J Neurol (2002) 249 : 138 – 145
© Steinkopff Verlag 2002

REVIEW

Thomas Foltynie
Carol Brayne
Roger A. Barker

The heterogeneity of idiopathic Parkinson's disease

Received: 23 March 2001
Accepted: 1 August 2001

C. Brayne, FRCP, MD, FFPHM
Institute of Public Health
University of Cambridge
Robinson Way
Cambridge, CB2 2SR, UK

T. Foltynie, MRCP, M.Phil (✉) · R. A. Barker, MRCP, PhD
Cambridge Centre for Brain Repair
University of Cambridge
Robinson Way
Cambridge, CB2 2PY, UK
Tel.: +44-12 23/33 11 60
Fax: +44-12 23/33 11 74
E-Mail: tf210@medschl.cam.ac.uk

Abstract The diagnosis of Idiopathic Parkinson's disease (IPD) requires post mortem neuropathological confirmation to be secure, since there is marked heterogeneity in the clinical phenotype of these patients. Pathologically confirmed IPD encompasses a spectrum of microscopic appearances with respect to the extent and distribution of Lewy Body deposition, which may reflect the clinical phenotypes observed during life. In this review, we discuss how IPD is currently defined and the purpose and applications of a classification of the disease. We have also performed a systematic review of the literature to present the quantitative evidence on which potential classifications of the disease might be based. This evidence suggests that sub-groups based on age of onset, motor presentation, or subsequent motor phenotype may have some use in predicting disease progression. However, further clinico-pathological studies are required to evaluate pathological heterogeneity within these groups.

Clinical sub-groups may be related to a variety of as yet unknown risks, including genetic factors for both the familial and sporadic forms of the disease, and may have far reaching consequences for our understanding of disease pathogenesis and treatment strategies.

Key words heterogeneity · Parkinson's disease · definition · classification · cluster

Introduction

The idea of sorting similar things into categories is fundamental to most branches of science. In biology the theory of classifying organisms is known as taxonomy, and uses a "polythetic" system in which classifications are based on many characteristics of the objects being studied, as opposed to "monothetic" systems, which use a single characteristic to produce a classification [76]. A similar approach may be employed in the study of diseases.

Different classifications of disease divide patients into groups based on a set of rules, and are not "right or wrong", but may be more or less useful depending on the particular disease, the clinical setting and the priorities of the individual using the classification. In this review, we explore the concept of heterogeneity in Idiopathic Parkinson's Disease (IPD), and discuss how the development of a classification may help both in clinical predictions of treatment response and prognosis, and in attempts to define the aetiology of the condition. A classification describing this heterogeneity ought to have use both in the clinical assessment and management of patients as well as being consistent with, and contributing towards our understanding of the underlying pathological disease processes.

JON 625

How is Idiopathic Parkinson's Disease defined?

In order to define heterogeneity, one first needs to establish the definition of the disease under consideration. Neuropathologically, IPD is defined as the selective degeneration of pigmented, dopaminergic neurons of the substantia nigra pars compacta (SNc) and other brainstem nuclei, with the presence of α-synuclein positive staining cytoplasmic inclusions (known as Lewy bodies) in the surviving neurons [1, 14, 16, 21, 77].

Indeed, the post-mortem neuropathological examination of the brain is widely accepted to be the only certain way to diagnose IPD [36] despite the fact that most cases are never confirmed neuropathologically. The precision of this pathological definition of the disease must be given substantial consideration, since this currently represents the most robust diagnostic tool.

Degeneration of pigmented neurons in IPD patients tends to be most marked in the ventrolateral region of the SNc, and this regional selectivity has been used as the basis for distinguishing between IPD and other neuro-degenerative diseases of the basal ganglia [14]. The extent of neuronal degeneration in other brainstem nuclei may also vary, as may the absolute number and location of Lewy bodies [21], therefore patients with quite variable pathological appearances currently fulfill the pathological definition for IPD.

Indeed, it seems that a spectrum of pathologies may exist, ranging from patients with a small number of subcortical Lewy bodies at post mortem examination and no parkinsonian symptoms in life – so called "Incidental Lewy body disease" [15], to patients with Lewy bodies spread throughout both cortical and subcortical areas with varying degrees of parkinsonian features and dementia – known as "cortical Lewy body disease" or "Dementia with Lewy bodies" [24]. However, the majority of "IPD" patients appear to have some cortical Lewy bodies [33] and distinguishing between IPD and "cortical Lewy body disease" is currently impossible on a qualitative or quantitative pathological basis [47]. Further, whilst Lewy bodies form part of the definition of IPD, they have also been seen in other conditions including progressive supranuclear palsy [18], amyotrophic lateral sclerosis [61], and Alzheimer's disease [9], and therefore the pathological diagnosis of IPD is heavily dependent on the pattern and extent of Lewy body distribution.

