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The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study

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Summary

We have used multiple sources to identify a population-representative cohort of newly diagnosed patients with parkinsonism and Parkinson's disease in the UK over a 2-year period. All patients have been invited to participate in a detailed clinical assessment either at home or in an outpatient clinic. These assessments have been used to refine clinical diagnoses of parkinsonism using established criteria, and describe some of the phenotypic variability of Parkinson's disease at the time of diagnosis. The crude incidence of Parkinson's disease was 13.6/10^{5yr-1} [confidence interval (CI) 11.8–15.6 and of parkinsonism was 20.9/10^{5yr-1} (CI 18.7–23.3). Age-standardized to the 1991 European population, the incidence figures become 10.8/10^{5yr-1} (CI 9.4–12.4) for Parkinson's disease and 16.6/10^{5yr-1} (CI 14.8–18.6) for parkinsonism. Thirty-six per cent of the Parkinson's disease patients had evidence of cognitive impairment based on their performance in the Mini-Mental State Examination, a pattern recognition task, and the Tower of London task. The pattern of cognitive deficits seen among these patients using these and further cognitive tasks suggests that sub-groups of patients based on cognitive ability might be identifiable even in the early stages of disease, which may reflect regional differences in the underlying neuropathological processes.

Keywords: incidence; Parkinson's disease; parkinsonism; cognitive

Abbreviations: CI = confidence interval; DLB = dementia with Lewy bodies; MMSE = Mini-Mental State Examination; NART = National Adult Reading test; PDBB = Parkinson's disease Brain Bank; PRM = pattern recognition memory; SRM = spatial recognition memory; PDD = patients with Parkinson's disease and dementia; TOL = Tower of London task; UPDRS = Unified Parkinson's Disease Rating Scale

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Parkinson's disease is a common, chronic neurodegenerative disorder characterized by a combination of motor problems including tremor, rigidity and bradykinesia as well as cognitive, autonomic and affective abnormalities. It is defined pathologically by the presence of α-synuclein-positive Lewy bodies in the substantia nigra, and biochemically by the loss of dopamine in the nigrostriatal tract.

Parkinson's disease, however, cannot be diagnosed with certainty during life. An individual patient with extrapyramidal signs represents a diagnostic challenge because of the heterogeneity of clinical phenotypes that will ultimately meet pathological criteria for Parkinson's disease, if and when they come to post-mortem. Indeed, the atypical forms of the disease that are being identified by functional imaging, and the phenotypic overlap between patients with genetic forms of the disease and the larger population of Parkinson's disease patients in general, makes case definition for Parkinson's disease even more problematic (Foltynie *et al*., 2002). In order to try and standardize the diagnosis of Parkinson's disease, the UK PDS Brain Bank established a set of clinical criteria for diagnosing the condition, which have recently been shown to usefully predict the pathological diagnosis of Parkinson's disease in the hands of neurology specialists in movement disorders (Hughes *et al*., 2002). By applying these criteria, some of the ambiguities of diagnosis can be avoided.

Further difficulties in comparing published Parkinson's disease frequency figures from one study to the next are also due to differing methods of case ascertainment, varying

inclusion and exclusion criteria and lack of follow-up or histology to confirm diagnoses. Although prevalence studies are easier and quicker to perform, it is more difficult to usefully compare prevalence figures from one study to the next, due to international differences in survival. Incidence studies are more useful, although crude rates of disease are less comparable due to the variation in age structure between populations studied and therefore age-standardized or age-specific rates are of much greater use. In general, studies using comparable methods have found an age-standardized incidence of approximately 8–19 per 100 000 population per year (Twelves *et al*., 2003). Such estimates are important not only in accurately describing the true incidence of Parkinson's disease but also in planning for appropriate health service provisions and enabling international comparisons of disease frequency for epidemiological research.

Parkinson's disease has an insidious onset and therefore generally has a subclinical period prior to any symptoms being noticed by the patient (Horstink and Morrish, 1999). The initial symptoms may be mild and progress over some months or years before prompting the patient to visit their doctor. Questioning patients about the date of onset of their symptoms may therefore be inaccurate, and is only a proxy marker for when the underlying neuropathology may have begun, although several incidence studies have adopted such an approach (Brewis *et al*., 1966; Dupont, 1977; Wender *et al*., 1989; Granieri *et al*., 1991; Mayeux *et al*., 1995; Sutcliffe and Meara, 1995; Fall *et al*., 1996; Bower *et al*., 1999). An alternative is to use the date that the diagnosis of Parkinson's disease is first suspected or diagnosed (Kurland, 1958; Jenkins, 1966; Hofman *et al*., 1989; Wang *et al*., 1991; Morens *et al*., 1996; MacDonald *et al*., 2000; Chen *et al*., 2001; Morioka *et al*., 2002).

In order to accurately predict the incidence of Parkinson's disease, a number of other issues should be addressed as recommended in a recent review (Twelves *et al*., 2003). These include the requirements that studies should (i) have an appropriate population base (between 250 000 and 500 000); (ii) be prospective; (iii) use multiple sources of case ascertainment; (iv) incorporate as many as possible of the cases being seen and assessed by a movement disorders expert; (v) use the date of diagnosis as the most practical definition of incidence if prospective methodology is used; (vi) apply broad criteria to ascertain cases followed by more stringent criteria at assessment; (vii) follow up patients where possible; and (viii) report incidence rates by standard age strata.

