How valid is the clinical diagnosis of Parkinson’s disease in the community?

A Schrag, Y Ben-Shlomo, N Quinn

Background: Many patients diagnosed with Parkinson’s disease are later found to have an erroneous diagnosis, often only when they come to necropsy; conversely, many patients with Parkinson’s disease in the community remain undiagnosed.

Objective: To assess the validity of a clinical diagnosis of parkinsonism in the general population according to strict published criteria.

Methods: As part of a population based study on the prevalence of Parkinson’s disease in London, all patients who had ever received antiparkinsonian drugs were identified with a diagnosis of parkinsonism, tremor with onset over age 50 years, or who had had previously not been diagnosed with Parkinson’s disease (19%) were found to have Parkinson’s disease. However, in 15% of patients the diagnosis was unequivocally rejected. Conversely, 13 patients who had previously not been diagnosed with Parkinson’s disease (19%) were found to have this disorder.

Conclusions: At least 15% of patients with a diagnosis of Parkinson’s disease in the population do not fulfill strict clinical criteria for the disease, and approximately 20% of patients with Parkinson’s disease who have already come to medical attention have not been diagnosed as such.
physiological tremor; the distinction of these syndromes is types of tremor such as essential, dystonic, and enhanced and still present on prevalence day.

months of treatment with dopamine receptor blocking drugs, parkinsonian symptoms was within six months of at least six tension, a wide based gait with small steps, cognitive decline, strokes, abrupt onset with stepwise progression, hyper-

presence of at least two of the following: a history of previous at their general practitioner’s surgery, or at home.

Diagnosis
All patients who agreed to participate had a general and neurological interview and examination, and a questionnaire—designed to detect signs and symptoms of typical and atypical parkinsonian disorders—was completed by one of the investigators (AS). If the subject agreed to this, a video recording of the neurological signs was made. The diagnosis was made according to published criteria (see below) after review and discussion of each subject and examination of their videotape. All patients in whom a diagnosis of parkinsonism was made received a questionnaire on atypical features and symptoms of progression (for example, development of falls) every three months for a period of one year. In addition, the general practitioners were asked about any new, atypical features in the eligible patients at the end of the study. Patients who had atypical features at the first visit, or developed them during follow up, and those in whom a probable diagnosis could not be made at the first visit, were reviewed after at least one year.

diagnosis was confirmed by one of the investigators (AS). If the subject agreed to this, a video recording of the neurological signs was made. The diagnosis was made according to published criteria (see below) after review and discussion of each subject and examination of their videotape. All patients in whom a diagnosis of parkinsonism was made received a questionnaire on atypical features and symptoms of progression (for example, development of falls) every three months for a period of one year. In addition, the general practitioners were asked about any new, atypical features in the eligible patients at the end of the study. Patients who had atypical features at the first visit, or developed them during follow up, and those in whom a probable diagnosis could not be made at the first visit, were reviewed after at least one year.

Diagnostic criteria
Parkinsonism was diagnosed if bradykinesia and at least one other cardinal sign (resting tremor, rigidity, or postural instability) were present. Parkinson’s disease was diagnosed according to the UK Parkinson’s disease society brain bank criteria with the exception that an isolated positive Babinski sign, for instance in an elderly patient with otherwise typical Parkinson’s disease, was not considered to invalidate the diagnosis. In addition, patients with isolated classical resting tremor only were diagnosed as having “possible Parkinson’s disease.” Multiple system atrophy (probable and possible) was diagnosed according to Quinn, and progressive supranuclear palsy (probable and possible) according to criteria proposed by the National Institute of Neurological Disorders and Stroke (NINDS) and the Society for PSP (SPSP).

Vascular parkinsonism was diagnosed when there was the presence of at least two of the following: a history of previous strokes, abrupt onset with stepwise progression, hypertension, a wide based gait with small steps, cognitive decline, and pseudobulbar or pyramidal signs.