The pathological definition of the disease remains the essential part of the investigation of the disease by scientists and possibly even epidemiologists; however, it is of little help for clinician and patient in the absence of any diagnostic test for the disease in life.

Clinical definitions of IPD describe a disorder of unknown aetiology, characterized by bradykinesia, resting tremor, cogwheel rigidity, and postural reflex impairment, present in varying degrees [81], and accompanied by a range of cognitive abnormalities, from subtle frontal lobe deficits [46, 62] to profound dementia [6]. Several diverse entities, including toxins, pharmacological agents and focal or vascular lesions of the basal ganglia can produce syndromes clinically indistinguishable from IPD, leading to lower precision in the clinical definition of the disease.

Clinico-pathological studies using case series show that an initial diagnosis of IPD is inaccurate in 35 % of patients, falling to 24 % after a mean disease duration of 12 years [36, 68, 85]. Most misdiagnosed patients turn out to have either progressive supranuclear palsy, multiple system atrophy, Alzheimer's disease or vascular parkinsonism [36].

Two studies have sought to identify the optimum combination of clinical criteria to make the diagnosis of IPD, by calculating the sensitivity, specificity and positive predictive value for 15 possible features among 100 patients with pathological evidence of diagnosis [34, 85]. Application of strict clinical criteria improves diagnostic accuracy to 82 %, but also leads to exclusion of more than 30 % of pathologically genuine IPD patients [34].

It is this variation in both the clinical spectrum of IPD patients and the underlying pathological appearance of the brain that suggests that genuine and meaningful heterogeneity exists. This heterogeneity will be under the influence of genetic factors, the extent of exposure to environmental agents and also the presence of co-pathologies.

Approaches to the classification of IPD

To date, the majority of attempts to classify IPD have been based on testing *a priori* hypotheses. Groups of patients are collected based on whether they share a particular feature, and then the subgrouping is evaluated by making further comparisons with respect to other features of the disease. This method has been criticized as being too arbitrary in the choice of initial sub-grouping [25] but has yielded much information that can be utilized in future studies. The following section is a systematic review of the basis for sub-classifying IPD, following a literature search of the Medline databases 1966–2000, using exploded MeSH headings, "Parkinson" and "Heterogeneity". Further publications were identified from the reference sections of those papers identified. It is clear that there is a degree of inter-dependence of the clinical features observed in all pre-defined groups of patients, which adds to the difficulty in producing any simple classification.

Heterogeneity based on Clinical Phenotype

Age of Onset

A classification of IPD on the basis of age, has distinguished juvenile onset (JOPD – onset pre age 21), young onset (YOPD – age 21 to 40) and late onset cases (LOPD – onset > 40 years) [23] using a variety of clinical features and outcome measures to estimate the usefulness of the classification.

Eight case series have found that IPD *progresses more slowly* in patients with earlier symptom onset [3, 8, 22, 37, 45, 72, 74, 87] although any case series may be subject to possible selection bias, and thus may not be representative of all cases within a population. For example, slower progressing, older onset cases may be less likely to present to tertiary hospital services and get included in this type of study. This selection bias is eliminated in the only population-based study [54], where a significant correlation between younger age at onset and slower rate of disease progression has also been reported. In contrast, Hoehn and Yahr found age of onset made no difference to the rate of progression in their case series [31], and two studies found less disability in patients with later symptom onset [48, 57].

A further criticism of these studies is that diagnosis was based on clinical grounds only without pathological confirmation of disease. Seventy seven per cent of juvenile onset parkinsonism cases are now thought to be due to "parkin" mutations which leads to a different pathological diagnosis [51, 58]. Thus the results of studies involving young onset cases of parkinsonism may be biased by the inappropriate inclusion of patients with "parkin" mutations.

When only pathologically confirmed cases are examined [20], mean disease duration before death still tends to be longer in young onset cases; however, the length of disease before death may not necessarily be any reflection on the rate of progression to extreme disability during life.

Increased age of onset of IPD has also been associated with increased *risk for incident dementia* in nine case series of IPD patients [10, 12, 29, 37, 49, 55, 66, 70, 79] and in two population studies [11, 54]. These studies took into account disease duration and used age matched controls for comparison, which excluded the effect of a higher background rate of dementia. Patients with early onset disease also perform less well than their age matched control subjects in memory tests requiring mental processing [10, 29]; however, the neuropsychological deficit of the late onset PD group is more global than that found in the early onset patients, when compared with their age matched controls [10]. Again, it is impossible to judge how many "parkin" patients might have been included in most of these earlier studies, and the only study of "parkin" patients showed no significant difference in MMSE score between juvenile parkinsonian patients, positive or negative for the mutation [51].

In one series with pathological confirmation of disease [35], the mean duration of disease at the time of developing dementia was longer in those with an early disease onset than in those with late onset. (Early onset in this study being defined as < 60 years). The overall risk of development of dementia was, however, independent of age at disease onset.