An increased prevalence of dementia among Parkinson's disease patients has long been recognized and has previously been quantified in the community by following up population-based cohorts of the disease (Marttila and Rinne, 1976; Mayeux *et al*., 1992; Aarsland *et al*., 1996; Hobson and Meara, 1999). However, less obvious cognitive deficits are also seen among non-demented Parkinson's disease patients. Isolated frontal lobe impairments have been described among clinical series of patients (Lees and Smith, 1983; Taylor *et al*., 1986; Owen *et al*., 1992; Dubois and Pillon, 1997), although the frequency of these and other patterns of cognitive deficits among a community-based cohort of patients has only been reported among prevalent patients with longstanding disease (Janvin *et al*., 2003). There is growing evidence that subtle frontal lobe deficits may be of prognostic value in identifying Parkinson's disease patients at risk of dementia (Woods and Troster, 2003).

In this study we present frequency figures for the incidence of Parkinson's disease and parkinsonism in Cambridgeshire, UK, with a population base of ~700 000: the **Cam**bridgeshire **Pa**rkinson's **I**ncidence from **G**P to **N**eurologist- (CamPaIGN) Study. Apart from the larger size of the population base, the study fulfils all of the recommendations listed above. Based on detailed assessments of these patients, we also describe, for the first time, the frequency and pattern of cognitive impairments among a population cohort of incident Parkinson's disease patients. Although we have performed a range of tests on our patients, we recognize that ideally our motor and cognitive assessments would have been even more detailed. However, the community basis of this study inevitably limits the number of assessments that can be performed with an elderly group of individuals.

Methods

Case definitions

Parkinsonism. We attempted to identify every new case of parkinsonism within Cambridgeshire, including all patients presenting with any extrapyramidal symptoms and signs (tremor, rigidity, bradykinesia, micrographia, loss of dexterity, hypomimia, reduced armswing, or parkinsonian gait). We subsequently sought to confirm and refine the diagnoses following assessment, and investigation as appropriate using accepted clinical criteria. The UK Parkinson's Disease Brain bank criteria (Gibb and Lees, 1988) were used to diagnose cases of Parkinson's disease. All assessments were carried out by T.F. with a review of all difficult diagnostic cases by R.A.B. Since increasing numbers of genetic forms of the disease are being discovered with phenotypes and pathology indistinguishable from the sporadic forms of the disease, patients with a family history of Parkinson's disease were not specifically differentiated from the Parkinson's disease group. The diagnosis of other parkinsonian syndromes were made using (i) the consensus criteria for the diagnosis of dementia with Lewy bodies (DLB) (McKeith *et al*., 1996); or the facts that (ii) exposure to neuroleptics at the onset of symptoms lead to a diagnosis of 'drug-induced parkinsonism' or (iii) repeated strokes or stepwise progression of symptoms lead to a diagnosis of 'vascular parkinsonism', and (iv) absent or minimal responses to dopaminergic therapies lead to a diagnosis of 'atypical parkinsonism'. 'Unspecified parkinsonism' was applied to those cases not seen and in whom insufficient information was available to precisely classify them. All cases irrespective of the original diagnosis have been recruited to the study and followed up, and cases of significant diagnostic uncertainty have been left without a firm diagnosis at this stage.

Incidence. Cases were identified for a 3-month run in period (September 1, 2000 to November 31, 2000), during which the study

was widely advertised, followed by a 25-month period of case collection (December 1, 2000 to December 31, 2002), followed by 6 months of post-collection monitoring (January 1, 2003 to June 30, 2003) to ensure that minimal numbers of cases were missed. Details regarding date of symptom onset and date of diagnosis were both noted. Cases suspected of parkinsonism prior to the onset of the study were excluded on the basis that they were prevalent rather than incident.

Cambridgeshire. The County of Cambridgeshire has been defined by the Office of National Statistics according to Local Authority divisions (Office of National Statistics). People living within the county of Cambridgeshire have free access to health-care and this region has been used as a population denominator in previous studies of neurological disease (Robertson *et al*., 1996, 1998). Only individuals resident inside the county of Cambridgeshire on the date of diagnosis were accepted as incident cases. The results of the 2001 population census for the County of Cambridgeshire (Office of National Statistics) were used as our denominator figures.

Case ascertainment

Patients who are diagnosed with Parkinsonism are managed in Cambridgeshire by neurologists, geriatricians and general practitioners (GPs). The neurology service is provided at a regional neurology unit in Cambridge, which includes a clinic specifically devoted to Parkinson's disease. There are further neurological outpatient facilities provided from District General Hospitals in Peterborough and Huntingdon. At least one consultant neurologist and their staff serve each hospital. Geriatric inpatient and outpatient facilities are also provided at all of these hospitals. Three specialist Parkinson's disease nurses work with both Parkinson's disease inpatients and outpatients within the county. Incident cases were detected using five sources within the Cambridgeshire, Huntingdon and Peterborough districts. Written requests for notification of patient details were sought from the following sources at 3-monthly intervals: (i) all GPs; (ii) all neurologists; (iii) all geriatricians; (iv) all Parkinson's disease specialist nurses; and (v) hospital discharge coding departments.

Frequent personal visits were made to all individuals among sources ii–v, to increase participation. The study was also advertised through presentations given to local branches of the Parkinson's Disease Society. To encourage GP participation, patients referred by GPs to the study were also given rapid access to NHS outpatient clinics for consultant opinion and management advice.

Case assessment

All patients seen received the same assessment, comprising a detailed history of their disease, level of education, current and all previous occupations; ethnic origin; family history of neurological disease; full drug history; significant co-morbidity; and referral source. In addition, a standardized neurological assessment was performed including the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn *et al*., 1987), timed motor tests for both hand-tapping and walking, and the PDQ 39 (Jenkinson *et al*., 1997) to assess the patients' quality of life. A further detailed neurological examination was also performed looking specifically for features of other extrapyramidal diseases (e.g. progressive supranuclear palsy, multiple system atrophy and corticobasal degeneration).

