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RESEARCH ARTICLE

Etiologies of Parkinsonism in a Century-Long Autopsy-Based Cohort

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Abstract

We investigated the distribution of different etiologies underlying Parkinsonism in a hospital-based autopsy collection, studied the demographic data and evaluated diagnostic accuracy using histopathological examination as the gold standard. Out of a total of 9359 consecutive autopsy cases collected between 1914 and 2010, we identified 261 individuals who carried a clinical diagnosis of a Parkinsonian syndrome at death. A detailed neuropathological examination revealed idiopathic Parkinson's disease (PD) in 62.2%, progressive supranuclear palsy (PSP) in 4.2%, multiple system atrophy (MSA) in 2.3%, corticobasal degeneration (CBD) in 1.2%, postencephalitic Parkinsonism (PEP) in 2.7%, vascular Parkinsonism (VaP) in 8.8% and Alzheimer-type pathology (ATP) of the substantia nigra in 8%. The diagnostic accuracy of PD in our cohort was lower (71.2%) than those reported in previous studies, although it tended to increase during the last decades up to 85.7%. Of particular interest, we found that PD, while being the most frequent cause of Parkinsonism, was greatly overdiagnosed, with VaP and ATP being the most frequent confounding conditions.

INTRODUCTION

Parkinsonism is a clinical syndrome characterized by the presence of bradykinesia variably associated with resting tremor, rigidity and postural instability. The most common underlying pathologies include neurodegenerative disorders such as idiopathic Parkinson's disease (PD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). Other etiologies are vascular, genetic, toxic, postencephalitic or drug-related conditions [see for review Ince *et al* (20)]. The differential diagnosis is often challenging, especially in the early phase of the disease. An accurate clinical diagnosis, however, is essential for assessing the prognosis, for choosing the adequate treatment or for quality cohort selection in clinical trials. Misdiagnoses, in fact, are not infrequent, though some improvement in diagnostic accuracy has been observed during the last years (14, 18, 21, 30, 37). In most of these studies, however, patients were followed at movement disorders clinics, thus the observed statistics may not be representative of Parkinsonian syndromes routinely managed in the community or by general neurologists.

The objective of our retrospective study was to investigate the distribution of the different etiologies of Parkinsonism in a large, hospital-based autopsy cohort and to evaluate the diagnostic accuracy of PD.

METHODS

Patients

Our study material covers the period between 1914 and 2010, of the Geriatric and Psychiatric Departments of the University Hospitals of Geneva. We reexamined all autopsy cases (n = 9359), in which any form of a Parkinsonian disorder had been clinically diagnosed, such as PD, vascular Parkinsonism (VaP), postencephalitic Parkinsonism (PEP), MSA, PSP, CBD and drug-induced Parkinsonism (DIP). The clinical diagnoses had been established by neurologists, psychiatrists or specialists of internal medicine. In order to assess the accuracy of the original clinical diagnoses, we used those as they appeared in the patients' final medical record at autopsy. Cases with "Parkinsonian gait," "Parkinsonian tremor" or "akinetic-rigid syndrome," but without the explicit mention of "PD," have been categorized as "unspecified Parkinsonian syndrome" (UPS). There was no suspected or diagnosed genetic Parkinsonian disorder in our series. Within the group of clinical PD, cases with or without dementia were not distinguished and both were classified as PD. Clinical diagnoses of striato-nigral degeneration, olivopontocerebellar atrophy and Shy–Drager syndrome were categorized as MSA. Additionally, age at death, gender, medical history of encephalitis or use of dopamine receptor

blocking agents and—when available—disease duration, main comorbidities and cause of death were noted.

Neuropathological study

Brains were fixed at autopsy in 15% formaldehyde for 4 weeks. In all cases, the mesencephalon was embedded in paraffin for neuropathological diagnosis. Brains were then stored in 5% formaldehyde for years or decades. For the present study, the original paraffin blocs of the mesencephalon, including the pars compacta of the substantia nigra (SN), were cut and stained with HE and antibodies anti-α-synuclein (AS—Sigma, St. Louis, MO, USA; 1/1'000), anti-tau (Pierce Biotechnology, Rockford, IL, USA; 1/1'000) and anti-ubiquitin (Sigma; 1/100). On the HE-stained slides, the degree of neuronal loss was assessed using a semiquantitative scale (absent, mild, moderate, severe).

