Parkinsonism and Related Disorders xxx (2016) 1–6

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Co-morbidity burden in Parkinson's disease: Comparison with controls and its influence on prognosis

Angus D. Macleod [a, *], Hannah Goddard [b], Carl E. Counsell [a]

[a] Institute of Applied Health Sciences, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, UK
[b] School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, UK

ARTICLE INFO

Article history:
Received 13 January 2016
Received in revised form
7 May 2016
Accepted 9 May 2016

Keywords:
Parkinson's disease
Co-morbidity
Charlson
Mortality
Dependency

ABSTRACT

Background: Many aspects of co-morbidity burden in Parkinson's disease (PD) are unclear, but it may be an important predictor of prognosis or confounder of associations in epidemiological studies.
Objectives: To determine how best to assess co-morbidity burden in PD, to compare with matched controls, and investigate its association with prognostic outcomes.
Methods: Data from an incident, community-based cohort with prospective follow-up (the PINE study) were used (198 patients with PD and 151 controls). The reliability of three co-morbidity scales (the Charlson co-morbidity index (CCI), the Cumulative Illness Rating scale and a simple disease count) were evaluated. The association with mortality and development of dependency was assessed with Cox regression. The co-morbidity burden in PD and controls was compared at baseline and over 5 years of follow-up using linear mixed modelling.
Results: The CCI was more reliable and was an independent predictor of mortality with a time-dependent effect (hazard ratio = 1.27 [1.08–1.49] in first four years of follow-up; no significant association after four years). Associations between the other scales and mortality and between each scale and development of dependency were non-significant once adjusted for confounders. Co-morbidity burden was similar between cases and controls at baseline and there was no evidence of differential accrual of co-morbidity between patients and controls ($p = 0.94$).
Conclusions: The CCI is probably the better scale for measuring co-morbidity burden in PD. There were no differences between PD and controls. Co-morbidity burden at diagnosis was associated with mortality in the early part of the disease course, but not later.

1. Introduction

Parkinson's disease (PD) predominantly occurs in the elderly [1], where other illnesses are common. Although certain specific co-morbid diseases have been studied in PD—for example, people with PD have a lower risk of cancer than in the general population [2]—very little is known about the overall co-morbidity burden in PD. Basic aspects of this are unclear, including whether co-morbidity burden differs from that of the general population and how best to measure it in PD. Additionally, although an increase in overall co-morbidity burden has been shown to increase mortality and disability in the general population [3,4], its influence on prognosis in PD is unclear. In PD, co-morbidity burden may be an important independent prognostic factor and a confounder of associations or an effect modifier in epidemiological studies; thus understanding its influence on prognosis is important for studies of prognosis in PD. Measuring overall co-morbidity as a single variable, rather than multiple individual diseases, is necessary for efficiency of statistical analyses [5].

We therefore aimed to determine which scale to use to measure co-morbidity in PD; to identify whether co-morbidity influences prognosis in PD; and compare the overall co-morbidity burden in PD and controls at diagnosis and during follow-up.

2. Methods

2.1. Study design

The PINE study is an incident cohort of PD and other forms of

* Corresponding author. Room 1:014, Polwarth Building, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, UK.
E-mail address: Angus.Macleod@abdn.ac.uk (A.D. Macleod).

http://dx.doi.org/10.1016/j.parkreldis.2016.05.013
1353-8020/

parkinsonism with prospective life-long follow-up in North-East Scotland [6,7]. Using multiple community-based ascertainment strategies we tried to identify all new diagnoses of degenerative or vascular parkinsonism (defined broadly as having at least two cardinal signs) during two incidence periods totaling 4.5 years (2002–2004 and 2006–2009). Patients were invited to consent to long-term follow-up. For each patient recruited, an age- and sex-matched control was sought from the same general practice. The only exclusion for patients was drug-induced parkinsonism, but controls were excluded if they were unable to give informed consent because of dementia or if they were found to be parkinsonian.

Consenting patients and controls were seen annually and underwent comprehensive clinical assessment including demographics, clinical history and examination, review of medical case notes, and both generic and PD-specific assessment scales. All participants were tagged to the NHS central register so that regular notifications of deaths were also received. Patients' diagnoses were reviewed at each appointment by a neurologist with a special interest in movement disorders or by a supervised trainee. Diagnoses of PD were guided by the UK PD Brain Bank criteria [8]. Only those who had a diagnosis of idiopathic PD at latest follow-up, and the controls matched to these patients, were included in the analyses described here.

Ethical approval for the PINE study recruitment and follow-up was obtained from the Grampian Research Ethics Committee and the Multi-Centre Research Ethics Committee for Scotland. The participants gave written informed consent and all data were stored securely.