Cognitive features of Parkinson's disease were assessed using standardized, previously validated tests; the mini mental state examination (MMSE) (Folstein *et al*., 1975), the National Adult Reading Test (NART) (Nelson and O'Connell, 1978) as a measure of premorbid IQ, a test of verbal fluency for words starting with the letters F, A and S for 1 min each (Benton, 1968), and a test of verbal fluency for animals in a 90-s period (Goodglass, 1972) (tests sensitive to frontal lobe impairment) (Miller, 1985).

The following subsets from the CANTAB battery (Sahakian *et al*., 1988; Robbins *et al*., 1994) were also performed. (i) Pattern recognition memory (PRM). This test is sensitive to impairment of temporal lobe function. (ii) Spatial recognition memory (SRM). This test is subserved by both frontal and temporal lobes (Owen *et al*., 1995*b*). (iii) The modified version of the Tower Of London task (TOL). This is a test of planning requiring working memory, at which some patients with Parkinson's disease have been shown to be impaired even in the early stages (Owen *et al*., 1992, 1995*a*; Cools *et al*., 2002). The modified version of the test involves 20 separate tasks, the first six of these being worked through verbally with the patient to ensure adequate comprehension of the task. No help was given for the last 14 tasks and patients were given 1 point for each task they solved correctly at the first attempt, giving a maximum possible score of 14 points. A Beck depression inventory was also performed on each patient (Richter *et al*., 1998).

Follow-up

Consenting patients are part of continued annual follow-up for repeat assessments and for confirmation of diagnoses. At the first annual follow-up visit, patients are given information about the Brain Donation Scheme, and invited to declare their intent to participate at post-mortem. The study received ethical approval from the Cambridgeshire Local Research Ethics Committee No. 98/166.

Analysis of data

Incidence figures are presented as crude estimates with confidence intervals (CIs), together with age-specific figures, and figures age-standardized to the 1991 European population. Only those patients meeting the UK Brain Bank criteria for Parkinson's disease were included in the analysis of cognitive deficits. Using our battery of cognitive tests, we have proposed a three-stage procedure to evaluate the cognitive performance of these patients. This is based on their scores at the MMSE, the PRM task and the modified version of the TOL task. A MMSE of <24 was used to divide patients into two groups in the first instance (Tangalos *et al*., 1996). Patients were then classified as cognitively intact if they also performed well at the PRM and the TOL, or as having a predominant frontostriatal impairment if they were poor at the TOL task only, predominant temporal lobe impairment if they were poor at the PRM task only, or a global pattern of impairment if impaired at tests in both domains (Fig. 2). Greater than 1 SD below normative mean scores for the PRM has been taken as indicative of impairment (CANTAB data), i.e. a cut-off score of <16/24. Age- and IQ-matched normative data for the modified TOL suggests an appropriate cut-off score of <8/14 (B. Sahakian, unpublished data; Lewis *et al*., 2003).

The validity of this three-stage process as a useful discriminatory method of detecting different types of cognitive impairment in Parkinson's disease has been explored using other cognitive domains: the verbal fluency for letters test (FAS), and, for animals, tasks sensitive to frontal lobe damage, and the SRM, which is sensitive to both frontal and temporal lobe deficits. Analysis of variance followed by *post hoc* pair-wise comparisons have been used

to evaluate the usefulness of distinguishing between these subgroups.

Results

Patient recruitment

Three hundred and ninety-one patients with suggested newly diagnosed parkinsonism were identified during the entire study, including our 3-month run in period. Of these, 73 had previously been diagnosed outside the 25-month incidence period or were not resident in Cambridgeshire at the time of diagnosis and were thus excluded from this incidence study. Of the 318 remaining, seven patients were also excluded since further inpatient assessments and investigations confirmed non-extrapyramidal diagnoses, including single cases of cord meningioma, motor neuron disease, chronic subdural haematoma, peripheral neuropathy, arthritis, depression, and Alzheimer's disease. Two further patients were excluded because of resolution of all symptoms and signs without treatment or obvious cause.

Of the 309 incident cases of parkinsonism, 239 patients (77%) consented to participate in our assessment. Seventy patients were not seen due to death (n = 15), could not be contacted despite numerous attempts (n = 18), or refused to consent (n = 37). The referral source for the 309 patients is presented in Table 1 and their diagnoses are presented in Table 2. For the 70 patients not assessed, diagnoses were based on hospital notes and/or GP records only.

Table 1 *Sources of initial case ascertainment*

Primary referral	No. of patients assessed	No. of patients not assessed	Total	Subsequently identified by 2nd source
GP	66	6	72	9
Neurologist	91	16	107	15
Geriatrician	54	12	66	15
Parkinson's disease nurse	13	4	17	9
Hospital discharge	15	32	47	3
Total	239	70	309	51

Incidence

Out of the 309 cases of parkinsonism, 201 were diagnosed as Parkinson's disease meeting Brain Bank criteria (PDBB). Age- and sex-specific incidence figures based on these 201 Parkinson's disease cases and for the 309 parkinsonism cases are presented in Table 3 and Fig. 1. Prevalent cases (therefore not at risk of incident Parkinson's disease) have not been excluded from the population denominator but are unlikely to substantially influence incidence estimates. Standardization to the 1991 European population age structure produces an incidence figure of 10.8 (CI 9.4–12.4) for Parkinson's disease and of 16.6 (CI 14.8–18.6) for parkinsonism, per 100 000 population per year.