In the presence of AS-immunoreactive classical brainstem-type Lewy bodies (LB), the diagnosis of idiopathic PD was retained as the origin of Parkinsonism, even if tau-immunoreactive inclusions coexisted. Moreover, to define the different subtypes (brainstem, limbic or neocortical) of Lewy body disease (LBD), the five cortical regions, proposed by the first Consortium on Dementia with Lewy bodies, were taken and examined using anti-AS immunohistochemistry (33).

To identify other neurodegenerative causes, in the absence of LBs, the neuropathological examination was extended to the following brain regions: the anterior hippocampus and the inferior temporal cortex, the peri-rolandic area (posterior frontal and anterior parietal gyri), the basal ganglia including the caudate nucleus, the putamen and the globus pallidus, the thalamus, the subthalamic nucleus, the pons at the level of the locus coeruleus (LC), the medulla oblongata at the level of the cranial nerve nuclei X and XII, the inferior olivary nucleus and the intermediate reticular zone, and the dentate nucleus of the cerebellum. Histological slides were stained with HE and immunohistochemistry, using the following antibodies: anti-tau AT8, anti-α-synuclein, anti-ubiquitin (see above) and anti-amyloid 4G8 (Signet Laboratories, Dedham, MA, USA; 1/2'000). In addition, for all cases the severity of cortical tau pathology was determined according to the Braak staging (5).

For the neuropathological diagnosis of CBD, PSP and MSA, we applied the most widely used neuropathological criteria (10, 11, 20, 28, 29). We retained "Alzheimer-type pathology" (ATP) as the origin of Parkinsonism when significant tau pathology and neuronal loss were present in the SN (15, 16) with Braak stage for neurofibrillary tangles (NFTs) three or more, after exclusion of any other etiology (5).

PEP was the neuropathological diagnosis when encephalitis, following the 1918 Spanish flu epidemics, was reported in the medical records and the SN showed widespread NFTs accompanied by neuronal loss and astrocytosis (20).

All macroscopic and histologic vascular lesions were noted. We retained VaP, in accordance with previously used criteria, in the absence of AS or tau inclusions, when a severe lacunar state was present in the basal ganglia or in the periventricular white matter or a vascular lesion in the SN with contralateral hemiparkinsonism (19, 23, 32, 45). We concluded DIP—after the exclusion of other etiologies—when the Parkinsonian syndrome appeared in relation to a documented treatment by a dopamine receptor-blocking drug.

The Ethics Committee of the University Hospitals of Geneva approved the study.

RESULTS

We found 261 cases out of 9359 autopsies, with a clinical diagnosis of a Parkinsonian syndrome. The vast majority (79.8%) carried a diagnosis of PD; the distribution of the other clinical diagnoses is shown in Table 1. There were 14 cases out of 20 in the UPS group dated before 1980. As expected, clinical diagnoses of PSP, MSA and CBD occurred only after the late 1960s, that is, after the princeps description of these disease entities.

In 74 out of the 126 psychiatric cases, autopsies were limited to the brain and in 66 cases somatic comorbidities could not be reliably determined in medical records. In the group of subjects

Table 1. Clinical diagnoses and distribution of the underlying pathologies. Abbreviations: ATP = Alzheimer-type pathology; CBD = corticobasal degeneration; DIP = drug-induced Parkinsonism; MSA = multiple system atrophy; PD = idiopathic Parkinson's disease; PEP = postencephalitic Parkinsonism; PSP = progressive supranuclear palsy; UPS = unspecified Parkinsonian syndrome; VaP = vascular Parkinsonism.

Clinical diagnosis	Number of cases	Neuropathological diagnosis
PD	209	148 PD
		17 no specific lesion (5 DIP, 2 neuronal loss, 10 no etiology)
		16 VaP
		15 ATP
		6 PSP
		2 MSA
		2 CBD
		1 PEP
		1 metastasis
		1 abscess
UPS	20	9 PD
		5 ATP
		3 no specific lesion (3 DIP)
		2 VaP
		1 PSP
VaP	12	4 no specific lesion (2 DIP, 2 no etiology)
		3 PD
		3 VaP
		1 MSA
		1 PSP
PEP	7	6 PEP
		1 PD
MSA	4	2 MSA
		2 VaP
PSP	4	3 PSP
		1 PD
CBD	2	1 CBD
		1 MSA
DIP	3	1 PD
		1 ATP
		1 no specific lesion (1 DIP)

from the geriatric department (135 cases), all but two had a full post-mortem study. This population was characterized by multiple comorbidities, of which the most frequent were cardiac pathologies (n = 85 cases), followed by stroke (34), malignancies (34), pulmonary diseases (32), arterial hypertension (20), renal failure (17) and diabetes (15).

