RESEARCH PAPER

The CamPaIGN study of Parkinson’s disease: 10-year outlook in an incident population-based cohort

Caroline H Williams-Gray,1 Sarah L Mason,1 Jonathan R Evans,1 Thomas Foltynie,2 Carol Brayne,3 Trevor W Robbins,4 Roger A Barker1

ABSTRACT

Background Prognosis in Parkinson’s disease (PD) remains poorly understood due to a lack of unbiased data on the natural history of treated PD. The CamPaIGN study has been the first to prospectively track disease evolution from diagnosis in an unselected population-representative incident cohort. We now report the 10-year follow-up data, focusing on three key irreversible milestones: postural instability (Hoehn and Yahr 3), dementia and death.

Methods The cohort was collected between December 2000 and 2002. Those meeting diagnostic criteria (n=142) were followed-up until 1 January 2012. Clinical, neuropsychological and genetic testing were performed. Progression to key milestones was evaluated using Kaplan–Meier and Cox regression survival analyses.

Results At 10 years, 55% had died, 68% of survivors had postural instability and 46% dementia. 23% had a good outcome at 10 years (surviving free of dementia/postural instability). Death rate was comparable with the UK population (standardised mortality ratio 1.29 (0.97–1.61)). Death certificates indicated PD was a substantial contributor in only 20%, with pneumonia being the commonest cause of death. Age, non-tremor-dominant motor phenotype and comorbidity predicted earlier postural instability. Baseline predictors of dementia were age, motor impairment, ‘posterior-cortical’ cognitive deficits and MAPT genotype.

Conclusions (1) outlook in PD is heterogeneous, with most dying or developing dementia or postural instability by 10 years from diagnosis, but a quarter still doing well, with preserved mobility and intact cognition; (2) death is not directly related to PD in the majority; (3) baseline clinical and genetic variables are predictive of outcome and may be helpful in selecting patients for clinical trials.

INTRODUCTION

Since levodopa was introduced for the treatment of Parkinson’s disease (PD) over 40 years ago, we have had an effective means of ameliorating the motor symptomatology of this disorder. However, prognosis still remains highly variable. Furthermore, many ‘non-motor’ features do not respond well to standard treatments and, indeed, can be exacerbated by them. A key problem is that current therapeutic strategies focus on the dopaminergic nigrostriatal deficit when, in fact, the pathology of PD is much more complex, affecting widespread areas of the brain and peripheral nervous system, and involving multiple neurotransmitter systems, with variability in the pattern and rate of spread of pathology. An important step in understanding how the disease evolves is an accurate epidemiological description of its natural history, but relatively few studies have explored this. Such information is potentially of great importance in (1) characterising the impact of this disease on patients, thus guiding future therapeutic priorities, (2) informing the selection of the most relevant outcome measures for clinical trials, (3) identifying risk factors which predict key outcomes, thus allowing selection of ‘enriched’ cohorts for future therapeutic trials.

Most currently available data on disease progression and mortality in PD come from prospective studies of selected cohorts recruited for clinical trials. The longest running of these is the Sydney Multicenter study of PD which has collected longitudinal data over 20 years, but the cohort was recruited according to specified clinical criteria and randomised to low-dose levodopa versus low-dose bromocriptine, so is not truly representative of PD within the population. Those studies which have been population-based have generally employed prevalent cohorts of varying disease duration, rather than more informative incident cohorts followed-up from diagnosis. One recently published study has followed newly diagnosed patients for 10 years and reported on motor and non-motor progression as well as mortality, but the cohort was recruited from a movement disorder clinic, and thus, is inherently biased. The CamPaIGN study (Cambridgeshire Parkinson’s Incidence from GP to Neurologist) was the first to follow an unbiased population-representative incident PD cohort longitudinally from diagnosis, and to include from the outset detailed neuropsychological testing as well as genetic analysis. The study has now reached 10 years from its inception and, arguably, provides the most comprehensive and true-to-life data available on the natural history of idiopathic PD.