Clinical features including cognitive deficits

One hundred and fifty-nine out of 201 Parkinson's disease patients participated in our detailed assessments. Based on their age and sex distribution (Table 4), these 159 incident Cambridgeshire Parkinson's disease patients appear to be representative of all patients identified in the incidence screen (Table 2). Figure 2 shows the cognitive performance of these 159 Parkinson's disease patients. Thirteen of the 159 (8%) patients scored <24 on the MMSE and therefore had evidence of marked cognitive impairment. Patients with a history of visual hallucinations or fluctuating cognitive ability suggesting a clinical diagnosis of DLB have not been included in this report. (It is possible, however, that these features may not always be recalled or reported by patients or their carers; see Discussion.) Of the remaining 146 patients scoring 24 or above on the MMSE, four became too fatigued to continue or had inability to complete any of the computerized tests due to

Table 2 *Clinical diagnoses among our incident cases of parkinsonism*

Extrapyramidal diagnosis	n	Assessed/not assessed	Male/female	Mean age at diagnosis: years (range)
PDBB	201	159/42	105/96	72.0 (37–94)
Drug-induced parkinsonism	32	23/9	16/16	72.5 (51–92)
Atypical Parkinson's disease	16	16/0	10/6	71.5 (43–88)
Dementia with Lewy bodies	16	13/3	10/6	77.4 (68–89)
Essential tremor	13	11/2	5/8	65.9 (40–93)
Unspecified parkinsonism	12	0/12	6/6	70.9 (44–89)
Vascular parkinsonism	10	10/0	5/5	77.0 (67–87)
Dystonic tremor	4	4/0	1/3	57.0 (40–70)
Corticobasal degeneration	2	2/0	0/2	65.4 (61–70)
Multiple system atrophy	1	1/0	0/1	47.4
Progressive supranuclear palsy	1	0/1	1/0	72.7
Orthostatic tremor	1	0/1	0/1	70.7

PDBB = Parkinson's disease cases meeting Brain Bank criteria.

Table 3 *Age- and sex-specific incidence figures for Parkinson's disease and parkinsonism in the CamPaiGN study*

Cambridgeshire population, 2001	All ages	30–39 years	40–49 years	50–59 years	60–69 years	70–79 years	80+ years
Men	349 678	55 537	48 372	45 088	30 467	21 506	9382
Women	359 037	55 933	48 648	45 211	31 269	26 183	17 890
All	708 715	111 470	97 020	90 299	61 736	47 689	27 272
Parkinson's disease incidence/10^{5yr-1}							
Men	14.4	0.9	3.0	8.5	41.0	98.2	117.7
Women	12.8	0.9	1.0	10.6	41.4	56.8	70.0
All (CI)	13.6 (11.8–15.6)	0.9 (0.22–3.6)	2.0 (0.75–5.3)	9.6 (6.0–15.2)	41.2 (31.5–53.9)	75.5 (60.2–94.6)	86.2 (65.1–114.1)
Parkinsonism incidence/10^{5yr-1}							
Men	21.8	1.7	6.0	13.8	58.3	145.1	184.2
Women	20.0	1.7	3.9	15.9	59.9	89.8	110.0
All (CI)	20.9 (18.7–23.3)	1.7 (0.6–4.5)	4.9 (2.6–9.1)	14.9 (10.3–21.6)	59.1 (47.2–73.9)	114.7 (95.5–137.8)	135.5 (108.4–169.4)

Table 4 *Description of the phenotypes of 159 Parkinson's disease patients assessed in this study*

	Male	Female	All
n	85	74	159
Ethnic origin	82 Caucasian 1 Afro-Caribbean 2 Asian	74 Caucasian	156 Caucasian 1 Afro-Caribbean 2 Asian
Premorbid IQ			
Mean	109	109	109
Range	(86–126)	(89–124)	
Age at onset (years)			
Mean	67.3	68.2	67.8
Range	(14.5–89.2)	(42.0–88.3)	
Age at diagnosis (years)			
Mean	69.9	70.7	70.3
Range	(37.7–89.6)	(46.8–90.2)	
Age at assessment (years)			
Mean	70.3	71.0	70.6
Range	(37.8–90.3)	(47.2–90.4)	
UPDRS motor score			
Mean	25.7	26.0	25.9
Range	(4–61)	(4.5–58)	
HY stage			
Mean	2.0	2.0	2.0
Range	(1–5)	(1–5)	
MMSE			
Mean	27.3	27.4	27.3
Range	(16–30)	(11–30)	
Parkinson's disease medication			
Treated	44	31	75
Untreated	41	43	84

HN = Hohn and Yahr.

visual impairment. Thirty patients scored <16 on the PRM test, suggesting a temporal lobe type cognitive impairment, of whom 12 were able to perform the TOL satisfactorily. An additional 14/106 (13%) patients who scored well at the MMSE and PRM tasks were poor at the TOL, suggesting an isolated frontostriatal type pattern of impairment. We therefore have evidence of some form of cognitive impairment for 13 + 30 + 14 = 57/159 (36%) of patients assessed.

Based on these three tests only, we have classified 92 patients as cognitively intact, 14 + 3 = 17 patients as having a specific frontostriatal type deficit, 12 patients as having a specific temporal lobe type deficit, and 16 + 5 = 21 patients as having deficits in both domains (global impairment) (Fig. 2). Twenty-two out of 159 (14%) of our patients had a Beck depression score >14, suggesting the presence of depression (Leentjens *et al.*, 2000).