In 185 cases, where the results of a full autopsy were available, the causes of death were the following: bronchopneumonia in 107 cases including 35 due to bronchoaspiration. Fifty-eight patients died because of cardiac failure, 20 after myocardial infarction and 12 with acute pulmonary edema. Other causes were pulmonary embolism (17 cases), sepsis (13 cases), respiratory insufficiency (4 cases), gastrointestinal hemorrhage and acute stroke (3 cases each), malignancies (3 cases), tuberculosis, acute renal insufficiency and endocarditis (1 case each).

The distribution of all neuropathological diagnoses is summarized in Table 2, together with the available demographic data of each neuropathological group. PD was by far the most frequent etiology (62.2%), yet not matching the rate of clinical diagnoses. In the group of 163 neuropathologically proven PD cases, all but 18 showed at least one LB in one cortical region. The distribution of the severity of cortical LB pathology in the remaining 145 cases was the following: 16 cases corresponded to brainstem type, 67 to limbic and 62 to neocortical type of LBD.

Other neurodegenerative causes were rare: PSP 4.2%, MSA 2.3% and CBD 1.2% of the cohort. PEP was found in seven cases; the last case was autopsied in 1962. Twenty-three cases (8.8%) met the pathological criteria of VaP. ATP was retained as causative in 21 cases (8.0%), including 4 cases with Braak stage III, 3 with stage IV, 10 with stage V and 4 with stage VI. In one case, metastases of a pulmonary carcinoma, and in another, multiple cerebral abscesses, involved the basal ganglia without any alternative pathology.

In 25 cases (9.5%) no pathognomonic lesion was found in the SN. In two of them, the SN displayed a moderate to severe neuronal loss, without abnormal protein inclusions, corresponding to pure nigral atrophy, which is consistent with PARK2 for example, yet this hypothesis cannot be confirmed in the absence of genetic analysis. In the remaining 23 cases, the SN showed strictly normal histology. In 11 cases out of them, a drug-induced mechanism appeared likely because of a long-lasting neuroleptic treatment for psychiatric condition. Finally, no cause of Parkinsonism could be identified in 12 cases (4.5%), in spite of a detailed examination of the brain including the cerebellum.

Mean age at death was 79.3 years. The women/men ratio was 0.93 (126/136). A slightly older age at death was found in the VaP group (81.3 years), a much younger in the MSA (65 years) and even younger in the PEP group (49.4 years). During the 95 years period that the collection spans, a slight continuous increase of age at death can be seen in the PD group: between 1914 and 1959—that is, before levodopa became available to patients—it was 74.7 years, whereas between 2000 and 2010, it raised to 81.4 years. Disease duration was available in 83 cases; for statistical analysis, we only included groups containing at least five cases (Table 2). The longest mean duration was observed in PEP (17.8 years); the shortest in MSA (4.0 years) and VaP (4.6 years).

Comparing clinical diagnoses with neuropathological findings as the diagnostic gold standard, the overall diagnostic accuracy in our sample was of 63.4%. For PD, it was of 71.2% for the entire study period, 70.4% for the period before 1968, 76.8% between 1969 and 2010, and 85.7% in the last decade (2000–2010). A diagnosis of PD carried a sensitivity of 90.8% (148/163) on the entire collection. Clinical misdiagnoses included nine UPS, one PEP, one PSP, three VaP and one DIP (Table 1). The clinical diagnosis was correct in 3 of 4 suspected PSP cases (75%), whereas from the 11 pathologically confirmed PSP cases, only 3 had been diagnosed in life, giving a diagnostic sensitivity of 27.3%. (6 cases were diagnosed as PD, 1 as UPS and 1 as VaP). The clinical diagnosis of MSA was correct in two cases out of four. From the six pathologically confirmed cases, only two had been diagnosed clinically as MSA, two as PD, one as VaP and one as CBD. There were six out of seven cases of PEP correctly recognized clinically

Table 2. Neuropathological diagnoses and corresponding demographic data. Abbreviations: ATP = Alzheimer-type pathology; CBD = corticobasal degeneration; MSA = multiple system atrophy; PD = idiopathic Parkinson's disease; PEP = postencephalitic Parkinsonism; PSP = progressive supranuclear palsy; VaP = vascular Parkinsonism; W/M = women/men.