The CamPaIGN cohort comprised new cases of parkinsonism diagnosed within a 2-year period (December 2000–2002) within the county of Cambridgeshire, UK, identified through multiple sources of case ascertainment to maximise capture rates. Detailed demographic, clinical and neuropsychological data, as well as genotypic data, were collected. We have previously published follow-up data at 3.5, 5 and 7 years from diagnosis, and shown there is not only motor but also significant cognitive heterogeneity in PD. In particular, a proportion of patients develop early dementia, and this is predicted at diagnosis by older age, poor performance on tests with a posterior cortical basis.

To cite: Williams-Gray CH, Mason SL, Evans JR, et al. J Neurol Neurosurg Psychiatry Published Online First: [please include Day Month Year] doi:10.1136/jnnp-2013-305277
Movement disorders

(semantic, as opposed to phonemic, fluency and pentagon copying) as well as tau (MAPT H1/H1) genotype. By contrast, executive dysfunction which is common in early PD does not herald global cognitive decline. In terms of motor progression, our data demonstrate that axial symptoms are the best indicator of this, and development of postural instability (Hoehn & Yahr stage 3 (HY3)) is a major milestone in terms of impact on quality of life. We have also shown that dyskinesias are less common than previously suggested, with a mean time to onset of 6.6 years in this cohort, with significant dependence on dopaminergic medication dose, as anticipated.

We now present the 10-year follow-up data from the CamPalGN study with the aim of better describing the prognosis of PD in the post-L-dopa treatment era. We have focused on three key irreversible milestones which have the greatest impact on patients, namely development of postural instability (ie, reaching HY3), onset of dementia and mortality. As well as determining the probability of these outcomes over time, we have identified early clinical and genetic predictors, present at diagnosis, which can help to inform prognosis. This work adds to our previously published CamPalGN papers by presenting new data on prognosis up to 10 years from diagnosis, presenting the first detailed analysis of mortality data, and exploring the relevance of genetic as well as early clinical predictors on all key outcome measures.

METHODS
Subjects
Between December 2000 and December 2002, we attempted to recruit all newly diagnosed cases of Parkinsonism within the county of Cambridgeshire, UK, using multiple sources of case ascertainment. Full details of the recruitment process have been published elsewhere. Idiopathic PD was diagnosed using UKPDS Brain Bank criteria. All cases were followed-up to the 3–4-year time-point, irrespective of whether they initially met these criteria, and at this stage, diagnostic re-evaluation was undertaken with repeated application of UKPDSBB criteria to these cases, and at this stage, diagnostic re-evaluation was undertaken by a neur-
compared using Student t tests, χ² tests or Fisher’s exact tests as appropriate. Comparisons were also made between those withdrawing without reaching an outcome and the rest of the cohort. All statistical analyses were performed using SPSS V19.

RESULTS
Cases included
Figure 1 summarises the numbers remaining in the study at each follow-up point. Survival analyses are based on a cohort of 142 individuals, comprising:
1. A core cohort of 121 classified as probable idiopathic PD following diagnostic reappraisal of all cases of parkinsonism at a mean of 3.5 years from diagnosis, as well as subsequent exclusion of cases not meeting diagnostic criteria on later follow-up assessments (full details of this process previously published12 13).
2. A further 21 cases meeting diagnostic criteria for PD at baseline, who died (n=14) or withdrew (n=7) prior to diagnostic reappraisal. Although there was no confirmatory follow-up data for these individuals, nonetheless based on an estimated positive predictive value of the UKPDS Brain Bank criteria of 90% in this cohort,13 the wide majority of these 21 cases will represent true PD cases.

Following diagnostic reappraisal, the core cohort of 121 was followed-up at 2-year intervals until the latest round of follow-up 9–10 years from diagnosis (figure 1). Overall mean (SD) duration of follow-up of all 142 patients was 7.2 (2.8) years. Mean age at diagnosis was 70.2 (9.6) years. DNA samples were available for genotyping in 129 out of 142 cases. Complete baseline neuropsychological datasets were available in 127 out of 142 cases.