Patients with either a global or a frontal pattern of cognitive impairment were significantly older, had higher UPDRS motor scores, and had lower premorbid IQs than patients who were cognitively intact. There were no differences in their scores on the Beck depression inventory. In an attempt to validate these four patient subgroups, further analysis using spatial recognition memory and verbal fluency tasks confirmed significant differences in scores among these patient groups (Table 5). As predicted, patients classified with either frontostriatal or global cognitive impairment performed less well at our other frontal cognitive tasks than patients without cognitive impairments. Patients classified as having temporal lobe impairments did not differ from the cognitively unimpaired group at these other tests of frontal lobe function.

Discussion

This is the first study to present the incidence of Parkinson's disease and the cognitive problems of a newly diagnosed cohort of Parkinson's disease patients using a community-based epidemiological approach. Phenotypic descriptions are far more useful when patient cohorts are derived from a resident population, as studies that have identified patients solely through movement disorder clinics will likely recruit a cohort of Parkinson's disease patients skewed towards the

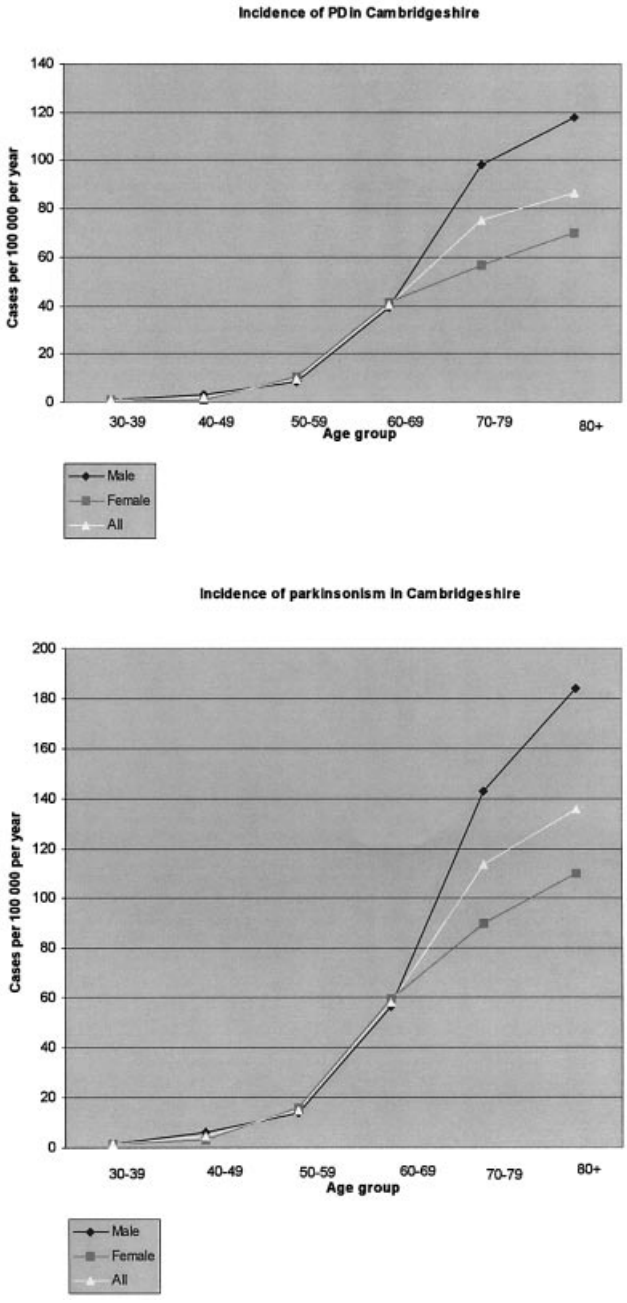

Fig. 1 Graphical representation of the age-specific figures for Parkinson's disease and parkinsonism in the CamPaiGN study.

young, the complicated or the interesting. Therefore, patients with late-onset or straightforward disease may be under-represented. Our age-standardized incidence figures for Parkinson's disease ($10.8/10^{5yr-1}$) and for parkinsonism ($16.6/10^{5yr-1}$) are similar to those for other European populations studied. In this cohort of incident Parkinson's disease patients, 36% performed poorly in at least one of three cognitive tasks.

The frequency of Parkinson's disease will vary widely depending on the choice of inclusion criteria, as demonstrated in the Olmstead county study (Bower *et al*., 2000), and we have therefore adopted the UK Brain Bank criteria (Hughes *et al*., 1992*a*, *b*) as this is regarded by many as the most reliable way of making the clinical diagnosis of Parkinson's disease. The cornerstone of these clinical criteria is that the patients exhibit 'bradykinesia' in some form or other, and so its absence excludes the diagnosis of Parkinson's disease. However, it is becoming more apparent from clinical series with follow-up data that a set of patients with asymmetrical postural or resting tremors in the absence of bradykinesia or rigidity may progress to more typical forms of Parkinson's disease responsive to dopaminergic therapy, many years after the onset of their disease (Pal *et al*., 2002). Indeed we have identified five patients with just such a presentation who, according to UK Brain Bank criteria would not have had Parkinson's disease as their initial diagnosis, but who ultimately met these criteria. Overlap between isolated postural tremor and Parkinson's disease is further exemplified by a recent study of PARK4 patients, where some individuals have a postural tremor only, whilst other relatives with the same 'at risk gene' have typical Parkinson's disease (Farrer *et al*., 1999).

Nevertheless the recent re-evaluation of the clinical diagnoses of Parkinson's disease by the authors of the Brain Bank criteria suggests that the positive predictive value of clinical diagnoses is high (98.6%), but that false negative cases suggest a broader clinical picture of disease than previously thought (Hughes *et al*., 2002). Whilst we accept the limitation of using these criteria, they were nevertheless adopted in our study so we can make comparisons between this and other studies. Our incidence figure for Parkinson's disease may, however, be an underestimate since a proportion of our atypical or unspecified parkinsonism patients are likely to have typical Parkinson's disease at post-mortem. Although the study attempted to identify all forms of parkinsonism, it is likely that underascertainment of non-Parkinson's disease diagnoses such as essential tremor occurred, as this condition is less likely to present to medical attention. The low frequency of progressive supranuclear palsy and multiple system atrophy within our cohort is also probably due to hitherto undiagnosed patients within the atypical parkinsonism group.