Neuropathological diagnosis	Number of cases	%	Mean age at death ± SD (age range)	W/M	Mean duration of the disease*
PD	163	62.2	79.6 ± 7.4 (56–96)	79/84	7.6 ± 6.1 (44)
PSP	11	4.2	79.8 ± 8.5 (60–88)	3/8	
MSA	6	2.3	65.0 ± 4.8 (58–73)	3/3	
CBD	3	1.2	74.3 ± 6.5 (68–81)	0/3	
PEP	7	2.7	49.4 ± 14.7 (32–70)	5/2	17.8 ± 9.2 (5)
VaP	23	8.8	81.3 ± 7.6 (67–98)	9/14	4.6 ± 5.0 (8)
ATP	21	8.0	84.9 ± 5.3 (73–93)	11/10	6.1 ± 2.0 (8)
No specific lesion	25	9.5	82.4 ± 6.0 (65–91)	15/10	
Moderate-severe neuronal loss	2	0.8	79 (79)	1/1	
Drug-induced Parkinsonism	11	4.2	81.8 (65–91)	5/6	
No etiology	12	4.5	83.5 (75–90)	9/3	
Metastasis	1	0.4	80	1/0	
Cerebral abscess	1	0.4	85	1/0	
Total	261	100	79.3 (32–98)	125/136	

*In brackets, the number of cases with available data; further explications in the text.

(85.7%). One case proved to be PD, and conversely; one suspected PD turned out to be PEP. The lowest accuracy among the clinical diagnoses was that of VaP (33.3%, 4/12). On the other hand, from the 23 pathologically confirmed VaP cases, only 3 had been diagnosed correctly in life, 16 as PD, 2 as MSA and 2 as UPS.

DISCUSSION

Distribution of neuropathological etiologies

Our study illustrates the distribution of the various types of Parkinsonian syndrome over a nearly century-long period in a hospital-based population according to both clinical and autopsy-derived neuropathological data. The prevalence of clinically significant Parkinsonism in this cohort was 2.8%, a figure that is consistent with the known frequency of Parkinsonism in the elderly population (8, 9). The vast majority of these cases were of neurodegenerative origin, by far the most common cause being PD. In accordance with previous findings (9, 16), a slight male preponderance was present in our PD population. The prevalence of PD (62.2%) was higher than that reported by Hughes *et al* (55%) and by Bower *et al* (42%) in their series issued from movement disorders clinics (4, 18), and lower than Jellinger's findings in a large autopsy series collected between 1957 and 2006 (73%–82%) (22). The prevalence of MSA (2.3%) and of PSP (4.2%) was lower than that published by Hughes *et al* (11% and 13%, respectively) (18) and by Bower *et al* (7.7% and 17%, respectively) (4), and similar to what Jellinger found (22). This difference could be explained by the fact that atypical cases are more likely to undergo autopsy (4). In fact, our series did not originate from a movement disorders clinic and was probably free from this selection bias. The lower prevalence of MSA in our series may also be explained by our—mainly—geriatric and psychogeriatric populations, as MSA patients are usually younger at disease onset and death (mean age at death in our series: 65 years). It is probably the result of lacking clinical data because of the retrospective manner of our study, that in 12 cases out of 261 we could not identify any etiology of Parkinsonism. Among these cases, some might have been drug induced. Indeed, the prevalence of DIP (4.2%) in our cohort is lower than expected according to population-based surveys, which estimate its prevalence at 10%–20% of all the cases of Parkinsonian syndromes, but in geriatric and psychiatric cohort it may even be higher (31).

An unexpected finding was the high number of cases (8%) in which the only neuropathological abnormalities were ATP changes, significantly affecting the brainstem and, particularly, the SN. This prevalence is higher than usually reported (3%–6%) in earlier studies [for review, see Jellinger (22)], although, in more recent series collected by Jellinger between 1989 and 2000 and between 2001 and 2006, and by Bower *et al*, 7.2%, 8% and 7.6% have been reported, respectively (4, 22). The relatively high prevalence of ATP in our cohort may be because of the higher prevalence of AD patients (15.3%) (27) in our autopsy population compared with 7%–12% reported by most autopsy series among subjects older than 65 years (2, 3, 12, 24, 25, 34, 36, 39, 42). The development of a Parkinsonian features during the course of AD is well known and LB pathology is not always associated with it. Neuronal loss of increasing severity and accompanying tau pathology can be observed in the SN, but such cases have been considered exceptional for a long time (13). Although other authors attribute the Parkinsonian syndrome to extranigral lesions or to an involvement of mesocortical dopaminergic pathways (6, 35), our results support nigral tau pathology as a major determinant of ATP-related Parkinsonism.