Focal dystonia has been shown to occur particularly frequently in YOPD cases in six case series [19, 20, 40, 42, 67, 83]. Four of these studies [19, 20, 42, 67] and one other [35] also found a higher frequency of *levodopa induced dyskinesias* in YOPD patients series. This result is consistent even in pathologically confirmed cases [20], which eliminates any misclassification bias due to inclusion of "parkin-mutation" positive patients. In the only study performed thus far, patients with mutations in the "parkin" gene are more likely than juvenile parkinsonism patients negative for "parkin", to have symmetric involvement at onset and improvement with levodopa, and to develop dystonia and levodopa induced dyskinesias [51].

Only one study has linked younger age of disease onset with a predominantly tremulous subgroup of PD [87]; two other studies present equivocal or contradictory findings [20, 72]. Overall, it would seem that YOPD patients have less cognitive problems than patients with later disease onset, and have a disease that progresses more slowly, but have a higher incidence of dystonia and levodopa-induced dyskinesias.

Motor Phenotype

Classifications of IPD on the basis of motor phenotype have been evaluated in a similar way. Distinctions are made between motor symptoms at *presentation* of the disease and the symptom dominance as the disease progresses, since some patients suffering from tremor at presentation become predominantly bradykinetic or rigid later in the disease [28, 63].

Two case series [31, 72] and one population based study [54] have found resting tremor at presentation to be associated with a slower *rate of disease progression*. Three further case series also found slower rates of progression in patients presenting with resting tremor compared to patients presenting with predominant bradykinesia or rigidity [22, 28, 37] although in these series levels of significance were not reached. It is possible that the results of studies such as this are biased by the inclusion of patients with Essential Tremor, rather than IPD.

Six case series have all concluded that patients who continue to have tremor dominance after 2 to 7 years have been found to progress more slowly than those

with predominance of rigidity, bradykinesia or gait disorder [28, 31, 32, 37, 73, 87].

Seven case series [32, 50, 60, 64, 66, 70, 87] and two population studies [11, 53] have shown associations between motor phenotype and *cognitive impairment*. Patients with predominant postural instability [87], gait disorder [50, 64], rigidity [32, 53] and bradykinesia [11, 32, 53] have been associated with greater cognitive impairment than patients with tremor dominant disease. A further study reported greater subjective intellectual impairment in patients with predominant postural instability and gait disturbance (PIGD), than patients with tremor dominant disease although formal neuropsychological tests failed to confirm this difference [37].

The only clinico-pathological study with data regarding motor onset found no *significant* relationship between type of onset or subsequent disease pattern and survival, and incidence of dementia [35]. This may have been influenced by low numbers of patients with tremor dominant disease –1/7 tremor dominant patients developed dementia compared with 9/16 akinetic-rigid patients. Of the patients with dementia, 29% had Alzheimer's disease, 10% had numerous cortical Lewy bodies, and 6% had a possible vascular cause, but no pathological cause for dementia was found in 55% [35]. This highlights the difficulty associated with co-morbidity in the investigation of the heterogeneity of disease.

In summary, patients with tremor dominant disease several years into their illness, seem to have a more slowly progressive disorder than those with PIGD, and less in the way of cognitive disturbance.

Rate of progression

The rate of progression of disease itself has also been considered as a basis for sub-classification. Most studies evaluate progression in disability using the scale devised by Hoehn and Yahr [31]. The major limitation of a classification based on disease progression is the difficulty in classifying patients at initial diagnosis, and is thus of limited value for the clinician. As discussed, both tremor dominant disease and younger age at symptom onset have been strongly associated with a slower rate of disease progression. It is possible that these relationships will lead towards a classification of the disease that is of use in the clinical setting.

Cognitive Impairment

Classifications of PD subgroups generally evaluate the extent of cognitive involvement among the groups as an outcome measure, rather than a basis for sub-grouping patients. One case series [59] and one population based study [52] defined patient groups on the basis of cognitive impairment, and found patients with either visuo-spatial deficits or dementia to have greater bradykinesia and rigidity than patients with lesser cognitive impairments. A further case series considered cognitive impairments in more detail [70], finding bradykinesia to be associated with widespread cognitive impairment, rigidity to be associated with impaired verbal fluency and visuo-spatial skill, and tremor was correlated with impaired auditory verbal learning, visual memory and choice reaction time.

Although there is no clear qualitative or quantitative neuropathological basis to distinguish IPD from dementia with Lewy bodies (DLB), clinical criteria to distinguish DLB from IPD and Alzheimer's disease have been proposed [56], in the hope that a patient's clinical course or therapeutic response may be more predictable. The criteria for DLB describe the core feature of a progressive dementia accompanied by fluctuating cognition, recurrent visual hallucinations or spontaneous motor features of parkinsonism. Possible surrogate markers to distinguish Lewy body diseases from Alzheimer's disease may also exist, including decreases in the catecholaminergic innervation of the heart [86]; however, the sensitivity, specificity and usefulness of these criteria and markers require further studies.

