Accuracy of Clinical Diagnosis in Parkinsonism — A Prospective Study

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ABSTRACT: Clinical diagnosis of Parkinson's syndrome (PS) is reasonably easy in most cases but the distinction between different variants of PS may be difficult in early cases. The correct diagnosis is not only important for counselling and management of patients but also in conducting pharmacological and epidemiological studies. There is very little critical literature on the pathological verification of the clinical diagnosis in PS. We report our 22 year experience to address that issue. Between 1968 and 1990, 65 PS patients came to autopsy. Complete data are available in 59 (M-50, F-19) cases. The initial diagnosis made by a qualified neurologist was idiopathic Parkinson's disease (IPD) in 43 cases. Of those 28 (65%) had Lewy body pathology. After a mean duration of 12 years the final diagnosis was IPD in 41 cases which was confirmed in 31 (76%). The IPD could not be clinically distinguished from cases with severe substantia nigra neuronal loss without inclusions or from those with neurofibrillary tangle inclusions and neuronal loss at the anatomical sites typically involved in IPD. All progressive supra-nuclear palsy, olivopontocerebellar atrophy, Jakob-Creutzfeldt's disease and the majority of the multiple system atrophy cases were diagnosed correctly during life. The correct clinical diagnosis in most non-IPD variants of PS was possible within 5 years of onset (range: 2 months to 18 years). We recommend that studies aimed at including only the IPD cases restrict the enrollment to those cases that have had PS motor manifestations for five years or longer duration.

RÉSUMÉ: Exactitude du diagnostic clinique dans la Parkinsonisme - une étude prospective. Le diagnostic clinique du syndrome de Parkinson (SP) est relativement facile dans la plupart des cas, mais la distinction entre les différentes variantes du SP peut être difficile au début de la maladie. Un diagnostic exact est important non seulement pour conseiller les patients et assurer la bonne conduite du traitement, mais aussi pour réaliser des études pharmacologiques et épidémiologiques. Il existe très peu de littérature critique sur la vérification anatomopathologique du diagnostic clinique du SP. Nous rapportons notre expérience de 22 ans à cet effet. Entre 1968 et 1990, 65 patients atteint de SP ont eu une autopsie. Des données complètes sont disponibles pour 59 cas (M-40, F-19). Le diagnostic initial fait par un neurologue certifié était celui de maladie de Parkinson idiopathique (MPI) chez 43 cas. Parmi ceux-ci, 28 avaient des corps de Lewy à la pathologie. Après une durée d'évolution moyenne de 12 ans, le diagnostic final était celui de MPI dans 41 cas, ce qui a été confirmé dans 31 cas (76%). La MPI ne pouvait pas être distinguée cliniquement des cas avec perte neuronale sévère au niveau du locus niger sans corps d'inclusion ou de ceux qui avaient des amas neurofibrillaires et une perte neuronale aux sites anatomiques typiques de la MPI. Tous les cas de paralysie supranucléaire progressive, d'atrophie olivopontocérébelleuse et de maladie de Jakob-Creutzfeldt et la majorité des atrophies multisystémiques ont reçu un diagnostic exact du vivant du patient. Un diagnostic clinique exact pour la plupart des variantes du SP qui ne sont pas une MPI était possible en dedans de 5 ans du début de la maladie (intervalle: 2 mois à 18 ans). Nous recommandons que, pour les études qui ne doivent inclure que des cas de MPI, le recrutement soit restreint aux cas qui ont des manifestations motrices du SP depuis cinq ans et plus.

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The cause of Parkinson syndrome (PS) is unknown in over 90% of the cases.[1] The term idiopathic Parkinson's disease (IPD) however is reserved by most neurologists for PS associated with Lewy body pathology.[2] The prognosis in PS associated with multiple system atrophy (MSA) is less favourable than in the IPD, therefore the distinction between different variants of PS during early stage of the illness is useful for counselling and for management in these cases. Several pharmacological studies that form the basis of drug therapy today are predicated upon the ability to clinically distinguished early IPD from other variants of PS.[3, 4] The correct diagnosis of IPD is also critical for analytic epidemiological studies to determine the etiology of Parkinson's disease.[5] Investigative tools such as positron emission tomography (PET)[6-8] and magnetic resonance imaging (MRI)[9, 10] are valuable in the diagnosis of PS but the gold standard to identify different forms of PS remains the histological

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examination. In spite of voluminous literature on PS to date there is only one small study that critically evaluated the accuracy of clinical diagnosis.[11]

In an effort to verify the accuracy of clinical diagnosis in PS we report our prospective observations in 59 cases that had autopsy studies during a 22 year period.

Materials and Methods

In 1962, Saskatchewan introduced universal health care system and in the 70's established a public funded prescription drug plan.[12] Residents of this province have thus had an easy and equal access to neurological services and to anti-parkinsonian drugs for many years.[13] Since 1968 a movement disorder clinic (MDC) has been conducted regularly at the Royal University Hospital Saskatoon (UH) by one of us (AHR). All PS cases seen at the MDC between December 1, 1968 and February 28, 1990 are included in this study.