Similarly unexpected, we found a relatively high prevalence (8.8%) of neuropathologically confirmed VaP cases, as compared with the 3%–6% commonly reported in the literature, which could be partially explained by a large proportion of geriatric cases in our cohort (23). However, Bower and collaborators reported even higher prevalence (12.5%) in their study (4).

Accuracy of clinical diagnostic

When comparing clinical with neuropathological diagnosis in each individual case, we found a relatively low level of concordance in general (63.4%), yet it varied considerably from one pathology to another. In fact, diagnostic accuracy of PD in our cohort was lower (71.2%) than those reported in previous studies (14, 21), although it tended to increase during the study period up to 85.7% between 2000 and 2010. This improvement in diagnostic performance corresponds to data published earlier. In the early 1990s, Rajput *et al* reported a 65% diagnostic accuracy (37). Hughes *et al* reported 76% in 1992 (15) and more than 90% in 2001 and 2002 (17, 18). The improvement probably started with the recognition of the efficacy of levodopa in 1967 (7) and the description of PSP, CBD, Shy–Drager syndrome and of striatonigral degeneration around the same time (1, 38, 41, 43). This trend is also reflected by our data, when comparing the accuracy before 1968 (70.4%) and after 1968 (76.8%) in our series. Further improvements of diagnostic capacities were probably related to the establishment of stringent diagnostic criteria, the development of ancillary tests, in particular structural and metabolic neuroimaging, and an increasing tendency to refer Parkinsonian patients to movement disorders centers. The positive predictive value of a clinical diagnosis of PD made by movement disorders specialists can be very high (98%) (18), whereas it is usually lower (84.7%) in the community (40). The diagnostic sensitivity for MSA and PSP in movement disorders centers varies around 85.7% and 80%, respectively, in the series of Hughes *et al* (18), and 88% and 84% in the series by Williams and Lees (44). The sensitivity of a clinical diagnosis of PSP was very low in our series (18%), although 10 out of our 11 PSP cases occurred after 1965, that is, after the description of this pathology (43).

We observed an inconsistent prevalence of PD in the clinically diagnosed (79.8%) compared with the autopsy-based (62.2%) populations with a Parkinsonian syndrome, suggesting that PD is greatly overdiagnosed in living patients. A variety of conditions may mimic PD and the usual diagnostic criteria for PD (eg, the UKPDS Brain Bank criteria) (15) are probably not reliably applied by nonspecialists. Schrag *et al* (40) estimated that at least 15% of patients with a diagnosis of PD in the population do not fulfill strict clinical criteria for the disease.

In our series, the lowest accuracy belonged to VaP, as most VaP cases were clinically diagnosed as PD. Kalra *et al* (26) reviewed systemically all studies that might distinguish VaP from idiopathic PD. They concluded that there are no specific clinical features or diagnostic tests that confidently differentiate VaP from PD and they urged further work on developing consensus criteria for this

disease entity. Our study supports this view, as about 8% of clinically diagnosed PD turned out to have VaP at autopsy, and VaP was one of the most common conditions mimicking PD in our cohort. Bower *et al* (4) also found a high clinical diagnostic inaccuracy of VaP as none of the five VaP cases of their series had been correctly diagnosed in life. Interestingly, two cases of suspected MSA turned out to be VaP and conversely, two (out of the six) suspected VaP were finally diagnosed as MSA.

Some limitations should, however, be considered when interpreting our data. The collection extends across more than 95 years during which PEP disappeared, diagnostic criteria for PD evolved, and new disease entities were defined including CBD and PSP in the late 1960s. Due to the retrospective nature of our study, information extracted from medical records was of variable quality and about 20% of the cases had limited clinical data, precluding more detailed clinicopathological correlations to be established. We should also take into account the selection bias related to our hospital-based autopsy collection with a higher proportion of geriatric and demented patients as well as of other psychiatric conditions. Finally, we should be cautious when interpreting statistical data related to atypical Parkinsonisms (MSA, PSP and CBD) because of the relatively low number of such cases in our series.