Each clinical feature of IPD appears to have a degree of inter-dependence with the other clinical features observed. In addition to the observed clinical heterogeneity, any classification of IPD into subtypes requires the support of further pathological examinations and correlations between clinical phenotype and pathological appearance. The recent identification of genetic mutations [17, 51, 65], and variation in the relative risks for particular environmental exposures in different patient subgroups [72] may assist in the production of a meaningful classification [82].

Heterogeneity based on Pathology

Only two studies have performed neuropathological examination of the substantia nigra of patients with IPD to look for heterogeneity of pathology between different patient motor phenotypes, and both found higher neuronal loss in the substantia nigra of patients with marked akinesia and rigidity, than in those with predominant resting tremor [63, 71]. Both these studies also found that loss of neurons from the medial SNc is more often associated with dementia.

The selection of patients for a neuropathological examination post mortem may lead to an additional bias in these studies if the selection process is based on particularly severe or unusual disease features. These study results should ideally be checked for consistency within a representative cohort of PD brains.

Heterogeneity based on Genetics

Two gene mutations causing neuropathologically typical IPD have been identified in a small number of families [17, 65]. Screening IPD patients for these mutations has, however, not proven useful owing to their low frequency [17, 44]. Both of these mutations are inherited in an autosomal dominant fashion and families carrying them tend to have parkinsonian symptom onset at a young age and progress rapidly. Whether a patient with PD symptoms due to a confirmed genetic mutation should be considered "Idiopathic", again questions the precision and specificity of our pathological definition of IPD, but may be useful in understanding the mechanisms of neurodegeneration and Lewy body formation. The issue is further complicated following the description of a patient carrying one of these mutations and suffering from symptoms of parkinsonism, but having no Lewy bodies on neuropathological examination (cited in [27]).

Mutations in a gene on Chromosome 6, now known as the "parkin" gene lead to disease in an autosomal recessive fashion [41]. Pathological examinations of patients with mutations in this gene have shown an absence of Lewy bodies [58], suggesting that the pathological process differs from that of IPD. This gene has been found to be responsible for 77 % of patients with parkinsonism with an age of onset of 20 years or younger, but only 3 % of patients with an onset between 30 and 45 years [51]. The intracellular function of normal "parkin" protein as a ubiquitin ligase and a possible role for this enzyme in the formation of Lewy bodies, may explain the lack of Lewy bodies seen in patients with mutations in the "parkin" gene [75]. It may also be that it is the failure of this enzyme, which leads to intracellular protein accumulation and dopaminergic cell loss [26, 75].

A genetic element may also be important in some cases of "sporadic" disease. Inheritance of certain genes may inevitably lead to the clinical and pathological features of IPD, whereas other genes may require the exposure to environmental agents, or multiple other gene mutations before the disease can evolve [38]. Multiple studies have sought association between various genes and the much more common, apparently sporadic forms of the disease, finding little consistency between heterogeneous populations of patients [80].

Heterogeneity based on Aetiology

The results of 30 studies investigating environmental risk factors for IPD have recently been reviewed [43]. Rural residence, well water consumption, pesticide or herbicide exposure, various dietary factors, smoking and head injury have all been identified as potential risk factors in case control studies. Relationships between these risk factors and varying groups of patients have been inconsistent, raising the possibility that there is heterogeneity in risk from different exposures for different people. Four studies have, however, found no change in relative risk for environmental exposures calculated separately in young or old onset cases of IPD [7, 43, 78, 84] .

Two studies have described greater frequency of rural living [72, 82] or head trauma among young onset cases, but no variation in exposure level for subgroups based on motor phenotype [72]. Whether heterogeneity in exposure risk exists between phenotypic sub-groups requires further studies, especially given the recent experimental data on rotenone [2].

Heterogeneity based on Brain Imaging

Both positron emission tomography (PET) and single photon emission computerised tomography (SPECT) imaging are sensitive means of detecting impaired striatal dopaminergic function [5]. Although there have as yet been no clinico-pathological studies of IPD that have included imaging data, PET studies have lead to greater understanding of the anatomical dysfunction underlying bradykinesia, rest tremor and the development of dyskinesias and fluctuations [4]. Imaging studies have recently also highlighted the importance of sites outside the nigro-striatal system in the disease process [69]. There have also been limited imaging comparisons of subgroups of IPD on the basis of gender [39] and "parkin positive" status [30] however more detailed comparisons based on clinical phenotype, or other genetic and environmental risks remain to be performed.