Mortality
Sixty-three of the 142 patients died during the follow-up period. The SMR was 1.29 with 95% CIs of 0.97 to 1.61 (p=0.06), indicating no statistically significant difference from expected mortality. The commonest recorded cause of death was pneumonia (33%), followed by cancer (19%) (figure 2). PD was recorded on the death certificate as the primary cause of death in only 10% (‘Part Ia’ on UK death certificate). In a further 10%, PD was recorded as substantially contributing to death (‘Part Ib’ on certificate), and was listed as a comorbid condition (‘Part II’) in 40%. In the remaining 40%, PD was not recorded at all on the death certificate.

Survival analysis indicated a cumulative probability of survival of 45% at 10 years (figure 3). Median time to death was 10.3 years. Only two baseline factors were significantly associated with increased mortality risk over this time period: older age at diagnosis (HR per year of increased age 1.08, p<0.001), and a history of smoking (HR 2.07, p=0.009). No relationship was identified between genotype and mortality (see online supplementary table).

Postural instability
Eighty-one cases reached HY3 during the course of the study, with a cumulative probability of HY3 of 68% at 10 years (figure 3). Median time to HY3 was 4.7 years. Baseline predictors were older age (HR per year 1.05, p=0.004), non-tremor-dominant phenotype (HR 4.07, p<0.001), and
Causes of death among the 63 patients who died within the 10-year follow-up period. Among those dying of cancer, primary sites were oesophagus (1), lung (1), breast (2), bile duct (1), pancreas (1), bladder (1), bowel (1), lymphoproliferative (2) and unknown (2). ‘Sepsis’ includes urinary sepsis (1), ascending cholangitis (1), gastroenteritis (1) and gram negative septicaemia (1). ‘Cardiac’ causes of death included acute myocardial infarction (2), ischaemic heart disease (2), cardiac arrest (2), congestive cardiac failure (3), cardiac arrhythmia (1). ‘Other’ includes chronic obstructive pulmonary disease (1), old age (4), exhaustion (1), fractured neck of femur (1), multiorgan failure (1), cerebrovascular ischaemic event (1).

Figure 3  Kaplan–Meier survival curves illustrating the cumulative probability of (A) remaining free of postural instability, (B) remaining free of dementia, (C) survival, (D) maintaining a good outcome (surviving without postural instability or dementia). Dotted lines indicate median latencies to outcomes.
greater comorbidity (HR 1.33, p=0.002). There was a tendency to over-representation of MAPT H1/H1 genotype among those with postural instability at 10 years (p=0.10) (see online supplementary table), but Cox regression analysis indicated this was not a significant predictor of HY3 outcome (p=0.40).

Dementia
By 10 years, 41 cases of dementia had occurred, and cumulative probability of dementia was 46% (figure 3). Estimated dementia incidence was 54.7 per 1000 person-years (95% CIs 35.4 to 74.1), 2.6 times the estimated dementia incidence in the Cambridge population aged over 65 years (incidence rate 20.7 (14.2 to 28.2) per 1000 person years, MRC-CFA study). Baseline predictors of later dementia were age (HR per year 1.08, p=0.001), semantic fluency <20 (HR 3.05, p=0.005), impaired pentagon copying (HR 2.55, p=0.001), UPDRS motor score ≥25 (HR 3.18, p=0.004). MAPT H1/H1 was the only genotype associated with dementia outcome, with no relationship identified for COMT val158met, SNCA rs356219 and APOE4 in bivariate analyses (see online supplementary table). Cox regression analysis confirmed MAPT H1/H1 was predictive of dementia (HR 3.08, p=0.005 after adjustment for age).

Good outcome
Median time to a poor outcome (postural instability, dementia or death) was 3.8 years. At 10 years, 23% have maintained a good outcome (figure 3). Those with good versus poor outcome are significantly younger at diagnosis, tend to have a tremor-dominant motor phenotype, and have lower UPDRS motor scores, higher semantic fluency, lower depression scores and less comorbidity (table 1).

DISCUSSION
These prospectively collected data from the first incident population-representative cohort of idiopathic PD demonstrate that at 10 years from diagnosis, 55% have died, and of those surviving, 68% have developed the major motor milestone of postural instability, and 46% have developed dementia. Only 23% have a good outcome at 10 years (figure 3).

