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Declining Quality of Life in Parkinson Disease Before and After Diagnosis

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Abstract

We sought to assess the quality of life in PD patients before the diagnosis, in comparison to age-matched individuals free of PD, among participants in two large prospective cohorts of men and women. Components of the Short-Form Health Status Survey (SF36) were administered to all participants in 1996 and 2008 in the Health Professionals Follow-up Study (HPFS), and in 1992, 1996, 2000 and 2004 in the Nurses' Health Study (NHS). We used scores in 7 health-related quality of life-dimensions, that were rated from 1(worst) to 100(best) points. We fitted a multivariate mixed-effect model with repeated measures to estimate the expected decline with age and compared that to the decline observed among PD cases by time to diagnosis. 454 men and 414 women with PD contributed data to the analyses. A decline in physical function in PD patients relative to the whole cohort began approximately 7.5 years prior to diagnosis in women and 3 years prior to diagnosis in men, and continued to decline thereafter with a rate of 2.35 and 1.43 points per year in women and men respectively ($p < 0.001$ for both). For comparison, the average yearly decline in individuals without PD was 0.42 and 0.23 points per year in women and men respectively. Other measures of quality of life (only available in women) declined in a similar pattern to physical function. In summary, the quality of life in PD patients begins to decline years before the diagnosis.

Keywords

Parkinson; Progression; Epidemiology; Quality of Life

Introduction

There is growing evidence that Parkinson disease (PD) often starts with non-motor symptoms that precede the diagnosis by several years[1,2] but there are no data on the physical and social functioning of PD patients before the disease is diagnosed. In a recent study, newly diagnosed PD patients showed evidence of limitations in the UPDRS Activities

of Daily Living (ADL) scale and lower functioning on most components of the SF36 compared to healthy controls.[3] Evidence is also limited on how different aspects of quality of life, such a physical and emotional well-being decline prior to and after the onset of clinically evident disease. Understanding the timing and pattern of decline in the different aspects of quality of life in relation to onset of PD could deepen the understanding of the timing and impact of the disease process.

Materials and Methods

The study populations include 51,530 male health professionals (Health Professionals Follow-up Study (HPFS)) and 121,701 female registered nurses (Nurses' Health Study (NHS).), who, at baseline in 1986 and 1976 respectively, provided detailed information on their medical history and lifestyle practices[4]. Participants filled out bi-annual questionnaires that asked about a variety of lifestyle characteristics and documented the occurrence of major chronic disease.

Our study was comprised of participants who were free of PD, stroke or cancer (other than nonmelanoma skin cancer) at baseline and who filled out one or more sections of the SF36 questionnaire (described below) as part of the regular cohort follow-up. The study follow-up lasted from baseline in both cohorts, 1986 in HPFS and 1976 in NHS through 2008 in both cohorts. The studies were approved by the Human Subjects Research Committees at the Harvard School of Public Health and the Brigham and Women's Hospital.

SF36 components

On the 1992, 1996, 2000 and 2004 questionnaires in the NHS, a slightly modified (excluding the General Health domain) version of the Medical Outcomes Study (MOS) Short-Form-36 (SF-36) Health Survey was included.[5] This questionnaire, originally developed for the Rand Corporation's Health Insurance Experiment,[6] is a self-administered 36 item questionnaire that measures health-related quality of life in eight domains: physical functioning, role limitations due to physical problems, role limitations due to emotional problems, vitality, bodily pain, social functioning, mental health, and general health perceptions. The SF36 questionnaire has been extensively validated[7,8] and has been found to have high construct validity, internal consistency and test-re-test reliability. In the NHS, all domains of the SF36 were assessed, with the exception of the General Health domain, on the 1992, 1996, 2000 and 2004 questionnaires. In the HPFS, only the physical functioning domain of the SF36 was assessed, on the 1996 and 2008 questionnaire. Thus, physical functioning is the only domain used in men in this study.