Previous studies of Parkinson's disease incidence within the UK have used GP and hospital records to estimate incidence figures retrospectively (Brewis *et al*., 1966; Sutcliffe and Meara, 1995) or have been based among smaller urban populations likely to have higher rates of population migration (Cockerell *et al*., 1996; MacDonald *et al*., 2000). The present study is the first UK study that has prospectively ascertained and assessed new diagnoses of Parkinson's disease and parkinsonism among a large, stable population base. In contrast to some records-based studies (D'Alessandro *et al*., 1987; Milanov *et al*., 2001) but consistent with others using screening methods of case ascertainment (de Rijk *et al*., 1997), we find no decline in the frequency of disease in the highest age groups, suggesting

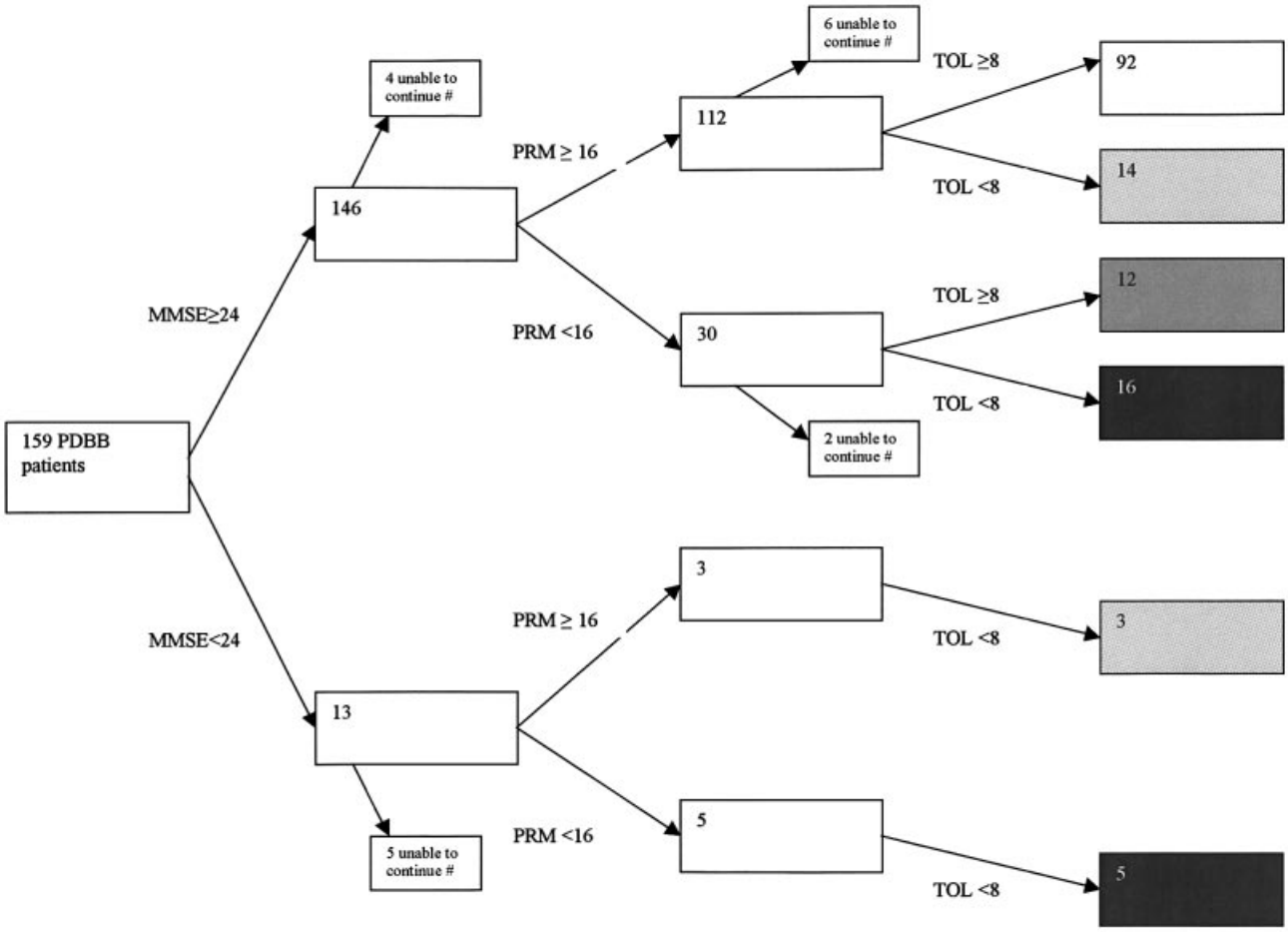

Fig. 2 Flowchart to show the abilities of our 159 Parkinson's disease patients at the MMSE, followed by the pattern recognition task and the Tower of London task. Conclusions regarding cognitive abilities are based on 142 patients with outcomes for all three tasks. Patients with fatigue or visual impairment did not perform all cognitive tests.

that we have reasonable case ascertainment in the older age groups, who are less often identified in epidemiological research. Our large population denominator has allowed us to identify large absolute numbers of cases in all of the older age groups, giving us greater precision in incidence estimates, and thus narrower confidence intervals. Age-specific incidence rates in this study are similar in the two sexes below the age of 70 years, with an excess incidence in men above this age. This is similar to the findings of previous screening studies (Tandberg *et al*., 1995; de Rijk *et al*., 1997) and the larger records-based studies (Kuopio *et al*., 1999; Van Den Eeden *et al*., 2003) and might suggest that sex-specific Parkinson's disease risk factors are most relevant for later-onset disease. Sex differences in disease risk and/or phenotype might be explained by the protective effects of sex hormones (for a review see Sawada and Shimohama, 2003), or by the influence of environmental or occupational risk factors to which men and women have differential exposures.