Drug induced parkinsonism was diagnosed if the onset of parkinsonian symptoms was within six months of at least six months of treatment with dopamine receptor blocking drugs, and still present on prevalence day.

The diagnosis of non-parkinsonian tremor included various types of tremor such as essential, dystonic, and enhanced physiological tremor; the distinction of these syndromes is still a matter of debate.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Initial and final diagnosis of patients seen in this population based study (n = 202)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Final diagnosis</strong></td>
<td><strong>Initial diagnosis</strong></td>
</tr>
<tr>
<td>Probable Parkinson’s disease</td>
<td>109</td>
</tr>
<tr>
<td>Possible Parkinson’s disease</td>
<td>2</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>3</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>4</td>
</tr>
<tr>
<td>Vascular parkinsonism</td>
<td>6</td>
</tr>
<tr>
<td>Non-parkinsonian tremor</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>131</td>
</tr>
</tbody>
</table>

Data analysis
Only patients who were seen and were resident in the study area on prevalence day (1 July 1997) were included. Sensitivity, specificity, and positive and negative predictive values were calculated using standard formulae (see appendix). We calculated these variables for the overall sample excluding the patients referred for diagnosis (both of whom had Parkinson’s disease), as well as separately for a specialist (neurologist or geriatrician) or non-specialist diagnosis. Group differences were analysed by the Mann–Whitney test. Categorical data were compared with the χ² test, and Fisher’s exact test if appropriate.

RESULTS
We identified 241 patients using our screening criteria and 202 patients agreed to be reviewed (participation rate 84%), the remaining patients refusing to take part in the study. Patients who declined were slightly older than those who participated (p < 0.05), but there was no significant sex difference. They did not differ with regard to the percentage of patients who had a previous diagnosis of Parkinson’s disease.

Among the 202 participants, 134 (66%) had received a diagnosis of parkinsonism (131 of Parkinson’s disease, one of atypical parkinsonism, and two of vascular parkinsonism). Ten additional patients (5%) had been prescribed antiparkinsonian drugs for parkinsonian symptoms without a further specified diagnosis. Fifty six patients (28%) had been noted to have a tremor with onset after the age of 50 without having been suspected of having parkinsonism, and two patients (1%) were referred to us for diagnostic purposes without a previous diagnosis (table 1).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Patients with an initial diagnosis of Parkinson’s disease (n = 131)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Final diagnosis</strong></td>
<td><strong>n</strong></td>
</tr>
<tr>
<td>Probable Parkinson’s disease</td>
<td>109</td>
</tr>
<tr>
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<td>Vascular parkinsonism</td>
<td>6</td>
</tr>
<tr>
<td>Non-parkinsonian tremor</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
</tbody>
</table>
possible Parkinson’s disease. However, in 20 of the 131 patients (15%) the diagnosis of Parkinson’s disease was unequivocally rejected (table 2). The alternative diagnoses were non-parkinsonian tremor in four patients (3%), vascular parkinsonism in six (5%), progressive supranuclear palsy in four (3%; probable in three and possible in one), and multiple system atrophy in three (2%; probable in two and possible in one). Two patients received a diagnosis of idiopathic torsion dystonia, and one of dementia without parkinsonism. When only those patients who had seen a specialist at some point in the past (97 patients, 74%) were considered, the diagnosis was changed from Parkinson’s disease to a different diagnosis in 11%.

**Patients with a previous diagnosis other than Parkinson’s disease**

Among all patients seen, two were referred for diagnostic purposes without a previous diagnosis, and 69 of 202 patients (34%) had a previous diagnosis other than Parkinson’s disease (tables 3 and 4). Among these, 56 patients (81%) had been given a diagnosis of non-parkinsonian tremor, two (3%) of vascular parkinsonism, one (1%) of atypical parkinsonism, and 10 (14%) had been prescribed an antiparkinsonian drug for parkinsonian features without a specific diagnosis (table 1). Thirteen of the 69 patients with different diagnoses (19%) and the two patients referred for diagnostic purposes fulfilled strict clinical criteria for Parkinson’s disease (table 1). In two additional patients who had a previous diagnosis of non-parkinsonian tremor, a diagnosis of “possible Parkinson’s disease” was made (3%). If only patients who had at some point in the past seen a specialist (26 of 69 patients, 38%) were considered, the diagnosis was changed to probable Parkinson’s disease in five (19%) and to possible Parkinson’s disease in one (4%).