Data Driven Classification of IPD

Classifications for diseases that are both useful and *objective* can also be achieved using statistical techniques known as "cluster analysis". These techniques seek to divide a set of patients into clusters, such that any patient belongs to one cluster only, and the complete set of clusters contains all the patients. Each cluster should ideally have internal cohesion and external isolation. Methods of cluster analysis are largely intended for generating rather than testing hypotheses [13]. The technique should be used with care, with awareness that the choice and number of variables selected for inclusion in a cluster analysis, as well as the number of clusters sought, can have profound effects on the results [13]. Clusters derived from the technique may be very valuable, but may also represent chance findings in a dataset, or may generate clusters on what is simply random variation in

measured variables. Clusters that are significantly different from each other on the basis of the variables included in the analysis are almost inevitable. Evidence for a meaningful clustering solution can be examined graphically or by comparing the clusters formed on the basis of other variables, which were not included in the analysis.

Cluster analysis has been applied to a case series of patients with IPD [25] with the formation of three subgroups of patients, a "motor only", a "motor and cognitive", and a "rapidly progressive" group. Not unexpectedly, these subgroups differed on the basis of the variables that were entered into the original clustering model. However, a few further differences were also found between these groups with respect to patient variables such as "postural instability" and "symptomatic orthostasis" that were not entered into the clustering model.

Any such classification derived through a cluster analysis requires repeat testing on further representative cohorts of patients of sufficient sample size, to ensure the validity and reliability of the clustering solution and its subsequent usefulness assessed for both clinician and / or scientist.

Discussion

There is some evidence that a classification based on phenotypic patterns of disease may be of some use for the clinician in predicting progression for different groups of patients with IPD. It is possible that age itself alters the expression of the disease although further clinical differences between a benign early onset group and a malignant late onset group persist even after adjustment for age at the time of assessment [37].

A classification is more likely to be of both clinical and scientific value if variation in clinical phenotype is accompanied by consistent pathological, aetiological or genetic evidence to support it. The possibility of diagnostic error in studies with only clinical data must also be stressed, since about 20 % of clinically diagnosed PD patients are found to have alternative diseases at autopsy [36]. When cases are restricted to those with pathological confirmation of disease, heterogeneity in young versus old subgroups of PD is restricted to greater nigral cell loss in the young onset cases in accordance with the longer disease duration [20]. The cellular morphology and frequency of Lewy bodies in the substantia nigra is identical in the young and old onset cases [20].

Currently, there is very little evidence derived from population-based studies on which to investigate heterogeneity and there are limited data from studies with neuropathologically confirmed disease. Further exploration of the heterogeneity of IPD can be conducted optimally using a population based cohort of cases with prospectively collected clinical and genetic data and with the ultimate, pathological confirmation of disease status being essential. Sensitivity of case detection can be maximised by being over-inclusive at the recruitment stage, and then refining the data using the neuropathological definition of IPD. Whether cluster analysis techniques can lead to objective and useful classifications of the disease requires further testing.

Acknowledgements TF is a Clinical Training Fellow in Epidemiology. The authors' own work is supported by the Wellcome Trust, the Medical Research Council, the Parkinson's Disease Society, and a Raymond and Beverley Sackler PhD Studentship

References

1. Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F (1973) Brain dopamine and the syndromes of Parkinson and Huntington. Clinical, morphological and neurochemical correlations. J Neurol Sci 20: 415–455
2. Betarbet R, Sherer TB, MacKenzie G, Garcia-Osuna M, Panov AV, Greenamyre JT (2000) Chronic systemic pesticide exposure reproduces features of Parkinson's disease. Nat Neurosci 3: 1301–1306
3. Birkmayer W, Riederer P, Youdim BH (1979) Distinction between benign and malignant type of Parkinson's disease. Clin Neurol Neurosurg 81: 158–164
4. Brooks DJ (1999) Functional imaging of Parkinson's disease: is it possible to detect brain areas for specific symptoms? J Neural Transm Suppl 56: 139–153
5. Brooks DJ (2000) Morphological and functional imaging studies on the diagnosis and progression of Parkinson's disease. J Neurol 247 Suppl 2: II11-II18
6. Brown RG, Marsden CD (1984) How common is dementia in Parkinson's disease? Lancet 2: 1262–1265
7. Butterfield PG (1996) Environment: seeking clues to Parkinson's disease. Reflections 22: 14–15
8. Diamond SG, Markham CH, Hoehn MM, McDowell FH, Muenter MD (1989) Effect of age at onset on progression and mortality in Parkinson's disease. Neurology 39: 1187–1190
9. Ditter SM, Mirra SS (1987) Neuropathologic and clinical features of Parkinson's disease in Alzheimer's disease patients. Neurology 37: 754–760
10. Dubois B, Pillon B, Sternic N, Lhermitte F, Agid Y (1990) Age-induced cognitive disturbances in Parkinson's disease. Neurology 40: 38–41
11. Ebmeier KP, Calder SA, Crawford JR, Stewart L, Besson JA, Mutch WJ (1990) Clinical features predicting dementia in idiopathic Parkinson's disease: a follow-up study. Neurology 40: 1222–1224
12. Elizan TS, Sroka H, Maker H, Smith H, Yahr MD (1986) Dementia in idiopathic Parkinson's disease. Variables associated with its occurrence in 203 patients. J Neural Transm 65: 285–302
13. Everitt BS (1993) Cluster Analysis. Edward Arnold. New York
14. Fearnley JM, Lees AJ (1991) Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain 114: 2283–2301
15. Forno LS (1969) Concentric hyalin intraneuronal inclusions of Lewy type in the brains of elderly persons (50 incidental cases): relationship to parkinsonism. J Am Geriatr Soc 17: 557–575