Door-to-door screening has been used as a method of identifying a population-based cohort of patients. Such studies may, however, be limited by low response rates and the validity of the initial screening questionnaire (Bermejo *et al*., 2001). Since we aimed to recruit a large number of incident Parkinson's disease patients in order to explore variable phenotypes, a door-to-door screening approach was considered less practical than targeting multiple sources. All of our five sources contributed large numbers of cases to the study. Inevitably, however, we recognize that some cases will have been missed. Capture–recapture analysis has been previously proposed as a method of estimating the number of cases not identified in a study using multiple sources of case ascertainment. This technique relies on source independence and the randomness of identification of cases from each source (Tilling and Sterne, 1999). Only 51/309 of our parkinsonism patients were identified from two or more sources. It became clear during the study that no patients were being seen in both neurology and geriatric outpatient clinics, and that, following GP referral for assessment in the study, neurologists, geriatricians and Parkinson's disease nurses would not subsequently re-notify the study if and when the patient came to their attention. The prerequisites for performing a capture–recapture analysis were therefore not met, and so we have not attempted to perform this.

Table 5 *Comparison of four subgroups of Parkinson's disease patients on the basis of cognitive ability*

	Cognitively intact	Frontostriatal deficits (TOL task)	Temporal lobe type deficits (PRM task)	Frontostriatal and temporal lobe type deficits (TOL + PRM)	Anova *P* value (df)
n	92	17	12	21	
Age diagnosed (years)					
Mean	66.5	74.0‡	70.7	76.4†	<0.001
Range	(37–83.7)	(63.3- 80.9)	(53.6- 82.5)	(60.5–87.3)	(3)
UPDRS motor					
Mean	21.9	32.6†	23.3	33.8†	<0.001
Range	(4.0- 50.5)	(4.0–54.5)	(8.0–56.5)	(5.5–58.0)	(3)
Duration since symptom onset					
Mean	3.1	2.2	2.3	2.2	0.74
Range	(0.4- 38.2)	(0.2- 6.2)	(0.7–5.4)	(0.4–13.8)	(3)
NART					
Mean score	112	106‡	103‡	100†	<0.001
Range	(86–126)	(90–121)	(89–125)	(86–124)	(3)
SRM					
Mean score	16.0	13.0†	14.8	11.8†	<0.001
Range	(3–20)	(9–18)	(11–18)	(0–18)	(3)
FAS fluency					
Mean score	37.3	30.5*	32.3	22.8†	<0.001
Range	(17–67)	(9–60)	(21–56)	(2–45)	(3)
Animal fluency					
Mean score	22.7	15.3†	19.3	13.6†	<0.001
Range	(10–46)	(8–26)	(10–44)	(8–26)	(3)
BDI score					
Mean score	7.4	8.7	7.6	7.4	0.88
Range	(0–24)	(2–19)	(1–20)	(0–25)	(3)

Analysis of variance followed by pairwise comparisons with cognitively unimpaired group. †Significantly different from cognitively unimpaired group ($P < 0.001$); ‡significantly different from cognitively unimpaired group ($P < 0.01$); *significantly different from cognitively unimpaired group ($P < 0.05$).

Table 6 *Frequency of positive family history among 159 Parkinson's disease patients*

Family history of Parkinson's disease	No. (%)	Mean age at diagnosis of proband (years)
>2 FDR with parkinsonism	7/159 (4%)	72.0 (range 64.0–76.5)
=1 FDR with parkinsonism	26/159 (16%)	68.9 (range 50.5–81.9)
=1 FDR or SDR with parkinsonism	32/159 (20%)	68.7 (range 50.5–84.8)

FDR = first-degree relative (parent, offspring, sibling); SDR = second-degree relative (grandparent, uncle, aunt, nephew, niece)

Four per cent of our cohort of incident Parkinson's disease cases had more than two first-degree relatives with features of parkinsonism as reported by the proband, although if we include second-degree relatives 20% of our incident cohort have a family history of the disease (Table 6). Only one of our incident Parkinson's disease patients was diagnosed below the age of 40 years, suggesting that young onset forms of the disease are, in fact, very rare. Given that it is this group that has the highest risk of carrying parkin-related disease (Lucking *et al*., 2000), our study is unlikely to be influenced by inclusion of parkin-related cases.

In this population-based cohort of incident Parkinson's disease patients, 36% performed poorly in at least one of three cognitive tasks. Follow-up of prevalent cases has estimated that between 20% (Brown and Marsden, 1984) and 75% (Aarsland *et al*., 2003) of Parkinson's disease patients will ultimately develop dementia. However, the frequency of the wider range of cognitive impairments at incidence has not previously been assessed. The threshold used to define cognitive impairment is always inevitably somewhat arbitrary, but a score below 24 on the MMSE has been previously accepted as indicative of cognitive impairment (Tangalos *et al*., 1996) and scores of 16/24 on the PRM and 8/14 on the TOL are greater than 1 SD below expected for unaffected age- and IQ-matched individuals in Cambridgeshire (B.Sahakian unpublished data). We have used data from age- and IQ-matched volunteers to derive these cut-off estimates for impairment, but there is always concern that data from volunteers do not represent the normal level of functioning among a true population-based cohort.

