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Epidemiology of Parkinson's disease

Ole-Bjørn Tysnes[1] · **Anette Storstein**[1]

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Abstract Parkinson's disease (PD) affects 1–2 per 1000 of the population at any time. PD prevalence is increasing with age and PD affects 1% of the population above 60 years. The main neuropathological finding is α-synuclein-containing Lewy bodies and loss of dopaminergic neurons in the substantia nigra, manifesting as reduced facilitation of voluntary movements. With progression of PD, Lewy body pathology spreads to neocortical and cortical regions. PD is regarded as a movement disorder with three cardinal signs: tremor, rigidity and bradykinesia. A recent revision of the diagnostic criteria excludes postural instability as a fourth hallmark and defines supportive criteria, absolute exclusion criteria and red flags. Non-motor symptoms in PD have gained increasing attention and both motor and non-motor signs are now included among the supportive criteria. The cause of PD is unknown in most cases. Genetic risk factors have been identified, including monogenetic causes that are rare in unselected populations. Some genetic factor can be identified in 5–10% of the patients. Several environmental factors are associated with increased risk of PD. Autopsy studies show that the clinical diagnosis of PD is not confirmed at autopsy in a significant proportion of patients. Revised diagnostic criteria are expected to improve the clinicians accuracy in diagnosing PD. Increasing knowledge on genetic and environmental risk factors of PD will probably elucidate the cause of this disease within the near future.

✉ Anette Storstein
astt@helse-bergen.no

[1] Department of Neurology, Haukeland University Hospital, 5001 Bergen, Norway

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Summary

Parkinson's disease (PD) is characterized by its main motor symptoms bradykinesia, rigidity and tremor, but also have additional motor and non-motor characteristics. The onset of the disease is usually at an age of 65 to 70 years. Onset before the age of 40 is seen in less than 5% of the cases in population-based cohorts. Earlier onset is seen in genetic variants. Monogenetic forms of PD are probably rare in unselected populations, but may be frequent in some ethnic groups. In general, genetic factors are thought to be involved in 5–10% of the cases, may be more. The disease is slightly more frequent in men than women. The prevalence of the disease is generally accepted to range from 100 to 200 per 100,000 people and the annual incidence is thought to be 15 per 100,000. There is an ongoing discussion whether there is increasing occurrence of the disease, exceeding what can be expected in an ageing population.

Introduction

PD is the most common movement disorder and represents the second most common degenerative disease of the central nervous system. The disease was originally described by James Parkinson in his "Essay on the shaking palsy" from 1817, carefully outlining the major motor signs of the disease that are still considered the hallmarks of PD; bradykinesia, rigidity and tremor. In addition, mental symptoms of the disease were also noted.

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PD is characterized neuropathologically by the presence of α-synuclein-containing Lewy bodies in the substantia nigra of the brain. Loss of dopaminergic neurons in the pars compacta of the substantia nigra leads to reduced facilitation of voluntary movements. α-synuclein accumulation becomes more widespread in the brain during the progression of PD (Braak et al. 2003) and over the last 10–20 years non-motor symptoms in PD have been given considerable attention (Garcia-Ruiz et al. 2014). Nevertheless, the motor signs of the disease making PD a movement disorder, still represent the hallmarks of the disease and are the most important characteristics for a diagnosis of PD, even today with modern imaging or laboratory tests to help with the diagnostic challenge.

Diagnosis of PD

PD was originally considered a pure movement disorder with three cardinal signs: tremor, rigidity and bradykinesia. Over the years postural changes in general and postural instability in particular was used as a fourth cardinal sign (Gelb et al. 1999). During the 1990s it became apparent that a considerable proportion of cases with a clinical diagnosis of PD did not fulfill histopathological PD criteria at autopsy, even at the most experienced hands. At best only 80% of cases clinically defined as PD met the criteria for the disease at autopsy (Larsen et al. 1994; Tolosa et al. 2006). Defined diagnostic criteria of PD, like the UK Brain Bank Criteria (Hughes et al. 2001), increased the accuracy, but even after clinical observation over years, as used in these criteria, cases with diagnostic uncertainty remain (Rizzo et al. 2016).