There was no significant excess of mortality in the cohort (SMR 1.29 (0.97–1.61)), although it is possible that this result failed to reach significance due to insufficient power (power 93% for SMR of 1.5 significant at the 5% level, but only 61% for SMR of 1.3). Nonetheless, the SMR was lower than most previous studies have reported (SMR/HR typically 1.5 to 2.5). Additionally, the population-based, rather than clinic-based, nature of our cohort is likely to be relevant, in part, due to the older age structure of our cohort (mean age at diagnosis 70 years). Those with earlier onset PD (<65 years) have a higher age-adjusted mortality risk than those with later onset PD (≥65 years), presumably because excess mortality is not seen in those who are older at diagnosis, as death rates in the control population are rising. This may also explain why the SMR in our cohort is lower at the 10-year time-point than that previously reported at the 7.9 year time-point (1.72 (1.16–2.46)).

In addition to the lack of significant excess mortality in the cohort, in 80% of cases, PD was not cited on the death certificate as a significant contributor to death. Furthermore, the only significant risk factors for earlier death were age and history of smoking, but not baseline motor or cognitive features of PD. Together, these findings support the message commonly given to patients in clinical practice that people die ‘with’ rather than ‘of’ PD. In keeping with other studies pneumonia was the commonest cited cause of death (n=21, 33%). In nine of these, pneumonia was cited as secondary to either aspiration or PD, presumably as a consequence of poor swallow, and indeed.

Table 1  Comparison of baseline characteristics of those with ‘good’ versus ‘poor’ outcomes at 10 years from diagnosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Good outcome (n=23)</th>
<th>Poor outcome (n=103)</th>
<th>p Value</th>
<th>Withdrawn (n=16)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60.8 (10.5)</td>
<td>72.6 (8.2)</td>
<td>&lt;0.001*</td>
<td>67.8 (8.66)</td>
<td>0.30</td>
</tr>
<tr>
<td>Gender: % male</td>
<td>60.9</td>
<td>58.3</td>
<td>1.00</td>
<td>37.5</td>
<td>0.12</td>
</tr>
<tr>
<td>UPDRS motor</td>
<td>20.4 (11.0)</td>
<td>28.6 (12.2)</td>
<td>0.004*</td>
<td>20.0 (11.6)</td>
<td>0.031</td>
</tr>
<tr>
<td>Equivalent levodopa dose</td>
<td>225.2 (361.3)</td>
<td>183.2 (224.2)</td>
<td>0.48</td>
<td>66.3 (113.4)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Motor phenotype: % TD</td>
<td>78.3</td>
<td>29.1</td>
<td>&lt;0.001*</td>
<td>62.5</td>
<td>0.10</td>
</tr>
<tr>
<td>National Adult Reading Test (IQ)</td>
<td>112.1 (8.7)</td>
<td>108.8 (10.5)</td>
<td>0.18</td>
<td>108.1 (9.5)</td>
<td>0.62</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.8 (1.2)</td>
<td>27.8 (1.5)</td>
<td>0.002*</td>
<td>27.9 (1.8)</td>
<td>0.84</td>
</tr>
<tr>
<td>Semantic fluency</td>
<td>24.9 (8.7)</td>
<td>18.6 (6.7)</td>
<td>&lt;0.001*</td>
<td>18.4 (4.4)</td>
<td>0.29</td>
</tr>
<tr>
<td>Pentagon copying: % impaired</td>
<td>8.9</td>
<td>23.3</td>
<td>0.16</td>
<td>28.6</td>
<td>0.50</td>
</tr>
<tr>
<td>Beck depression score</td>
<td>5.2 (4.1)</td>
<td>8.3 (5.8)</td>
<td>0.005</td>
<td>7.8 (6.2)</td>
<td>0.94</td>
</tr>
<tr>
<td>Comorbidity: median (range)</td>
<td>0 (0–2)</td>
<td>2 (0–6)</td>
<td>&lt;0.001*</td>
<td>1 (0–5)</td>
<td>0.38</td>
</tr>
<tr>
<td>MAPT: % H1/H1</td>
<td>57.1</td>
<td>68.4</td>
<td>0.32</td>
<td>57.1</td>
<td>0.56</td>
</tr>
<tr>
<td>SNCA: % G/G</td>
<td>23.8</td>
<td>21.1</td>
<td>0.74</td>
<td>21.4</td>
<td>1.00</td>
</tr>
<tr>
<td>APOE: % ε4 carrier</td>
<td>28.6</td>
<td>29.7</td>
<td>1.00</td>
<td>7.7</td>
<td>0.11</td>
</tr>
<tr>
<td>COMT: % val/met</td>
<td>61.9</td>
<td>44.7</td>
<td>0.25</td>
<td>35.7</td>
<td>0.64</td>
</tr>
<tr>
<td>% met/met</td>
<td>14.3</td>
<td>30.9</td>
<td>42.9</td>
<td>21.4</td>
<td></td>
</tr>
</tbody>
</table>