Case Ascertainment

A question regarding lifetime occurrence of PD was first asked in 1988 in HPFS and 1994 in NHS. In subsequent years, participants in both HPFS and NHS were asked if they had been diagnosed with PD in the previous 2 years. Participants who reported a new PD diagnosis on any of the follow-up questionnaires were asked for permission to contact their treating neurologist or internist, who in turn, was asked to complete a questionnaire confirming the diagnosis of PD. The neurologist or internist was also asked to provide his or her judgment regarding the certainty of the diagnosis and/or to send a copy of the medical record.[9] The medical records were reviewed by a movement disorder specialist (MAS). A PD case was confirmed if the treating neurologist or internist indicated the diagnosis either definite or probable, or if a review of the medical record by a movement disorders neurologist showed either a final PD diagnosis made by a neurologist or evidence of two or more of the three cardinal signs of PD (rest tremor, rigidity, and bradykinesia) in the absence of indications for other diagnoses.

Statistical Analysis

Results are presented separately by gender because, as discussed above, while nearly the full SF36 was available in women, only the physical function component was available in men. For each PD case, we calculated the difference between the date return of each questionnaire and the date of PD diagnosis and then categorized this difference using the date of diagnosis as the reference time in 5 year intervals (years: >15 years prior to diagnosis, 10-14.9 years prior to diagnosis, 5-9.9 years prior to diagnosis, 0-4.9 years prior to diagnosis, 0-4.9 years after diagnosis, 5-9.9 years after diagnosis, 10-14.9 years after diagnosis, 15-19.9 years after diagnosis, 20-24.9 years after diagnosis, 25-29.9 years after diagnosis and 30 or more years after diagnosis). We then plotted the mean score of the PD cases on each of the components of the SF36 as a function of time to diagnosis. To adjust for age and age-related changes in function and well being, we used a mixed linear model to regress each of the SF36 components on age among all cohort participants. We then calculated the mean of the 'predicted' scores for each category of time to diagnosis. Thus, these predicted values and their means derived from this model represent the decline in the cohort due to age only.

The rate of decline was calculated by taking the physical function at the furthest point from the diagnosis that the data would allow and subtract it from the physical function at the earliest point before the diagnosis available in the data, dividing by the total number of years elapsed.

Parkinson Disease Recontact

As part of pilot study within the NHS and HPFS, between 2004 and 2005, a sub-sample of cohort participants who reported PD from the beginning of the study up to those in the 2000 follow-up were sent an Activities of Daily Living (ADL), a UPDRS-based questionnaire, a brief questionnaire on medication use, as well as a permission form for contacting their treating neurologist. Letters were sent to 204 participants in the NHS and to 235 participants in the HPFS. On average in both cohorts, approximately 80% of the cohort participants returned the permission forms and, of those, approximately 70% gave permission to contact their treating neurologist. The letter to the treating neurologists asked the doctor to confirm the diagnosis of PD, and, among other questions, to rate the patient on the Hoehn and Yahr Staging (HYS) scale. Completed letters from the neurologist were obtained for 129 nurses and 109 health professionals.

We plotted the mean ADL scores and the HYS of the patients participating in this pilot sub-study by category of time to diagnosis, where the categories of time to diagnosis were the same as those used in the analyses of SF36.

Results

Quality of Life (SF-36) before and after PD diagnosis

454 men and 414 women with PD contributed data to the analyses. The means of physical function by categories of time to diagnosis in PD cases are shown in Figure 1. The dashed line in the figure represents the age-adjusted or 'predicted' mean scores, based on a decline due to age only. At 7.5 years prior to diagnosis, physical function among PD cases, in both men and women, was comparable to that in the overall cohort. A decline in physical function in PD patients relative to the whole cohort began approximately 3 years prior to diagnosis in men and 7.5 years prior to diagnosis in women, and continued to decline thereafter with a rate of 1.43 and 2.35 points per year in men and women, respectively ($p < 0.001$). For comparison, the average yearly decline in individuals without PD was 0.23 and 0.42 points per year in men and women respectively. At the time of diagnoses, women

had somewhat lower relative physical function (compared to women without PD) than did men.