The diagnosis of PS at the MDC was made when at least two of the three cardinal signs — bradykinesia, rigidity and resting tremor were present. Those that had no identifiable cause and no clinical evidence of widespread central nervous system lesions were regarded as having IPD. The patients were usually evaluated at 6 to 12 month intervals by the same neurologist.[13] Tremor, bradykinesia and rigidity were measured using the criteria of Webster[14] and the overall disability was measured by the Hoehn and Yahr scale.[15] Formal psychometric evaluations were not done in all the cases. Those with an unequivocal progressive cognitive and memory impairment were considered as having dementia.[13] Status of antiparkinsonian drug therapy including the side effects and the severity of PS[14,15] were evaluated at each visit and entered in the central university computer data bank. Neuropathological examination in nearly all cases was done by the same neuropathologist (BR).

Where the diagnosis of a given variant of PS had been made by a neurologist prior to the first MDC visit it was regarded as the initial clinical diagnosis (ICD). In the cases previously not assessed by a neurologist the initial diagnosis at MDC was considered as the ICD. Where a list of differential diagnosis was compiled the variant noted as the most likely diagnosis was regarded as the ICD. Based on the accumulated information the final clinical diagnosis (FCD) was that recorded at the last MDC visit. The ICD and FCD each was verified against the pathological findings. For the purpose of this report even if the correct pathological diagnosis was noted in the differential diagnosis but was not considered as the most likely pathological basis of PS, the clinical diagnosis was regarded as being incorrect. Response to levodopa was classified only when the patient received at least half the usual dose[13] for a minimum of two consecutive months.[16, 17]

The pathological diagnosis was made independently of the clinical observations. Where the substantia nigra (SN) neuronal loss was estimated at more than 50% (formal counts were not done) and Lewy body (LB) inclusions were detected in some neurons the case was classified as IPD. If rare LB without SN neuronal loss was noted the LB inclusion was regarded as incidental. The pathological diagnosis of other variants of PS was made using the standard criteria for each entity.

Results

During the 22 years, 65 patients (27% of deaths) came to autopsy but satisfactory pathological examination was not possible in six cases. Of the remaining 59 (M-40, F-19), the initial clinical diagnosis was IPD in 43 patients. Lewy body pathology was verified in only 28 (65%) of those 43 cases. The final clinical diagnosis after an average 11.7 (range: 2 - 39) year duration of illness was IPD in 41 patients. Pathological observations confirmed LB disease in 31 (76%) of this group. In all the pathologically proven Lewy body disease cases the FCD was IPD. In the 10 cases who had an incorrect FCD the average duration of symptoms was 15 years at the time of final MDC evaluation. These included striatonigral degeneration (SND) 4, profound SN neuronal loss without inclusions (PSNL) 2, neurofibrillary tangle parkinsonism (NFTP) 2, drug-induced parkinsonism (DIP) 1, and one case that had only Alzheimer's disease (AD) (Table 1).

On the other hand, all the olivopontocerebellar atrophy (OPCA), progressive supranuclear palsy (PSP), Jakob-Creutzfeldt's disease (JCD) cases and those with sequential emergence of IPD and Alzheimer's disease (IPD & AD) were correctly diagnosed during life. Table 2 shows the pathological diagnosis in all 59 cases.

Discussion

The cause of PS is unknown (idiopathic) in most variants of this syndrome yet the label "idiopathic" Parkinson's disease is often restricted to Lewy body disease.[2] The scientific justification for such classification has been questioned by some authorities.[18, 19] We have retained that terminology[2] for the purpose of uniformity with the literature.

The most promising laboratory research tool for the diagnosis of the PS today is the PET scan.[6] Further refinements to PET technology are necessary before it can distinguish IPD from all other forms of PS.[20] Response to levodopa[16, 17] though a valuable guide is not specific for the underlying pathology and the apomorphine response[21] needs further correlative studies. In the absence of specific diagnostic tools pathological studies remain the major source of information for confirmation of diagnosis in PS.

There have been several attempts at correlating clinical diagnosis with the pathological findings in PS.[11, 22-26] A closer review indicates that most of these studies are based on pathological observations which were followed by a retrospective review of clinical records and the diagnostic labels were not meticulously adhered to. By contrast our report is based on prospective clinical observations and data collection with strict adherence to the clinical diagnosis and subsequent pathological verification. We are aware of only one similar study in the English literature.[11] Forno[11] noted that 6 of the 9 (67%) cases that were diagnosed as IPD had LB pathology. By contrast the FCD of IPD was correct in 31 of 41 (76%) in our cases. Both these studies indicate the limitations of clinical assessments in predicting the pathological diagnosis of IPD — the most common variant of PS.[1, 22] The uncommon variants of PS are usually reported in small series as novel observations.[27-31] Such communications usually do not address the accuracy of clinical diagnosis as we have done.