Despite these limitations, our results confirm existing data from previous studies and, perhaps more importantly, offers new insights into the distribution of the diverse etiologies and diagnostic accuracy of Parkinsonian syndromes. It strongly suggests that PD, while being the more frequent cause, is overdiagnosed in patients with Parkinsonism and that VaP and ATP, rather than other degenerative atypical Parkinsonian syndromes, may be the most common confounding conditions. These results should prompt physicians to mitigate their diagnostic confidence in some cases.

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COMPETING INTEREST

The authors declare that they have no conflicting interest related to this article.

REFERENCES

1. Adams R, Van Bogaert L, Van Der Eecken H (1961) [Nigro-striate and cerebello-nigro-striate degeneration. (Clinical uniqueness and pathological variability of presenile degeneration of the extrapyramidal rigidity type]. *Psychiatr Neurol (Basel)* **142**:219–259.
2. Attems J, Konig C, Huber M, Lintner F, Jellinger KA (2005) Cause of death in demented and non-demented elderly inpatients; an autopsy study of 308 cases. *J Alzheimers Dis* **8**:57–62.
3. Bermejo-Pareja F, Benito-Leon J, Vega S, Medrano MJ, Roman GC (2008) Incidence and subtypes of dementia in three elderly populations of central Spain. *J Neurol Sci* **264**:63–72.
4. Bower JH, Dickson DW, Taylor L, Maraganore DM, Rocca WA (2002) Clinical correlates of the pathology underlying Parkinsonism: a population perspective. *Mov Disord* **17**:910–916.
5. Braak H, Braak E (1991) Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol* **82**:239–259.
6. Burns JM, Galvin JE, Roe CM, Morris JC, McKeel DW (2005) The pathology of the substantia nigra in Alzheimer disease with extrapyramidal signs. *Neurology* **64**:1397–1403.
7. Cotzias GC, Van Woert MH, Schiffer LM (1967) Aromatic amino acids and modification of Parkinsonism. *N Engl J Med* **276**:374–379.
8. de Rijk MC, Breteler MM, Graveland GA, Ott A, Grobbee DE, van der Meche FG, Hofman A (1995) Prevalence of Parkinson's disease in the elderly: the Rotterdam Study. *Neurology* **45**:2143–2146.
9. de Rijk MC, Tzourio C, Breteler MM, Dartigues JF, Amaducci L, Lopez-Pousa S *et al* (1997) Prevalence of Parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON Collaborative Study. European community concerted action on the epidemiology of Parkinson's disease. *J Neurol Neurosurg Psychiatry* **62**:10–15.
10. Dickson DW, Bergeron C, Chin SS, Duyckaerts C, Horoupian D, Ikeda K *et al* (2002) Office of rare diseases neuropathologic criteria for corticobasal degeneration. *J Neuropathol Exp Neurol* **61**:935–946.
11. Dickson DW, Rademakers R, Hutton ML (2007) Progressive supranuclear palsy: pathology and genetics. *Brain Pathol* **17**: 74–82.
12. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M *et al* (2005) Global prevalence of dementia: a Delphi consensus study. *Lancet* **366**:2112–2117.
13. Grinberg LT, Rueb U, Heinsen H (2011) Brainstem: neglected locus in neurodegenerative diseases. *Front Neurol* **2**:42.
14. 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.
15. 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.
16. Hughes AJ, Daniel SE, Blankson S, Lees AJ (1993) A clinicopathologic study of 100 cases of Parkinson's disease. *Arch Neurol* **50**:140–148.
17. Hughes AJ, Daniel SE, Lees AJ (2001) Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease. *Neurology* **57**:1497–1499.
18. Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ (2002) The accuracy of diagnosis of Parkinsonian syndromes in a specialist movement disorder service. *Brain* **125**:861–870.
19. Hunter R, Smith J, Thomson T, Dayan AD (1978) Hemiparkinsonism with infarction of the ipsilateral substantia nigra. *Neuropathol Appl Neurobiol* **4**:297–301.
20. Ince PG, Clark B, Holton JL, Revesz T, Wharton S (2008) Diseases of movement and system degenerations. In: *Greenfield's Neuropathology*. S Love, DN Louis, DW Ellison (eds), pp. 889–1030. Arnold: London.
21. Jellinger KA (2001) The pathology of Parkinson's disease. *Adv Neurol* **86**:55–72.
22. Jellinger KA (2007) Morphological substrates of Parkinsonism with and without dementia: a retrospective clinico-pathological study. *J Neural Transm Suppl* **72**:91–104.
23. Jellinger KA (2008) Vascular Parkinsonism. *Therapy* **5**:237–255.