**Sensitivity, specificity, and predictive value of a previous diagnosis of Parkinson’s disease**

Of 126 patients with a pre-existing clinical diagnosis of probable and possible Parkinson’s disease in the overall sample (patients identified through an initial diagnosis of parkinsonism, a record of tremor with onset after age 50, or identified through previous prescription of antiparkinsonian drugs, excluding those who were referred for diagnosis), 111 were confirmed as having Parkinson’s disease, resulting in a sensitivity of 88.1% (95% confidence interval, 81.1% to 92.2%); similarly, it was confirmed that 54 of 74 patients did not have Parkinson’s disease, resulting in a specificity of 73.0% (61.3% to 82.6%). The positive and negative predictive values of a previous clinical diagnosis of Parkinson’s disease were 84.7% (77.4% to 90.4%) (111 of 131 patients) and 78.3% (66.7% to 87.3%) (54 of 69 patients). In other words, in 85% of patients with a previous diagnosis of Parkinson’s disease this diagnosis was confirmed, and 78% of patients with a diagnosis other than Parkinson’s disease did not have the disease (table 4).

When this was broken down by a specialist or other doctor diagnosis, the diagnostic validity was as follows. Neurologists and geriatricians had a sensitivity and specificity of 93.3% (86.3% to 97.6%) (86 of 92 patients) and 64.5% (45.4% to 80.8%) (20 of 31 patients), respectively, compared with 73.5% (55.6% to 87.1%) (25 of 34 patients) and 79.1% (64.0% to 90.0%) (34 of 43 patients) for non-specialists. The positive predictive values were greater for specialists (88.7%; 80.6% to 94.2%) than for other doctors (73.5%; 55.6% to 87.1%), but the negative predictive values were equivalent (specialist 76.9% (56.4% to 91.0%) v non-specialist 79.1% (64.0% to 90.0%).

**Likelihood of referral according to final diagnosis**

Overall, 74% of all cases with a diagnosis of Parkinson’s disease had been seen by a specialist. However, when these cases were classified by final diagnosis (table 2), it was observed that, paradoxically, fewer cases with atypical disease (54.5%) had been seen by a specialist compared with those with classical Parkinson’s disease (78.0%) (difference in proportions 23.4% (1.2% to 45.6%); p = 0.02).

**Comparison of patients in whom a diagnosis of Parkinson’s disease was maintained or rejected**

Patients in whom a diagnosis of Parkinson’s disease was confirmed had more severe disease as measured by the Hoehn and Yahr stage (p < 0.05), more often had a tremor at rest (p < 0.01) or a classical pill rolling tremor (p < 0.01), and more often reported a good initial and sustained response to levodopa (both p < 0.001) than those in whom it was rejected. Patients in whom the diagnosis was changed to non-parkinsonian tremor had no other parkinsonian features such as rigidity, bradykinesia, hypomimia, or monotonous speech. They also reported falls significantly less frequently (p < 0.01) and had higher mini-mental state scores (p < 0.05). Those in whom the diagnosis was changed to atypical parkinsonism (multiple system atrophy or progressive supranuclear palsy) had more severe akinesia (p < 0.05), rigidity (p < 0.01), and postural instability (p < 0.05), less commonly reported an initially or currently good response to levodopa (both p < 0.01), but more often had incontinence (p < 0.01) and additional features incompatible with Parkinson’s disease. Those in whom the diagnosis was changed to vascular parkinsonism were older than those in whom a diagnosis of Parkinson’s disease was confirmed (p < 0.05), had a larger number of previous parkinsonian features, and had higher mini-mental state scores (p < 0.05).

