OPINION

Parkinson's disease mortality and clinical milestones

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Nichols C. Parkinson's disease mortality and clinical milestones. Neurosurg J. 2022; 5(3):37-39.

ABSTRACT

For the purpose of patient education, disease management, and the design of upcoming clinical studies, it is critical to identify the variables predicting and driving death in PD. Newly diagnosed PD patients and healthy controls (NC) from a population-based study that underwent recurrent evaluations over a ten-year period were included in this study. We estimated survival using the Kaplan-Meier method, identified baseline risk factors for mortality using Cox proportional hazards regression models, and assessed the effect of four clinical milestones of advanced PD (visual hallucinations, recurrent falls, dementia, and nursing home placement) on mortality risk using Cox regression models with time-dependent covariates. Three independent baseline predictors of death were older age, more severe motor impairment, and the Postural Instability-gait Difficulty (PIGD) phenotype. The cumulative effect of each clinical milestone on mortality more than quadrupled the probability of death, with an HR of 10.83 (95% CI 4.39-26.73) in patients who experienced all four clinical milestones. Patients with PD are more likely to die, and this increased risk is disease-related and manifests early in the course of the illness. Clinical milestones showed a significantly higher risk of death later in the illness course, but motor severity and the PIGD phenotype were early risk factors for mortality. This suggests that clinical milestones may be important for clinical disease staging and prognosis.

INTRODUCTION

Even while the majority of studies indicate that Parkinson's Disease (PD) is associated with higher mortality, the reported estimates might vary widely, and some even indicated that survival is unaffected. The variation in several mortality risk factors, such as demographics and motor and non-motor symptoms, is comparable. Nevertheless, critical clinical turning points including visual hallucinations, frequent falls, dementia, and nursing home placement are still poorly understood. According to earlier research, PD patients have an increased mortality risk that can vary from 0.9 to 3.8. Heterogeneity in study design may help to partially explain the lack of precise estimations. For instance, because hospital-based studies are more prone to enrol advanced or atypical cases, the use of non-representative cohorts may result in greater death estimates than those seen in the general PD population.

Furthermore, chronic comorbidities are frequently present in the older population, where PD is more prevalent, and few studies have taken these factors into account. These factors may be a significant source of confounding. For the purpose of planning medical care and identifying clinical traits that can affect survival in clinical trials, accurate survival estimations and the identification of early and late risk factors are important.

However, more research is necessary to fully assess the effect of PD on mortality due to the shortcomings of earlier studies. In light of this, our goal was to compare the survival of incident PD patients who were followed for ten years after their diagnosis to controls who had comparable comorbidities. Additionally, we looked to determine how important clinical milestones of advanced PD contributed to excess death.

METHODS

Study design and population

The continuing Norwegian ParkWest project, a prospective, population-based research of the incidence, pathophysiology, and prognosis of PD, includes the current work. The hiring cycle lasted from November 1, 2004, to August 31, 2006. Prior detailed descriptions of the study's design and recruitment procedures were provided. 212 incident PD cases and 205 controls approved to participate in the ParkWest trial in total. There were 393 eligible participants for this study after 24 (22 patients and 2 normal controls (NC)) participants were later eliminated due to re-diagnosis. At their most recent interview, all patients met the criteria for Parkinson's Disease (PD) as forth by the UK Brain Bank, and 42 patients who underwent autopsy had post-mortem agreements.

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Received: 08-June-2022, Manuscript No. PULNJ-22-5157; Editor assigned: 10-June-2022, PreQC No. PULNJ-22-5157(PQ); Reviewed: 17-June-2022, QC No. PULNJ-22-5157(Q); Revised: 19-June-2022, Manuscript No. PULNJ-22-5157(R); Published: 30-June-2022, DOI: 10.37532/pulnj.22.5(3).37-39

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Examination program

At baseline, we conducted thorough medical and neurological tests as well as semi-structured interviews to gather information on demographics and medical history. Patients underwent standardised clinical follow-up every six months, and after one year and every two years after that, patients and NC underwent longer visits. We used the Hoehn and Yahr scale to assess disease stage at baseline and follow-up, and the Universal PD Rating Scale (UPDRS) motor score (part III) to assess the severity of motor impairment. Patients were evaluated as either drug-naive (97.3%, n=185) or in an off-state at baseline but in a "on-state" at the time of the follow-up. The motor phenotype was categorised using the classification algorithm proposed by Jankovic et al. as Postural Instability and Gait Disorder (PIGD), tremor-dominant, or intermediate. The 10-item Neuropsychiatric Inventory (NPI), the Montgomery-Sberg Depression Rating Scale, and the Mini-Mental State Examination (MMSE) were used to evaluate overall cognitive function, neuropsychiatric symptoms, and depressive symptoms, respectively (MADRS). Clinical milestones were assessed for the current study in accordance with the following criteria: visual hallucinations were considered present when scoring 2 on UPDRS I item 2 ("benign" hallucinations with insight retained or worse) or 1 on NPI item 2. (presence of hallucinations). A score of 2 on UPDRS II item 13 (occasional falls, less than once daily or worse) or 3 on UPDRS II item 14 was considered recurrent (occasionally falls because of freezing or worse). The movement disorders society diagnostic criteria at level II were used to describe dementia associated with Parkinson's Disease (PD), and the first admission to a long-term care facility with a nurse staff was considered nursing home placement.