Other measures of quality of life (only available in women) declined in a similar pattern to physical function, as shown in Figure 2. Role limitations due to (1)physical and (2)emotional Health, and (3)pain score began to decline approximately 7.5 years prior to diagnosis, and declined in a linear fashion at a rate of 2.34, 1.04, and 0.73 points per year thereafter ($p < 0.001$), respectively compared to 0.41, 0.13, and 0.08 points per year that was predicted based on age alone. Emotional well being and social function showed a pattern of decline similar to each other, with a slow decline starting approximately 7.5 years prior to diagnosis and continued decline in a super-linear/quadratic fashion. The rates of decline in emotional well being and social function were 0.13 (emotion) and 0.62 (social) in the 12.5 years preceding the diagnosis and 3.73 (emotion) and 2.42 (social) in the 12.5 years after the diagnosis ($p < 0.001$). In comparison, the linear rates of decline predicted based on age alone for the entire period were 0.01 for emotional well being and 0.18 for social function.

Parkinson Disease Recontact

Mean ADL scores increased (indicating worse functioning) with increasing time after diagnosis in both men and women as shown in Figure 3. In women, where more data was available, the rate of increase (worsening) in ADL: was slow at first and then accelerated. In female patients who were within the first 5 years of diagnosis, the mean ADL score was 24.9. Subsequently, the ADL scores were 24.2, 27.1, 33.1, 46.7 in the 5-10, 10-15, 15-20 and 20-25 years after diagnosis respectively. The rate of increase (worsening) in ADL was 0.22 points per year within the first 15 years after diagnosis and 1.95 points per year thereafter.

Mean HYS also increased (worse staging) with increasing time since diagnosis in a pattern similar to ADL (Figure 4). For female participants with PD who were within 0 to 5 years post-diagnosis, the mean HYS was 2.39. The HYS then increased to 2.47, 2.65, 3.32, and 4.13 for participants 5-10, 10-15, 15-20, and 20-25 years post-diagnosis. The increase in HYS in women was also slow in the first 15 years after diagnosis, with an average increase of 0.026 units per year and was steeper thereafter, with an increase of 0.15 units per year.

The correlation (Pearson) between the HYS and ADL was 0.68 (0.55, 0.78; $p < 0.0001$; $n = 92$) in women and 0.61 (0.48, 0.72; $p < 0.0001$; $N = 105$) in men. In women, the correlation (Pearson) between the ADL scores and the SF-36 physical function scores was 0.64 (0.46, 0.76; $p < 0.0001$; $N = 62$) and the correlation between the HYS and the SF36 physical function score was 0.54 (0.35, 0.70; $p < 0.0001$; $N = 65$). The correlation coefficients with SF36 were not calculated in men because no physical function was available in men in 2004.

Discussion

In this study within two large prospective cohorts of men and women, we found that quality of life, including both physical and mental health (measured only in women) begins to decline before the diagnosis of PD. We observed that a decline in physical function in PD patients relative to the whole cohort began approximately 3 years prior to diagnosis in men and 7.5 years prior to diagnosis in women, and continued to decline thereafter with a rate of 1.43 points per year in men and 2.35 points per year in women. These rates of decline are 5 to 7 times faster than the average yearly decline in individuals of the same age and sex without PD.

The duration between the initial decline in physical function and the date of diagnosis in this study (3 years in men and 7.5 years on women) is somewhat longer than has been reported

in the past. For example, in the DATATOP trial, the investigators reported an approximately one year lag between onset of symptoms and date of diagnosis of PD[15] The difference could be due to the fact that SF36 scores were collected as part of general cohort follow-up, irrespective of PD, and for some NHS and HPFS participants were likely collected before they recognized their symptoms as PD. The length of the time between the beginning of decline in quality of life and PD diagnosis, as well as the 2-fold difference in the time between the beginning of the decline in physical function and the time of diagnosis in men compared to women should be investigated in other studies.