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**Table 3** Patients with a final diagnosis of probable Parkinson’s disease (n = 124)

<table>
<thead>
<tr>
<th>Initial diagnosis</th>
<th>n (%)</th>
<th>Mean age (years)</th>
<th>Seen by specialist (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s disease</td>
<td>109</td>
<td>87.9</td>
<td>85.9 (78%)</td>
</tr>
<tr>
<td>Atypical parkinsonism</td>
<td>1</td>
<td>0.8</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Vascular parkinsonism</td>
<td>1</td>
<td>0.8</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Non-parkinsonian tremor</td>
<td>9</td>
<td>7.3</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>On antiparkinsonian drugs</td>
<td>2</td>
<td>1.6</td>
<td>0</td>
</tr>
<tr>
<td>Referred for diagnosis</td>
<td>2</td>
<td>1.6</td>
<td>2 (100%)</td>
</tr>
</tbody>
</table>

**Table 4** Sensitivity, specificity, and predictive values for the overall sample* and by type of clinician

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Specialists</th>
<th>Non-specialists</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Final diagnosis</td>
<td></td>
<td>Final diagnosis</td>
</tr>
<tr>
<td></td>
<td>PD, PD, PD</td>
<td>Not PD, PD</td>
<td>Total</td>
</tr>
<tr>
<td>Previous diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>111</td>
<td>20</td>
<td>131</td>
</tr>
<tr>
<td>Not PD</td>
<td>15</td>
<td>54</td>
<td>69</td>
</tr>
<tr>
<td>Total</td>
<td>126</td>
<td>74</td>
<td>200</td>
</tr>
</tbody>
</table>
of smoking years (p < 0.01), more often had gait difficulties as their first complaint (p < 0.05), and had more severe postural instability (p < 0.001); they never had a rest tremor.

Patients in whom a diagnosis of Parkinson’s disease was or was not previously made

Patients in whom a diagnosis of Parkinson’s disease was previously made had a longer disease duration (p < 0.05) and greater disease severity (p < 0.01), with more severe akinesia (p < 0.01), postural instability, and rigidity (both p < 0.001) than those in whom the diagnosis was not made before. They were also more likely to be depressed (p < 0.05), to have experienced dyskinesias (p < 0.05), and to live alone or with their family than in a nursing home (p < 0.05).

DISCUSSION

The results of this study, on a community level, correspond with results from pathological studies indicating that Parkinson’s disease is often confused with other disorders. The main areas of diagnostic difficulty concern the distinction from other types of isolated, late onset tremor, vascular parkinsonism, and atypical types of parkinsonism, which are often mistakenly diagnosed as Parkinson’s disease. On the other hand, patients with Parkinson’s disease are sometimes not recognised as having this disorder, particularly those with mild disease or a relatively isolated tremor.

The rate of underdiagnosis is likely to be even higher, as we included only patients who had already come to medical attention with tremor or parkinsonian features. Some patients not meeting our screening criteria, particularly elderly people with akinetic-rigid parkinsonism without tremor, would have been missed in this study if postural instability and other parkinsonian features were attributed to old age. In door to door studies on the prevalence of Parkinson’s disease, the proportion of previously undiagnosed patients has ranged from 12% to 60%.16 We employed wide screening criteria in this study in order to detect as many patients with a parkinsonian syndrome as feasible. For this reason, and owing to the comparatively easy access to and high density of neurologists in the study area of London, we believe that our rate of underdiagnosis is relatively low and comparable to that of 12% found in an earlier door to door study with otherwise similar study design in the Netherlands.17

As may have been expected, Parkinson’s disease was more often recognised in patients with greater disease severity, who had had the disease for longer, and had already developed complications such as depression and dyskinesias, and were more likely to live alone or with their family than in a nursing home.