16. Forno LS (1996) Neuropathology of Parkinson's disease. J Neuropathol Exp Neurol 55: 259–272
17. Gasser T, Muller MB, Wszolek ZK, Oehlmann R, Calne DB, Bonifati V, Bereznai B, Fabrizio E, Vieregge P, Horstmann RD (1998) A susceptibility locus for Parkinson's disease maps to chromosome 2p13. Nat Genet 18: 262–265
18. Gearing M, Olson DA, Watts RL, Mirra SS (1994) Progressive supranuclear palsy: neuropathologic and clinical heterogeneity. Neurology 44: 1015–1024
19. Gershanik OS, Leist A (1987) Juvenile onset Parkinson's disease. Adv Neurol 45: 213–216
20. Gibb WR, Lees AJ (1988) A comparison of clinical and pathological features of young- and old-onset Parkinson's disease. Neurology 38: 1402–1406
21. Gibb WR, Lees AJ (1988) The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 51: 745–752
22. Goetz CG, Tanner CM, Stebbins GT, Buchman AS (1988) Risk factors for progression in Parkinson's disease. Neurology 38: 1841–1844
23. Golbe LI (1993) Risk factors in young-onset Parkinson's disease. Neurology 43: 1641–1643
24. Gomez TE, Ingraham AO, Irizarry MC, Hyman BT (1998) Dementia with Lewy bodies. J Am Geriatr Soc 46: 1449–1458
25. Graham JM, Sagar HJ (1999) A data-driven approach to the study of heterogeneity in idiopathic Parkinson's disease: identification of three distinct subtypes. Mov Disord 14: 10–20
26. Haass C, Kahle PJ (2001) Neuroscience. Parkin and its substrates. Science 293: 224–225
27. Hayashi S, Wakabayashi K, Ishikawa A (2000) An Autopsy case of Autosomal-Recessive Juvenile Parkinsonism with a Homozygous Exon 4 Deletion in the Parkin gene. Mov Disord 15: 884–888
28. Hershey LA, Feldman BJ, Kim KY, Commichau C, Lichter DG (1991) Tremor at onset. Predictor of cognitive and motor outcome in Parkinson's disease? Arch Neurol 48: 1049–1051
29. Hietanen M, Teravainen H (1988) The effect of age of disease onset on neuropsychological performance in Parkinson's disease. J Neurol Neurosurg Psychiatry 51: 244–249
30. Hilker R, Klein C, Ghaemi M, Kis B, Strotmann T, Ozelius LJ, Lenz O, Vieregge P, Herholz K, Heiss WD, Pramstaller PP (2001) Positron emission tomographic analysis of the nigrostriatal dopaminergic system in familial parkinsonism associated with mutations in the parkin gene. Ann Neurol 49: 367–376
31. Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression and mortality. Neurology 17: 427–442
32. Huber SJ, Paulson GW, Shuttleworth EC (1988) Relationship of motor symptoms, intellectual impairment, and depression in Parkinson's disease. J Neurol Neurosurg Psychiatry 51: 855–858
33. Hughes AJ (1997) Clinicopathological aspects of Parkinson's disease. Eur Neurol 38 Suppl 2: 13–20
34. Hughes AJ, Ben Shlomo Y, Daniel SE, Lees AJ (1992) What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. Neurology 42: 1142–1146
35. Hughes AJ, Daniel SE, Blankson S, Lees AJ (1993) A clinicopathologic study of 100 cases of Parkinson's disease. Arch Neurol 50: 140–148
36. Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 55: 181–184
37. Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golbe L, Huber S, Koller W, Olanow C, Shoulson I, et al. (1990) Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. Neurology 40: 1529–1534