Statistics

For categorical data, counts and proportions, and for continuous variables, means and standard deviations, are used to report the cohort's baseline characteristics. Student's t-tests, mann-whitney u tests, and chi-square tests, where necessary, were used to compare the groups. As medians and interquartile ranges, each milestone's time to occurrence for individuals who reached it within the 10-year follow-up period was displayed (IQR). The Kaplan-Meier estimator was used to examine the survival time after the inclusion date (to account for censoring), and the median survival time (either IQR or 95% confidence interval) and Kaplan-Meier plots were used to summarise the results. Using Cox proportional hazards models, we contrasted the mortality risk in PD and NC. In order to avoid a duplicate adjustment and a clinical pack-year measurement of cigarette smoking, we adjusted models for sex, baseline age, and comorbidities using the CCI total score. With their 95% Confidence Interval (CI), we calculated the hazard risk, which we then assessed using Wald testing. Using log minus log plots, the proportional hazards assumption was evaluated. We once more employed Cox models to investigate the early mortality risk variables in PD. The model includes baseline data for age, CCI total score (without age consideration), hoehn and yahr scale, MMSE, smoking pack-year exposure, and MADRS, as well as baseline values for sex. The median (IQR) survival time from the beginning of each clinical milestone and from the beginning of the kth milestone was calculated using the kaplan-meier estimator in a similar manner to assess late-stage PD mortality risk variables. Then, each clinical milestone was separately entered into a Cox model as a time-dependent variable with a value of zero prior to the milestone's occurrence and a value of one following it. When the kth milestone occurred, the cumulative count of milestones was updated (to k) and treated as a categorical variable.

DISCUSSION

We discovered excess mortality associated with PD in this prospective population-based study of an incident PD cohort. This excess mortality was present early in the course of the disease and more than doubled the risk of death over the course of the 10-year follow-up period, regardless of age, sex, smoking, or comorbidity status. While phenotypic and motor severity were early illness-related risk factors for mortality in Parkinson's Disease (PD), the emergence of clinical milestones signified a significantly elevated chance of death later in the disease's progression. Therefore, analysing these clinical milestones could be a useful technique to determine the disease stage and prognosis for PD. Other incident PD cohorts have reported a comparable hazard rate for mortality in PD after comorbidities were taken into account, with patients with PD having a slightly higher than double risk of dying. However, each of these cohorts only included one sex due to the original design of their studies. Additionally, studies based on medical records have revealed a comparable risk while controlling for the same confounders and have shown how this risk steadily rises with the progression of the disease. As opposed to the meta-analysis of other incident PD cohorts, the risk of death seen in our study is higher. This may be because we adjusted for comorbidities in our model, which may have revealed a more significant influence of PD on mortality than was previously thought. The various methodologies used to report risk are another factor influencing the variations in the reports of mortality risk attributed to PD in the literature. Our findings contradict certain early PD studies that claim patients are not at greater risk of mortality until the later stages of the disease. We demonstrated significant disparities in mortality became apparent early during the course of PD. Instead, a study's low statistical power or the use of an unbalanced control group in terms of comorbidities, which lessens the chance of spotting the true effect, could be used to explain why the risk of death linked to PD was not detected in these studies. However, in our study, the lengthy follow-up period and stringent diagnostic procedures make it unlikely that we have included atypical parkinsonism cases in our cohort. This assertion is further supported by our post-mortem findings in a sizable subset of patients. Previous studies have shown that life expectancy is lower in atypical parkinsonism patients than in PD patients3. The early disparities shown on a group level in our study are likely driven by individuals who have a higher motor severity and PIGD phenotype who are at the highest risk of early death. Similar correlations have been found between PIDG phenotype and motor impairment, as well as between more severe PD and dopaminergic and non-dopaminergic brain structural changes. Our study's findings demonstrated that motor symptoms, as measured by the MMSE and MADS scales, predicted long-term survival at baseline, whereas comorbidities and non-motor symptoms were not connected to mortality. The latter result suggests that the elevated mortality risk in PD is disease-related and not associated with baseline comorbidities. Reaching PD clinical milestones has also been linked to dementia especially with a higher risk of mortality and more severe types of PD utilising distinct clinical subtyping systems. In this investigation, the occurrence of any of these clinical milestones throughout time was linked to a PD patient's death risk being at least two times higher. Additionally, we could see that the occurrence of clinical milestones had a cumulative effect, with an HR of over 10 in patients who experienced all four milestones. In general, PDD development and admission to a nursing institution were the clinical milestones with the shortest time between onset and death, followed by falls and hallucinations.

The hypothesis that clinical characteristics of the advanced disease stage and the scores for cortical lewy bodies may be correlated is supported by the same sequential order of presentation. Since other commonly used approaches, such the hoehn and yahr scale, mainly rely on motor dysfunction and undervalue the complex character of the disease, evaluating these clinical milestones may represent an alternate approach to evaluating severe PD. Despite the fact that this study is population-based and typical of the Norwegian community, not all of its findings may apply to populations with various backgrou-nds, particularly those related to demographics, comorbidities, and healthcare access. This restriction, however, is not exclusive to our investigation and has no impact on the veracity of the concerns presented here. The population-based controlled design, frequent and standardized examinations from the time of diagnosis, the ten years of prospective follow-up, and the aforementioned post-mortem agreement of the diagnosis in a notable proportion of PD patients is additional important strengths of our work.