2.2. Co-morbidity data

Two sources of co-morbidity data were available: research files from the PINE study and electronic summaries of primary care records. The research files contained information about co-morbid illness gathered from participants at clinical interview at baseline (i.e. at diagnosis for patients and at recruitment for controls) and subsequent visits, and also from review of hospital case notes.

We evaluated three different scales of co-morbidity burden, two weighted scales (the Charlson co-morbidity index [CCI] [9], the Cumulative Illness Rating Scale [CIRS]) [10] and a simple unweighted disease count. The first two of these scales were chosen as they are commonly used in the epidemiological literature and have previously been used in PD [5,11–13]. The CCI uses a specified list of mostly chronic diseases which are weighted between one and six. It has been validated in several populations and various diseases [5,11]. The CIRS counts co-morbid diseases by body system and includes grading of severity of disease, from zero (no disease, or previous problems with no sequelae) to four (an extremely severe problem). It has been shown to be valid and reliable for use in several situations, including older populations [5,14]. We also used an unweighted disease count as it is arguably a simpler method of evaluating co-morbidity and simple counts of disease have previously been shown to perform similarly to complex measures when predicting most outcomes, including mortality [11]. For the disease count we defined a disease as any condition requiring ongoing treatment or one that causes disordered organ function, after Gross et al. [15].

2.3. Comparison of co-morbidity scales and investigation of association with prognostic outcomes

We compared these three scales in PD at baseline only. Using the available data on co-morbidity, scores were calculated using each scale. The reliability of the scales was compared by assessing the intra- and inter-rater reliability with intraclass correlation coefficients [ICCs]). The first 40 cases were scored by one assessor (HG) who re-scored the first 20 of these cases 8 weeks later, blind to the first scoring. A second researcher (ADM) re-scored the other 20 cases, also blind to the first scoring.

In order to (i) assess the construct validity of the scales and (ii) to assess the effect of co-morbidity on prognosis, we investigated the association between each co-morbidity scale and two important prognostic outcomes: mortality and dependency. Dependency, (needing help with basic activities of daily living) was defined as a sustained score of <80 on the Schwab & England scale [16]. We firstly plotted Kaplan-Meier survival probabilities by categories of each co-morbidity scale. We then performed survival analysis using Cox regression using data until the end of follow-up. Separate models were created with each scale in turn as the exposure of interest (as a continuous variable), for each outcome. We generated both unadjusted models (univariable associations) and also adjusted multivariable models by adding potential confounding variables measured at diagnosis. These potential confounders were variables likely to be associated with both co-morbidity and mortality: age, sex, smoking status (ever or never), an area-based socioeconomic deprivation measure (DepCat score) [17] and severity of parkinsonian impairment (Unified Parkinson's disease rating scale [UPDRS] motor score) [18]. The potential confounders were included in the model irrespective of their statistical significance. Smoking was not included separately in models with CIRS since it is scored within this rating scale itself. Patients lost to follow-up, or those still alive/independent at the time of data extraction from the study database were censored. Patients dependent at baseline were excluded from the models of dependency. There were no missing data for any of the baseline variables in the models.

The proportional hazards assumption was tested by formal testing based on Schoenfeld residuals [19]. If there was evidence of violation of the proportional hazards assumption for the co-morbidity scales, an interaction term between the scale and time period was added (time divided into two intervals with approximately similar numbers of events in each). A likelihood ratio test was used to compare a model with and without this interaction. Otherwise, interactions were not assessed due to lack of power. Because we found a time-varying effect of co-morbidity on mortality we reviewed the clinical data available (research records, hospital case notes, and general practice records where available) to identify whether the proportion of deaths related to PD (such as due to general frailty, pneumonia, complications of fractures, or complications of immobility) varied over time.

2.4. Comparison between patients and controls

For comparisons between patients and controls we used only the CCI as it demonstrated the best reliability and was the only scale to be independently associated with mortality. The distribution of baseline co-morbidity was compared between PD and controls both graphically and with the Wilcoxon rank-sum test. The effect of time on change in co-morbidity over the first five years of follow-up was assessed using a linear mixed-model to adjust for repeated measures. CCI defined the dependent variable, and time (year of follow-up) was included in the model as the co-variate of interest. An interaction between patient/control status and time was included to assess whether change in CCI varied between patients and controls. Potential confounders (age, sex, and smoking status) were included as fixed effects in the model. An autoregressive covariance structure was assumed.

Statistical analyses were performed using Stata version 12.1 (StataCorp, College Station, TX).

Please cite this article in press as: A.D. Macleod, et al., Co-morbidity burden in Parkinson's disease: Comparison with controls and its influence on prognosis, Parkinsonism and Related Disorders (2016), http://dx.doi.org/10.1016/j.parkreldis.2016.05.013