24. Jellinger KA, Attems J (2010) Prevalence of dementia disorders in the oldest-old: an autopsy study. *Acta Neuropathol* **119**:421–433.
25. Jellinger KA, Attems J (2011) Prevalence and pathology of dementia with Lewy bodies in the oldest old: a comparison with other dementing disorders. *Dement Geriatr Cogn Disord* **31**:309–316.
26. Kalra S, Grosset DG, Benamer HT (2010) Differentiating vascular Parkinsonism from idiopathic Parkinson's disease: a systematic review. *Mov Disord* **25**:149–156.
27. Kövari E, Hof PR, Bouras C (2011) The Geneva brain collection. *Ann N Y Acad Sci* **1225**(Suppl. 1):E131–E146.
28. Lantos PL, Quinn N (2003) Multiple system atrophy. In: *Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders*. DW Dickson (ed.), pp. 203–214. ISN Neuropath Press: Basel.
29. Ling H, O'Sullivan SS, Holton JL, Revesz T, Massey LA, Williams DR *et al* (2010) Does corticobasal degeneration exist? A clinicopathological re-evaluation. *Brain* **133**:2045–2057.
30. Litvan I (1998) Parkinsonian features: when are they Parkinson disease? *JAMA* **280**:1654–1655.
31. Lopez-Sendon JL, Mena MA, de Yebenes JG (2012) Drug-induced Parkinsonism in the elderly: incidence, management and prevention. *Drugs Aging* **29**:105–118.
32. Lowe JS, Leigh N (2002) Disorders of movement and system degenerations—Akinetic rigid movement disorders. In: *Greenfield's Neuropathology*, Chapter 6. DI Graham, PL Lantos (eds), p. 350. Arnold: London.
33. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA *et al* (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.
34. Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM *et al* (1991) The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology* **41**:479–486.
35. Morris JC, Drazner M, Fulling K, Grant EA, Goldring J (1989) Clinical and pathological aspects of Parkinsonism in Alzheimer's disease. A role for extranigral factors? *Arch Neurol* **46**:651–657.
36. Ott A, Breteler MM, van Harskamp F, Claus JJ, van der Cammen TJ, Grobbee DE, Hofman A (1995) Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam study. *BMJ* **310**:970–973.
37. Rajput AH, Rozdilsky B, Rajput A (1991) Accuracy of clinical diagnosis in Parkinsonism—a prospective study. *Can J Neurol Sci* **18**:275–278.
38. Rebeiz JJ, Kolodny EH, Richardson EP, Jr (1967) Corticodentatonigral degeneration with neuronal achromasia: a progressive disorder of late adult life. *Trans Am Neurol Assoc* **92**:23–26.
39. Reitz C, Brayne C, Mayeux R (2011) Epidemiology of Alzheimer disease. *Nat Rev Neurol* **7**:137–152.
40. Schrag A, Ben-Shlomo Y, Quinn N (2002) How valid is the clinical diagnosis of Parkinson's disease in the community? *J Neurol Neurosurg Psychiatry* **73**:529–534.
41. Shy GM, Drager GA (1960) A neurological syndrome associated with orthostatic hypotension: a clinical-pathologic study. *Arch Neurol* **2**:511–527.
42. Sicras A, Rejas J, Arco S, Flores E, Ortega G, Esparcia A *et al* (2005) Prevalence, resource utilization and costs of vascular dementia compared to Alzheimer's dementia in a population setting. *Dement Geriatr Cogn Disord* **19**:305–315.
43. Steele JC, Richardson JC, Olszewski J (1964) Progressive supranuclear palsy. A heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. *Arch Neurol* **10**:333–359.
44. Williams DR, Lees AJ (2010) What features improve the accuracy of the clinical diagnosis of progressive supranuclear palsy-Parkinsonism (PSP-P)? *Mov Disord* **25**:357–362.
45. Zijlmans JC, Daniel SE, Hughes AJ, Revesz T, Lees AJ (2004) Clinicopathological investigation of vascular Parkinsonism, including clinical criteria for diagnosis. *Mov Disord* **19**:630–640.