38. Johnson WG, Hodge SE, Duvoisin R (1990) Twin studies and the genetics of Parkinson's disease–a reappraisal. Mov Disord 5: 187–194
39. Kaasinen V, Nurmi E, Bruck A, Eskola O, Bergman J, Solin O, Rinne JO (2001) Increased frontal [(18)F]fluorodopa uptake in early Parkinson's disease: sex differences in the prefrontal cortex. Brain 124: 1125–1130
40. Kidron D, Melamed E (1987) Forms of dystonia in patients with Parkinson's disease. Neurology 37: 1009–1011
41. Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, Yokochi M, Mizuno Y, Shimizu N (1998) Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature 392: 605–608
42. Kostic V, Przedborski S, Flaster E, Sternic N (1991) Early development of levodopa-induced dyskinesias and response fluctuations in young-onset Parkinson's disease. Neurology 41: 202–205
43. Kuopio AM, Marttila RJ, Helenius H, Rinne UK (1999) Environmental risk factors in Parkinson's disease. Mov Disord 14: 928–939
44. Langston JW (1998) Epidemiology versus genetics in Parkinson's disease: progress in resolving an age-old debate. Ann Neurol 44: S45-S52
45. Lee CS, Schulzer M, Mak EK, Snow BJ, Tsui JK, Calne S, Hammerstad J, Calne DB (1994) Clinical observations on the rate of progression of idiopathic parkinsonism. Brain 117: 501–507
46. Lees AJ, Smith E (1983) Cognitive deficits in the early stages of Parkinson's disease. Brain 106: 257–270
47. Lennox GG, Lowe JS (1997) Dementia with Lewy bodies. Baillieres Clin Neurol 6: 147–166
48. Lesser RP, Fahn S, Snider SR, Cote LJ, Isgreen WP, Barrett RE (1979) Analysis of the clinical problems in parkinsonism and the complications of long-term levodopa therapy. Neurology 29: 1253–1260
49. Lieberman A, Dziatolowski M, Kupersmith M, Serby M, Goodgold A, Korein J, Goldstein M (1979) Dementia in Parkinson Disease. Ann Neurol 6: 355–359
50. Lieberman AN (1974) Parkinson's disease: a clinical review. Am J Med Sci 267: 66–80
51. Lucking CB, Durr A, Bonifati V, Vaughan J, De Michele G, Gasser T, Harhangi BS, Meco G, Denefle P, Wood NW, Agid Y, Brice A (2000) Association between early-onset Parkinson's disease and mutations in the parkin gene. French Parkinson's Disease Genetics Study Group. N Engl J Med 342: 1560–1567
52. Marttila RJ, Rinne UK (1976) Dementia in Parkinson's disease. Acta Neurol Scand 54: 431–441
53. Marttila RJ, Rinne UK (1976) Epidemiology of Parkinson's disease in Finland. Acta Neurol Scand 53: 81–102
54. Marttila RJ, Rinne UK (1977) Disability and progression in Parkinson's disease. Acta Neurol Scand 56: 159–169
55. Mayeux R, Denaro J, Hemenegildo N, Marder K, Tang MX, Cote LJ, Stern Y (1992) A population-based investigation of Parkinson's disease with and without dementia. Relationship to age and gender. Arch Neurol 49: 492–497
56. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, Salmon DP, Lowe J, Mirra SS, Byrne EJ, Lennox G, Quinn NP, Edwardson JA, Ince PG, Bergeron C, Burns A, Miller BL, Lovestone S, Collerton D, Jansen EN, Ballard C, de Vos RA, Wilcock GK, Jellinger KA, Perry RH (1996) Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 47: 1113–1124
57. Mjones H (1949) Paralysis agitans; clinical and genetic study. Acta Psychiat Neurol 54 (suppl): 1–194