Despite this concern, these thresholds, which we have used to identify cognitive impairment, are very low, and therefore are unlikely to misclassify individuals with intact cognitive ability.

Our cognitively intact subjects were younger at diagnosis and had significantly higher estimated premorbid IQ scores (based on the NART test) than those with cognitive impairment. This might suggest that older age at disease onset is a risk factor for cognitive impairment, although in this analysis we have not made adjustment for the background effects of ageing. While some patients may have been misclassified as cognitively impaired due to a genuinely low premorbid IQ, without further follow-up, we cannot be sure that performance on the NART test is completely uninfluenced by the disease process. Patients with frontal or global types of cognitive impairment also had significantly higher UPDRS motor scores than patients without cognitive impairment. However, they had similar duration from onset of motor symptoms, suggesting that the patients with cognitive impairment had a more aggressive form of the disease.

The relationship between performance at our cognitive tasks and regional cortical dysfunction is the subject of ongoing studies. For example, imaging data suggest involvement of the dorsolateral prefrontal and anterior cingulate cortices and the caudate nucleus in normal individuals performing the TOL (Dagher *et al*., 1999), and that further areas may be recruited in the presence of Parkinson's disease (Dagher *et al*., 2001). In addition, parietal cortical areas have also been seen to activate during this task, suggesting the presence of wider cortical circuits (Baker *et al*., 1996). The importance of the dorsolateral prefrontal cortex in performing the TOL is, however, clear, exemplified by the observation that patients with parietal lesions have no problems performing the TOL task (M, Mehta, B. Sahakian, T. W. Robbins, unpublished data), whereas patients with frontal lobe lesions do (Owen *et al*., 1990). We recognize that identification of region or circuit-specific subtypes of cognitive impairment among patients can only be made with certainty following serial tests of cognition that use the same cortical circuits. However, comparisons of our three groups of impaired patients with our unimpaired patients using tests of verbal fluency and spatial recognition confirmed that those classified as frontally or globally impaired on the basis of MMSE, PRM and TOL were indeed less able to perform other frontal tasks. Patients with a temporal lobe pattern of impairment were no different from the cognitively intact group at frontal lobe tasks.

The descriptive results presented here suggest that a range of cognitive impairment is common even in the early stages of Parkinson's disease. We have limited our analysis to patients with Parkinson's disease and excluded patients meeting clinical criteria for DLB. DLB patients are currently distinguished from Parkinson's disease + dementia patients (PDD) by the respective timing at which cognitive impairment occurs in relation to the symptomatic onset of parkinsonism. A minimum of 12 months with 'motor-only' symptoms is recommended to define PDD (McKeith *et al*., 1996), but consensus criteria do not give guidance of how to retrospectively time the onset of symptoms of dementia, even though both the cognitive and motor symptoms of parkinsonism often develop insidiously. Since the presence of visual hallucinations or fluctuating cognitive ability may not be reliably reported by patients or carers (McKeith *et al*., 1999), some DLB patients may be misclassified after a single assessment as Parkinson's disease. There are therefore some conceptual problems distinguishing between patients with DLB and PDD, although all patients reporting less than 12 months of 'motor-only' symptoms before demonstrating marked cognitive deficits in this study have been classified as DLB and excluded from this cognitive analysis. It is likely that, in reality, considerable overlap between these groups exists (Ballard *et al*., 2002).

Scores of <24 at the MMSE (8%) or scores of <16 at the PRM *and* <8 at the TOL are seen in 13 + 16 = 29/159 (18%) of our incident patients, which may suggest the presence of diffuse Lewy bodies in cortical regions (Apaydin *et al*., 2002), may represent specific anterior cingulate cortex or caudate nucleus involvement (Ito *et al*., 2002) or may also represent the concurrent development of Alzheimer pathology (Hughes *et al*., 1993). Isolated frontostriatal-type impairments are also seen in a further 17/159 (11%) of our cohort and may represent dopaminergic deficiency of the dorsolateral prefrontal cortex (Cools *et al*., 2002) or may also be part of a prodromal period heralding the onset of dementia (Woods and Troster, 2003). Eight per cent of our Parkinson's disease patients had isolated impairment in temporal lobe function based on the PRM test. Previous studies of Parkinson's disease patients derived from clinical series have shown apparently conflicting PRM data due to inclusion of patients with differing dementia ratings (Sahakian *et al*., 1988; Owen *et al*., 1993). However, recent imaging studies (Hu *et al*., 2000; Camicioli *et al*., 2003) and pathological studies (Braak *et al*., 2000) suggest that temporal lobe dysfunction does indeed occur in some Parkinson's disease patients with the presence of Lewy bodies, Lewy neuritis and Alzheimer changes (Braak *et al*., 2000). None of our results seem to be due to a differential presence of depression among the groups. There will inevitably be a large number of variables, including the variety of drug treatments used for Parkinson's disease, which may have independent or interacting effects on cognitive ability. However, in this account we have deliberately kept the description of these patients simple as this gives the most accurate account of the population identified. All of our patients will be followed up to look at how their cognitive impairments develop.

Comparing the incidence figure from this study with those previously produced suggests that there is reasonable uniformity of incidence of Parkinson's disease among European populations. Incidence studies with good methodology and presentation of age- and sex-specific figures among non-Caucasian populations are, however, still required to confirm whether other populations have similar or different rates of

disease. Future studies should where possible also perform phenotypic assessments (including cognitive assessments) on their patients and collect DNA samples to make future epidemiological and genotypic/phenotypic comparisons possible.

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