The accuracy of the diagnosis of Parkinson’s disease has been conspicuously poor in the few studies assessing patients with this clinical diagnosis. When compared to pathological diagnosis, the rate of false positive clinical diagnosis of Parkinson’s disease in life was 24% in one study of 100 patients.2 This rate improved to 18% when strict clinical criteria were used retrospectively. In a second later study, the same group reported that the rate of misdiagnosis in a series of 100 patients who had died with a diagnosis of Parkinson’s disease had fallen to 16% and later to 10%.3 In another study of 43 patients with a clinical diagnosis of Parkinson’s disease, the rate of correct diagnosis at the initial visit was only 65% compared with the pathological diagnosis, but rose to 76% at the final visit.4 Samples from brain banks and specialist clinics are, however, likely to overrepresent atypical disorders owing to the referral bias inherent in such samples.5 Nevertheless, prevalence studies of Parkinson’s disease which have employed strict clinical diagnostic criteria have also yielded rates of false positive diagnoses ranging from 14.5% to 44%, the commonest alternative diagnoses being essential tremor, vascular parkinsonism, dementia, and drug induced parkinsonism.18 In a more recent population based study8 assessing the accuracy of diagnosis in patients with presumed Parkinson disease, using the same criteria for diagnosis as in the present study, only 53% of 402 patients were clinically confirmed to have Parkinson’s disease. Patients with drug induced parkinsonism and dementia before the onset of parkinsonism, who were excluded in our study, constituted 12% and 4%, respectively, and patients who did not fulfil full criteria for probable Parkinson’s disease, which would have been labelled “possible Parkinson’s disease” in our study, were included in the group of “unspecified parkinsonism.” Thus if these cases are excluded, the rate of false positive diagnosis was similar in the two studies. However, in the study cited,9 the diagnosis was more frequently changed to essential tremor (12%), which was the final diagnosis in only 3% of patients previously diagnosed as Parkinson’s disease in our study. A possible explanation for this finding may be earlier referral to neurology clinics and earlier diagnosis in this study owing to the high density and relatively easy access to neurology departments in London.

We found that a false positive diagnosis of Parkinson’s disease was made predominantly in patients with other neurodegenerative causes of parkinsonism, such as multiple system atrophy and progressive supranuclear palsy, and in patients with vascular parkinsonism. This is in agreement with pathological studies, where approximately 6% of incorrectly diagnosed patients had progressive supranuclear palsy, 5–9% had multiple system atrophy, and 3% had vascular parkinsonism.1,2 As we excluded patients with dementia who later developed parkinsonism, the rate of false positive diagnosis of Parkinson’s disease in patients with Alzheimer’s disease, which represented 2–6% in pathological studies, was smaller in our sample. Likewise, patients who had used neuroleptic drugs within six months of the onset of symptoms were excluded a priori, and the rate of misdiagnosis of drug induced parkinsonism was therefore lower. The accuracy of diagnosis of Parkinson’s disease in the general population in this study is thus very similar to the pattern of diagnostic difficulties in the clinicopathological studies.

In order to improve the accuracy of diagnosis, this study was specifically designed to detect atypical features (which is more problematic in a retrospective analysis of case notes of patients coming to necropsy examination). We therefore believe that the accuracy of our clinical diagnosis is relatively high. However, some patients do not develop or display features permitting unequivocal diagnosis of atypical disease during life. When using the same diagnostic criteria that were applied in this study, Hughes et al still found an 18% rate of misdiagnosis of Parkinson’s disease at necropsy.1 Although in a later study by the same group the rate of misdiagnosis was lower,12 we therefore estimate that at least another 10% of the patients diagnosed with Parkinson’s disease in our study may nevertheless have a different disorder.