Tabulated values are mean (SD) or percentages, unless otherwise stated. Those withdrawing from the study prior to an outcome being reached are excluded, and characteristics of this ‘withdrawn’ group have been compared with the rest of the cohort as a whole (good+poor outcome).

* Indicates p value remains significant after Bonferroni correction for multiple testing.
correlation between onset of dysphagia and mortality has been demonstrated in a postmortem study of parkinsonian disorders. However, an important caveat to this data is that the accuracy of information recorded on death certificates is generally suboptimal. This is evidenced here by the fact that PD was not recorded at all on 40% of death certificates, and highlights the point that epidemiological studies identifying PD through death certificates will miss many cases.

Postural instability is generally the first milestone reached in PD, occurring at a median of 4.7 years and affecting 2/3 of survivors by 10 years. This latency to HY3 is no better than estimates from the prelevodopa era of 5.5–7 years. Similarly, the Sydney study reported a median latency to HY3 of only 3.5 years in their prospectively followed trial cohort. These data suggest that dopaminergic treatment has had little impact on development of this key milestone, in keeping with the hypothesis that the underlying basis of postural instability in PD is non-dopaminergic dysfunction of brainstem regions such as the pedunculopontine nucleus. In addition to older age and baseline motor phenotype, level of comorbidity was a significant predictor of HY3, providing an important reminder that gait and balance dysfunction in the elderly is frequently multifactorial, with conditions, such as osteoarthritis, visual impairment, peripheral vestibular dysfunction and cerebrovascular disease being important contributors. Hence, comorbidity must be carefully adjusted for if using HY3 as an outcome measure for clinical trials.

Dementia evolves more slowly than postural instability, with 46% affected by 10 years. Its incidence was 2.6 times that in an age-matched and geographically matched population. Dementia incidence has increased with disease duration throughout the CamPaIGN study (30.0 (16.4–52.9) per 1000 person-years at 3.5 years, 38.7 (23.9–59.3) at 5 years, 54.7 (35.4–74.1) at 10 years) as anticipated in an aging cohort. Nonetheless, our 10-year dementia incidence estimate is still lower than many historic estimates from prevalent community-based studies in PD, presumably reflecting lower disease duration in our incident cohort. Other longitudinal studies following PD cohorts from diagnosis have reported cumulative probabilities of dementia more in keeping with our data (49% over 10 years; 48% over 15 years; and 50% over 10 years in a cohort over 65 years at diagnosis). It should be borne in mind that new MDS criteria for dementia have been established since this study began, and although they have not been compared with DSM-IV/MMSE criteria in any large-scale validation studies, they recommend an MMSE cut-off of <26, hence, are likely to produce higher estimates of dementia incidence in future studies.

Cox regression analysis confirmed our previous findings with respect to predictive factors for later dementia, which were age, deficits on semantic fluency and pentagon copying tests and MAPT H1/H1 genotype, supporting our hypothesis that the dementia is largely due to an age-dependent and tau-dependent posterior cortically based process rather than dopaminergic dysfunction in frontostriatal networks. Higher baseline UPDRS motor score, presumably reflecting more advanced PD, was also predictive of dementia outcome at 10 years. Genetic variants in COMT, APOE and SNCA were not associated with dementia risk. By contrast with other authors, we did not find evidence of a direct association between motor phenotype and cognitive outcome, and no overlap in predictors of postural instability and dementia other than age, suggesting that these two important milestones might evolve independently with different underlying pathological bases. However, our focus here was exclusively on baseline predictive factors: development of a non-tremor-dominant phenotype later in the disease course may be associated with dementia, as others have reported.

