disease duration at study start, the proportion of patients reporting hallucinations increased from 23 to 56% during four years of follow-up.[9,10] However, these figures are likely to be underestimates as none of these studies captured the whole spectrum of psychosis in PD. Population-based data suggest that hallucinations are one of the main risk factors for hospitalisation and nursing home placement in PD.[42]

Apathy

As yet there are no longitudinal studies of apathy in PD, and thus it is uncertain whether and how characteristics of apathy may change over time. In addition, currently there is a lack of generally accepted diagnostic criteria for apathy. In population-based studies of apathy in PD, prevalence estimates range from 16.5%, as measured by the Neuropsychiatric Inventory, to 38% using the motivation/initiative item of the UPDRS.[43] These figures are lower than some of those observed in clinic-based studies, where prevalence rates of up to 70% were reported.[44] In community-based studies,[43] similar to clinic-based studies, apathy relates to higher depression scores, cognitive impairment and more severe motor symptoms. Hence, prevalence rates of apathy are anticipated to increase with advance in PD, particularly in the context of progressive cognitive decline.

Fatigue

Fatigue in PD may occur as a physical or mental problem, and both dimensions of fatigue are more prominent in PD than in the general population. Population-based data demonstrate that fatigue has a substantial negative impact on quality of life in patients with PD.[45] Recent clinic-based data suggest that fatigue may precede the onset of the disease and is frequent in newly diagnosed subjects not on dopaminergic treatment.[46] However, population-based data from early PD cohorts are not yet available to support this. In the only population-based longitudinal study to date, fatigue prevalence increased from 36 to 56% during eight years of follow-up.[47] This increase was related to disease severity, depression and excessive daytime sleepiness (EDS). However, even in patients without depression and EDS more than one-third of subjects complained about fatigue, suggesting that fatigue in PD may develop independently of other non-motor problems with possible overlapping symptomatology. In more than half of patients, fatigue was a persistent feature once experienced.[47]

Sleep Disorders

Insomnia is the most common sleeping problem in PD, and a major contributor to reduced quality of life.[34,48] After an average nine years of disease duration, 60% of a population-based sample reported nocturnal sleeping problems,[49] with sleep fragmentation and early awakening being the main complaints.[49] Longitudinal follow-up of this cohort revealed similar prevalence rates of insomnia over eight years, but considerable variation of sleeping problems in individual patients over time.[50] The presence of insomnia over time was associated with disease duration, depressive symptoms and female sex.[50]

EDS is also common in PD,[51] and not a consequence of nocturnal sleeping problems.[52,53] Clinical EDS has been found in 15% of PD patients in a population-based cohort with mean disease duration of nine years, compared with only 1% of EDS in healthy elderly control subjects.[52] Two longitudinal studies in this population observed an increase of EDS prevalence to 29 and 41% of surviving patients after four and eight years of follow-up, respectively.[52,53] EDS was found to be a persistent complaint in most patients and was associated with age, gender, use of dopamine agonists and disease severity, suggesting multifactorial underlying pathophysiology.[52,53]

REM sleep behaviour disorder (RBD) is a parasomnia characterised by prominent motor activity due to loss of the normal skeletal muscle atonia during REM sleep. Typical clinical features of RBD include vocalisations and movements of limbs and body, often associated with dreams. Patients with idiopathic RBD are at high risk of

developing PD and related neurodegenerative disorders, and thus RBD is considered as an early sign of an evolving synucleinopathy.[54] In a population-based study of prevalent PD cases that were followed prospectively over eight years, prevalence of clinically probable RBD varied with time, affecting 15–27% of subjects, and was independently associated with male gender, lower disease severity and higher daily levodopa-equivalent doses.[55]

Dysautonomia

There are very few representative studies on autonomic dysfunction in PD. In a cross-sectional community-based survey of prevalent PD patients, 47% met criteria of orthostatic hypotension,[56] and in a community-based longitudinal study of patients with six years of disease duration at baseline the prevalence of self-reported bladder problems increased from 11 to 40% during a four-year period.[9]

Impulse Control Disorders

There is increasing awareness that impulse control disorders, such as compulsive gambling, buying, eating and hypersexuality may complicate the course of PD.[57] However, longitudinal data from population-based cohorts on this issue remain to be published.

Summary

Population-based data suggest that the motor course in PD is generally slowly progressive, with average annual progression rates of 3% or less. However, there is a considerable inter-individual variation in motor decline, with more rapid progression in older subjects and possibly in early stages of the disease. The clinical phenotype of PD tends to change during the course of the disease, and after 17 years of disease duration about 90% have developed predominant gait and postural impairment. Twenty to 40% of patients with newly diagnosed PD show cognitive deficits. These usually worsen over time and progress into dementia, which approximately 80% of PD subjects develop during the course of their disease. Population-based studies indicate rather high frequencies of other non-motor symptoms in moderate to advanced stages, such as depression, fatigue, apathy, sleep disorders and autonomic dysfunction, although prevalence rates often are lower than those observed in clinic-based studies. However, as several population-based studies were cross-sectional and uncontrolled and did not use currently accepted rating scales or diagnostic criteria, the relative risk and clinical course of many disease-related features remain unclear in the general PD population. Hence, there is need for further population-based studies to extend current knowledge on the clinical course of PD. Prospective longitudinal case-control studies in representative incident PD cohorts appear the gold standard for this purpose. ■

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