58. Mori H, Kondo T, Yokochi M, Matsumine H, Nakagawa HY, Miyake T, Suda K, Mizuno Y (1998) Pathologic and biochemical studies of juvenile parkinsonism linked to chromosome 6q. Neurology 51: 890–892
59. Mortimer JA, Jun SP, Kuskowski MA, Webster DD (1987) Subtypes of Parkinson's disease defined by intellectual impairment. J Neural Transm Suppl 24: 101–104
60. Mortimer JA, Pirozzolo FJ, Hansch EC, Webster DD (1982) Relationship of motor symptoms to intellectual deficits in Parkinson disease. Neurology 32: 133–137
61. Oda M, Akagawa N, Tabuchi Y, Tanabe H (1978) A sporadic juvenile case of the amyotrophic lateral sclerosis with neuronal intracytoplasmic inclusions. Acta Neuropathol (Berl) 44: 211–216
62. Owen AM, James M, Leigh PN, Summers BA, Marsden CD, Quinn NP, Lange KW, Robbins TW (1992) Fronto-striatal cognitive deficits at different stages of Parkinson's disease. Brain 115: 1727–1751
63. Paulus W, Jellinger K (1991) The neuropathologic basis of different clinical subgroups of Parkinson's disease. J Neuropathol Exp Neurol 50: 743–755
64. Pillon B, Dubois B, Cusimano G, Bonnet AM, Lhermitte F, Agid Y (1989) Does cognitive impairment in Parkinson's disease result from non-dopaminergic lesions? J Neurol Neurosurg Psychiatry 52: 201–206
65. Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, Pike B, Root H, Rubenstein J, Boyer R, Stenroos ES, Chandrasekharappa S, Athanassiadou A, Papapetropoulos T, Johnson WG, Lazzarini AM, Duvoisin RC, Di Iorio G, Golbe LI, Nussbaum RL (1997) Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science 276: 2045–2047
66. Portin R, Rinne UK (1987) Predictive factors for cognitive deterioration and dementia in Parkinson's disease. Adv Neurol 45: 413–416
67. Quinn N, Critchley P, Marsden CD (1987) Young onset Parkinson's disease. Mov Disord 2: 73–91
68. Rajput AH, Rozdilsky B, Rajput A (1991) Accuracy of clinical diagnosis in parkinsonism–a prospective study. Can J Neurol Sci 18: 275–278
69. Rakshi JS, Uema T, Ito K, Bailey DL, Morrish PK, Ashburner J, Dagher A, Jenkins IH, Friston KJ, Brooks DJ (1999) Frontal, midbrain and striatal dopaminergic function in early and advanced Parkinson's disease A 3D [(18)F]dopa-PET study. Brain 122: 1637–1650
70. Reid WG, Broe GA, Hely MA, Morris JG, Williamson PM, O'Sullivan DJ, Rail D, Genge S, Moss NG (1989) The neuropsychology of de novo patients with idiopathic Parkinson's disease: the effects of age of onset. Int J Neurosci 48: 205–217
71. Rinne JO, Rummukainen J, Paljarvi L, Rinne UK (1989) Dementia in Parkinson's disease is related to neuronal loss in the medial substantia nigra. Ann Neurol 26: 47–50
72. Rohl A, Friedrich HJ, Ulm G, Vieregge P (1994) The relevance and clinical subtypes for disease course, family history and epidemiological variables in Parkinson's disease. Eur J Neurol 1: 65–72
73. Schwab RS, England ACJ, Peterson EL (1959) Akinesia in Parkinson's Disease. Neurology 9: 65–72
74. Scott RM, Brody JA (1971) Benign early onset of Parkinson's disease: a syndrome distinct from classic postencephalitic parkinsonism. Neurology 21: 366–368
75. Shimura H, Schlossmacher MG, Hattori N, Frosch MP, Trockenbacher A, Schneider R, Mizuno Y, Kosik KS, Selkoe DJ (2001) Ubiquitination of a new form of alpha-synuclein by parkin from human brain: implications for Parkinson's disease. Science 293: 263–269
76. Sokal RR, Sneath PHA (1963) Principles of Numeric Taxonomy. WH Freeman & Co. London
77. Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M (1997) Alpha-synuclein in Lewy bodies [letter]. Nature 388: 839–840
78. Stern M, Dulaney E, Gruber SB, Golbe L, Bergen M, Hurtig H, Gollomp S, Stolley P (1991) The epidemiology of Parkinson's disease. A case-control study of young-onset and old-onset patients. Arch Neurol 48: 903–907
79. Stern Y, Marder K, Tang MX, Mayeux R (1993) Antecedent clinical features associated with dementia in Parkinson's disease. Neurology 43: 1690–1692
80. Tan EK, Khajavi M, Thornby JI, Nagamitsu S, Jankovic J, Ashizawa T (2000) Variability and validity of polymorphism association studies in Parkinson's disease. Neurology 55: 533–538
81. Tanner CM (1992) Epidemiology of Parkinson's disease. Neurol Clin 10: 317–329
82. Tanner CM, Chen B, Wang WZ, Peng ML, Liu ZL, Liang XL, Kao LC, Gilley DW, Schoenberg BS (1987) Environmental factors in the etiology of Parkinson's disease. Can J Neurol Sci 14: 419–423
83. Tanner CM, Kinori I, Goetz CG, Carvey PM, Klawans HL (1985) Clinical course in Parkinson's disease: relationship to age at onset. J Neurol 232(suppl): 25
84. Tzourio C, Rocca WA, Breteler MM, Baldereschi M, Dartigues JF, Lopez PS, Manubens-Bertran JM, Alperovitch A (1997) Smoking and Parkinson's disease. An age-dependent risk effect? The EUROPARKINSON Study Group. Neurology 49: 1267–1272
85. Ward CD, Gibb WR (1990) Research diagnostic criteria for Parkinson's disease. Adv Neurol 53: 245–249
86. Yoshita M, Taki J, Yamada M (2001) A clinical role for [123I]MIBG myocardial scintigraphy in the distinction between dementia of the Alzheimer's type and dementia with Lewy bodies. J Neurol Neurosurg Psychiatry – in press.
87. Zetusky WJ, Jankovic J, Pirozzolo FJ (1985) The heterogeneity of Parkinson's disease: clinical and prognostic implications. Neurology 35: 522–526