Recently the clinical diagnostic criteria for PD were revised (Postuma et al. 2015a). Bradykinesia, rigidity and rest tremor are still highlighted as cardinal signs of the disease. The obligate symptom of bradykinesia must occur in combination with rest tremor, rigidity or both. However, postural changes, and especially postural instability, are left out. The new diagnostic criteria define supportive criteria, absolute exclusion criteria and red flags. A diagnosis of "clinically established PD" requires at least two supportive criteria, the absence of absolute exclusion criteria, and no red flags. The supportive criteria include both motor and non-motor aspects of the disease, namely effect of dopaminergic therapy, presence of levodopa-induced dyskinesia, asymmetric rest tremor and positive tests on cardiac sympathetic denervation or olfactory loss. Absolute exclusion criteria are cerebellar abnormalities, supra nuclear gaze palsy, frontotemporal cognitive changes, slow progression, use of anti-dopaminergic therapy, absence of levodopa response, cortical findings like apraxia, and normal DAT scan. Red flags are early gait impairment, absence of progression, early bulbar dysfunction, inspiratory respiratory dysfunction (most frequently seen in MSA), severe autonomic failure during the first year of the disease, recurrent falls due to reduced balance, early antecollis, pyramidal tract signs, bilateral symmetric parkinsonism throughout the disease course and absence of any of the common non-motor features seen in PD like sleep dysfunction, autonomic dysfunction or hyposmia. The new diagnostic criteria for PD will most probably improve the diagnostic accuracy to achieve a better concordance between the clinical diagnosis and the neuropathologically confirmed disease.

Prevalence and incidence of PD

Several studies report data on the epidemiology of PD. However, methodological differences between studies make direct comparison of prevalence estimates difficult. It is generally accepted that the prevalence of the disease range from 1 to 2 per 1000 in unselected populations (von Campenhausen et al. 2005) and that the disease affects 1% of the population above 60 years (de Lau and Breteler 2006). PD is rare before age of 50 years and reaches a prevalence of 4% in the highest age groups (de Rijk et al. 1995, 2000).

The incidence of the disease varies considerably in different reports. This is probably due to methodological differences, in particular differences in case ascertainment and use of diagnostic criteria. The annual incidence per 100,000 inhabitants ranges from less than 10 to more than 20. Incidence studies may be affected by under-diagnosing of PD, especially among the most elderly.

The public health care system in the Nordic countries is well organized and the population is very stable. Few people move to other regions of the country when they reach the age of increasing risk of PD. In the Park West study (Alves et al. 2009) medical files of MDs in general practice (GP) were scanned for cases diagnosed as PD. We identified no cases of PD in the GP's files that were not already included in the study. The annual incidence of the disease was calculated to 13.5/100,000. Only 8 cases (3%) of the 265 identified PD patients during the inclusion period were younger than 50 years of age (Alves et al. 2009). The NYPUM study in Umeå in Sweden reports a thorough evaluation of PD in the very oldest age group (Linder et al. 2010). This study reported an annual incidence of 18.8 cases per 100,000 and a mean age of onset at 70.6 years, slightly above the mean age of onset that we reported from Norway. Early-onset of PD is rare in population-based studies. Only 4% of patients develop cardinal signs of PD before the age of 50 (Van Den Eeden et al. 2003).

An important question is whether there is an actual increase in PD prevalence and incidence. Already in 2000

we reported that there was an increasing occurrence in neurodegenerative disease like ALS and PD in Norway (Seljeseth et al. 2000). Most of the increase could be attributed to the general increase in age of the population. However, recently published data support an increase in risk of PD, especially in men. It was hypothesized that the increase in risk of PD could be related to the dramatic changes in smoking behavior that has been taken place during the last part of the twentieth century (Savica et al. 2016b). Increased occurrence of PD has also been related to increase in traffic-related air pollution (Lee et al. 2016). However, other reports have not been able to demonstrate an increased risk of PD (Rocca et al. 2001; Liu et al. 2016).