Neurologists and geriatricians performed better than non-specialists, despite the fact that they were probably more likely to see more difficult cases. Our figures for sensitivity and specificity for both groups of clinicians are slightly unfair as referral to a specialist in itself may reflect the general practitioners’ uncertainty about the diagnosis, and as we had the benefit of making the diagnosis after some time had elapsed. In this way we may have been able to detect additional features that were atypical but not present when the initial diagnosis was made. This highlights the importance of reassessment of patients, even after a diagnosis has been made. Non-specialists performed reasonably well in this study, however, it should be noted that we may have overestimated the specificity of their diagnosis as it is possible that additional patients with Parkinson’s disease who had presented to their general practitioners were not detected by our methods. In this case the “true” false positive rate would be higher than reported.
Objective: To study the characteristics of patients referred to a neurological service with a symptom of tremor, and to develop a strategy for identifying patients with idiopathic Parkinson’s disease (PD) in primary care.

Methods: A total of 1347 patients referred to a movement disorder service from 65 general practices in the United Kingdom over a period of 18 months were included. The characteristics of patients referred with tremor were compared with those referred with other movement disorders, and between cases and controls. Characteristics found to be more common in PD than non-PD cases were identified. These were then used to develop a clinical algorithm for diagnosis.

Results: The mean age of patients referred for tremor was 66±19 years. Of these, 12% were referred for PD. The presence of several characteristics, such as classical pill rolling rest tremor and lack of rigidity, was significantly more common among those referred for PD than those referred for other movement disorders. These were then used to develop a diagnostic algorithm.

Conclusions: The algorithm developed may be useful in identifying patients with PD in primary care. Further research is needed to validate the algorithm in a larger population.

APPENDIX

Definition of terms used in the analysis

<table>
<thead>
<tr>
<th>Previous diagnosis</th>
<th>Final diagnosis</th>
</tr>
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<tbody>
<tr>
<td>Parkinson’s disease</td>
<td></td>
</tr>
<tr>
<td>Not Parkinson’s disease</td>
<td></td>
</tr>
</tbody>
</table>

Sensitivity: Proportion of patients with a final diagnosis of Parkinson’s disease who were previously diagnosed as having Parkinson’s disease: A/(A+C).

Specificity: Proportion of patients without a final diagnosis of Parkinson’s disease who were previously diagnosed as not having Parkinson’s disease: D/(D+B).

Positive predictive value: Proportion of patients with a previous diagnosis of Parkinson’s disease who received a final diagnosis of Parkinson’s disease: A/(A+B).

Negative predictive value: Proportion of patients with a previous diagnosis of not having Parkinson’s disease who received a final diagnosis of not having Parkinson’s disease: D/(D+C).
REFERENCES
9 Quinn N. Multiple system atrophy – the nature of the beast. J Neurol Neurosurg Psychiatry 1989;52(suppl):78–89.

NEUROLOGICAL PICTURE

Footprints of coagulopathy

A 68 year old man with chronic atrial fibrillation and a St Jude valve in mitral position discontinued warfarin several days prior to a coronary angiogram. Forty eight hours after restarting his warfarin, while also on low molecular weight heparin and aspirin, he developed an acute motor aphasia and right hemiparesis. Computerised tomography (CT) in the emergency room revealed a large left frontal haemorrhage with multiple fluid blood levels (Fig 1). His INR was 2.4 on admission. Worsening in consciousness prompted emergent evacuation of the haematoma. Three months post-operatively he had only trace right sided weakness.

On CT, fluid blood levels in acute cerebral haematomas have a 95% sensitivity and 98% specificity for indicating underlying coagulopathy. The sharply demarcated interface represents a boundary between plasma and sedimented blood. Although all patients with intracerebral haemorrhage should routinely have PT, PTT, and platelet count performed, the fluid blood level on head CT may denote bleeding dyscrasias as the aetiology of haemorrhage. In fact, the CT scan may be available before the laboratory values return.

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References

Figure 1  Sequential axial non-contrast computerised tomography scans of the head demonstrating a large left frontal haemorrhage with multiple fluid blood levels and intraventricular extension.
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