Overall, outlook in the majority remains relatively poor despite treatment, with fewer than 50% surviving free of postural instability and dementia 4 years from diagnosis. It must be borne in mind, however, that death due to non-PD-related causes contributes to poor outlook in this elderly population, as previously discussed. Approximately one in four have a relatively benign course and are still doing well at 10 years (figure 3). As might be anticipated, this group is younger at baseline, with less motor and cognitive impairment, less depression and less comorbidity, and most have a tremor-dominant motor phenotype (table 1). Although these characteristics are largely reflected in the Cox regression analyses identifying predictors of individual outcomes, this is not the case for depression, hence it may represent a confounding effect rather than a true predictor of outcome. However, associations between depression and higher rates of cognitive decline, motor progression and increased mortality have been reported by others, suggesting depression might be a marker of spreading pathology in a more rapidly progressive type of disease. Although no genetic differences were identified in those with a good outcome on our limited screen, further genotypic investigation of this subgroup would be interesting to look for protective genetic factors which might be slowing disease progression.

The key attributes of this study lie in the incident, population-representative nature of the cohort, providing true-to-life natural history data over 10 years of PD for the first time in the post-L-dopa period. Furthermore, the comprehensive range of demographic, clinical and genotypic variables measured at baseline enabled a thorough evaluation of predictors of outcome. The main methodological concern in longitudinal studies of this type is attrition. Although survival analyses adjust for this through censoring, withdrawal can potentially introduce bias if those lost to follow-up differ clinically from those assessed. In this study, those who withdrew without a known outcome (n=16) had lower baseline UPDRS motor scores and were on less dopaminergic medication than the rest of the cohort (n=126) (table 1), but did not differ in terms of age, cognitive characteristics or genotypes. Nonetheless, their withdrawal might have led to underestimation of the proportion with good outcomes. Similarly, attrition due to death may have led to an underestimation of cumulative probabilities of dementia and HY3 if there was an increased incidence of these outcomes in the period immediately before death. Although baseline motor and cognitive phenotype were not predictive of death in this study, others have reported that both dementia and motor severity in later disease are associated with increased mortality.

In conclusion, 10-year longitudinal follow-up of an incident population-representative PD cohort reveals heterogeneous outcomes. While over half suffer significant disability or death within 4 years, a quarter are doing well at 10 years, surviving with relatively little motor disability and intact cognition. Further biological investigation of this latter subgroup may prove informative in identifying protective factors in PD which can be exploited in the search for disease-modifying therapies.

Acknowledgements We would like to thank all patients, as well as their carers, who generously gave up their time to participate in this study.

Contributors CHWG wrote the manuscript, which was critically reviewed by all authors. All authors were involved in the design of the study. CHWG, SLM and TF were involved in the organisation of the project and data collection. Statistical analysis was performed by CHWG and reviewed by RAB.

Funding This work was supported by Medical Research Council grant number RG38582, Parkinson’s UK grant number RG39 906, the National Institutes of Health Research Biomedical Research Centre Award to the University of Cambridge.
and the Cure Parkinson’s Trust. CHWG was supported by a Patrick Berthoud Clinical Research Fellowship, JRE was supported by the Van Geest Foundation through a Gussy Marlowe Clinician Fellowship, and TF was supported by a Wellcome Trust Clinical Research Fellowship. CHWG, JRE and TF were recipients of Raymond and Beverly Sackler Studentships.

Competition of interests TWR consults for Cambridge Cognition (supplier of CANTAB neuropsychological tests).

Ethics approval Cambridge Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES
Notes

Advance online articles have been peer reviewed, accepted for publication, edited and typeset, but have not yet appeared in the paper journal. Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include the digital object identifier (DOIs) and date of initial publication.

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/