Etiology

The cause of PD is unknown for most identified cases. Over the last years genetic risk factors have been identified. First degree family members of affected patients have a 2- to 3-fold increased risk to develop the disease compared to subjects in the general population or controls (Sveinbjornsdottir et al. 2000; Savica et al. 2016a). Monogenetic causes of PD have been identified, but were considered very rare until the identification of leucine-rich repeat kinase (LRRK2) mutations (Gilks et al. 2005) that in selected populations cause up to 40% of the cases (Lesage and Brice 2012). It is generally considered that known genetic causes may be relevant in more than 5% of the total PD population and that monogenetic causes are rare, but some propose that monogenetic causes may be involved in as many as 5–10% of the PD population (Lill 2016). Monogenetic forms of PD may differ from sporadic PD both pathologically and clinically. The exception is the LRRK2 mutation which to a high degree resembles sporadic PD with asymmetric onset and frequent tremor. LRRK2 PD is, as sporadic PD, heterogeneous with respect to progression and occurrence of non-motor symptoms. PD associated with SNCA mutation is more early-onset, has a moderate response to levodopa with more rapid progression, and pyramidal signs, psychiatric symptoms and cognitive decline are frequently evident. The recessive PD forms are typically early-onset cases with good response to levodopa and early development of dyskinesias. Cognitive impairment is relatively uncommon (Thenganatt and Jankovic 2014).

The Norwegian Park West study is a population-based study and included 212 patients of a total of 265 identified PD cases (Alves et al. 2009). All patients included in the study were exome-sequenced. Only one patient had a monogenetic form of the disease (LRRK2) (Gaare et al. 2016). Monogenetic forms of PD are probably rare in unselected general populations. In addition to monogenetic forms of PD, genetic risk factors have been identified. Heterozygous GBA mutations, α-synuclein variants and tau variants are examples of genetic risk factors for PD (Rana et al. 2013; Kalia and Lang 2015). Well-known environmental risk factors of PD may attribute to genetic risk factors to influence the general risk of the disease. Cigarette smoking, alcohol, vitamin D exposure and urate levels are examples of environmental factors that may influence the risk of disease, in addition to acknowledged and unknown genetic factors (Kalia and Lang 2015). However, some data also indicate that the influence of environmental factors may be less important (Bellou et al. 2016).

Presymptomatic PD

During the last few years, there has been a considerable interest in prodromal signs of PD. Constipation was early identified as a risk factor of PD (Abbott et al. 2001). Less than 1 bowel movement per day represented a 2.7-fold increase in risk of PD. These data have recently been confirmed in a Danish study showing clearly increased risk of PD in patients with a previous diagnosis of constipation (Svensson et al. 2016) and are also reported in other studies (Stirpe et al. 2016). Hyposmia (Haehner et al. 2007) and REM-sleep behavior disorder (Jankovic et al. 2015) are considered to be particularly associated with the risk of later clinical PD. RBD may in more than 50% of cases end up as a form of synucleinopathy and especially PD, after 10 to 20 years of observation (Postuma et al. 2015b). There is still a lack of studies to give a more precise idea on the risk of PD in individuals with symptoms that could be prodromal.

Conclusions

PD represents a frequent cause of morbidity that affects 1–2 per 1000 of the population at any time, clearly most often in the older age groups. It affects men slightly more frequently than women. There may be an increase in occurrence of the disease that cannot be explained by demographic changes of the population alone. Revised diagnostic criteria are expected to improve the clinical diagnostic accuracy. Increasing knowledge on the genetic risk factors of PD together with data on environmental risk factors will probably increase the understanding of the cause of the disease within the near future.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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