Most studies that have compared PD patients to healthy controls have reported that quality of life, measured with a variety of instruments, is lower among PD patients than among healthy controls.[10,11] Quality of life in PD also appears to be lower than in many other chronic conditions. PD patients appear to have a lower quality of life than patients with diabetes mellitus, multiple sclerosis, spinal cord injury, stroke, chronic lower back pain, angina, coronary heart disease and depressive symptoms.[14]

In the DATATOP trial, 362 patients with early PD filled out the SF-36 questionnaire once beginning 5 to 6 years after enrollment and 2nd time then 1.7+/- 0.1 years after. The authors investigated the predictors of decline in Physical and Mental Component Summary Scores of the SF36 and found that depression and poor self-rated cognitive function were associated with a future decline in physical component summary scores. Older age at onset and worse Schwab and England activities of daily living scores were associated with subsequent decline in the mental component summary scores[15].

To our knowledge, this is the first study to examine patterns in quality of life in PD patients before the diagnosis of PD. In a case-control study nested within a community-based population study in Sweden, Hariz et al. observed that untreated PD patients newly diagnosed with PD, at their first visit to a neurological center, had lower ADL scores and rated lower on most measures of the SF36 (with the exception of pain). [3] In our study, due to the availability of prospective data on both PD patients and the healthy comparison group, we were able to chart the deterioration in functioning and quality of life in PD patients over the whole study follow-up, which included many years prior to diagnosis. Such an approach was possible in this study because it is carried out in the context of a large prospective cohort of initially healthy men (HPFS) and women (NHS) for many of whom the SF36 was first administered before the onset of symptoms of PD and then again after onset. We were also able to uniquely compare participants with PD to similarly aged participants without PD within our cohort. Additionally, in a subset of participants with PD, we measured ADL and Hoehn and Yahr Staging scale at various stages after disease onset and were able to chart the change in those scales associated with progression of PD.

General measures of functioning and well being, such as the SF-36, reflect qualities that are important to the daily experience of PD patients and allow comparison across conditions.[7] For example, a 9-point difference in physical functioning is equivalent to the effect of having arthritis or back problems.[7] Likewise, having diabetes or congestive heart failure, would translate to a 13 point difference in role limitations due to physical health.[7] Although there is no well-established minimally clinically important difference for the SF36 scales in PD research, [15] a study among arthritis patients (a disease area where the SF36 is extensively used) showed that decreases of 5.3 in the SF36 physical function score were clinically important.[16]

The SF-36 is a widely used and accepted instrument for measuring health related quality of life. In the NHS higher body weight has been linked with lower scores on the SF36 physical function domain[17] and weight loss was associated with improved physical function and

pain, as measured by the SF36.[18] The Hoehn and Yahr Staging scale and the Activities of Daily Living Scale of the UPDRS are also well-characterized instruments and have been shown to have good sensitivity to change over time in PD patients.[19] Although the UPDRS ADL is most commonly administered by clinicians, it is a patient-oriented outcome and has been used in the prior studies with good results.[20] Furthermore, PD patients are reasonably good at reporting their level of disability [21]

In summary, in a prospective cohort of men and women, we found a deterioration in all aspects of quality of life, as measured by the SF-36 scale, including physical and mental health, pain, emotional health, role physical and role emotional health and social health that started several years before the onset of PD and continued to decline thereafter. This result provides strong support to the notion that the pathological process leading to PD start many years before the onset of the first neurological symptoms, and suggests that biological markers of the disease process may be recognizable in this preclinical phase.

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Figure 1.
Physical Functioning component of the SF36 in PD cases from NHS and HPFS relative to their respective whole

Figure 2.

Other components of the SF36 including role physical function, role emotional function, fatigue, emotional well being, social function and pain among participants of the Nurses Health Study (in the HPFS, data was available only on the physical function component of the SF36)

Figure 3. Change in the UPDRS Activities of Daily Living Scale (UPDRS-ADL) scale with time to diagnosis.

Figure 4.
Change in the Hoehn and Yahr Staging (HYS) with time to diagnosis.