All clinical observations in our study were made by the same neurologist (AHR), and most autopsies were done by the same neuropathologist (BR) — thus excluding inter-observer bias. Our major interest was not to focus on the "percentage" of clinical diagnostic accuracy but rather on the reasons for the errors so they could be avoided in the future. We therefore strictly retained the initial diagnosis made by a neurologist as well as the FCD. This study includes cases that were first diagnosed in the 1950's and 60's when several of the currently well known forms of PS[27-34] were unknown, therefore the proportion of accurate diagnosis by contemporary standards would be lower.

Prognosis in the PS due to widespread pathology is less favourable than when SN is the main site of lesion. Idiopathic Parkinson's disease[2] is the most common variant of PS[1, 15, 22, 24] and was the most frequently diagnosed variant during early stage in our cases. The diagnostic accuracy of IPD increased from 65% to 76% with the follow-up. Most of the alternate (correct) diagnoses were made during the first 5 years after onset of PS.

The SND[35], NFTP[30] and the PSNL were the most difficult entities to distinguish from IPD — even after long duration of illness and repeated assessments. There were no clues to distinguish NFTP or PSNL from IPD. The two PSNL patients had the FCD made long (19 and 30 years) after onset as was also the case in NFTP patients.[30] The response to levodopa in the NFTP and PSNL was comparable to IPD.[16, 17]

Most SND cases had akinetic-rigid syndrome (one had prominent tremor) with or without dysautonomia. Absence of resting tremor during the entire course of illness thus favours the SND diagnosis but the correct diagnosis during early stage is difficult. The majority (75%) of SND cases did not respond to levodopa. Where other features of multiple system atrophy (MSA) emerged, the delay ranged between 3 to 18 years after the motor onset of PS though in most cases evidence of widespread pathology was present within 5 years. Postural hypotension, urinary retention or sexual impotence in the males were the most common early manifestations. The disability was more rapidly progressive in the MSA after the other features emerged than in the IDP cases with same duration of illness.

All three PSP cases were correctly diagnosed at FCD though the the ICD was incorrect in all patients. Supranuclear opthalmoplegia which is the major manifestation in PSP was evident within 3.5 years after onset in two and after 8 years in the third case. The earliest clinical clues were: inability to cope with job pressures, declining reading ability, unusually erect posture, postural instability or blepharospasm. All OPCA patients were diagnosed correctly at early stage of illness as were the 2 JCD cases.

In each of the two DIP patients that had been on phenothiazines there was no histological abnormality in the brain. Because of asymmetrical PS features, one DIP case was suspected to have additional underlying IPD pathology.[36] The lone misdiagnosed Alzheimer's disease case presented as unilateral PS and was soon noted to have dementia. Clinical diagnosis in this patient was IPD and AD.

Our data illustrate some of the difficulties in accurately predicting the underlying pathology in the early PS cases. In consideration of that the studies aimed at including only the IPD cases e.g. epidemiological studies to determine the cause of this disorder should include only those PS cases that have had motor manifestations for 5 years or longer duration. On the other hand, carefully planned drug trials where early PS cases are randomly assigned to an active agent or placebo[3, 4] the results would, by and large, be free of the bias due to the underlying pathology as the diagnostic inaccuracy would be equally represented in the two groups.

Table 1: Pathological findings in 10 cases where the final clinical diagnosis of IPD was incorrect.

Pathology	Number of	Interval from onset to last visit to MDC (in years)
Only SND	2	6, 6.25 years
SND & Postural Hypotension	2	9, 7.5 years
Profound SN cell loss but no inclusions	2	30, 19 years
Alzheimer's disease only	1	2 years
Drug-induced parkinsonism	1	uncertain
Only NFT pathology	2	30.5, 34 years

SND = striatonigral degeneration
SN = substantia nigra
NFT = neurofibrillary tangle pathology in substantia nigra and in locus ceruleus[30]

Table 2: Neuropathological diagnosis in 59 cases

(M=40, F=19)	No. of Cases	(%)
IPD (only	26	(44)
IPD & Alzheimer's disease	6	(10)
Multiple System Atrophy (SND, Shy-Drager, OPCA, MSA)	13	(22)
PSP	3	(5)
NFT parkinsonism	2	(3)
IPD & NFT (Pathology)	1	(2)
DIP	2	(3)
Substantia nigra cell loss (no inclusions)	2	(3)
Jakob-Creutzfeldt's disease	2	(3)
Other*	2	(3)
Total	59	

IPD = Idiopathic (Lewy body) Parkinson's disease
SND = Striatonigral degeneration
OPCA = Olivopontocerebellar atrophy
MSA = Multiple system atrophy
IPD & Alzheimer's disease - two coexisting illnesses
PSP = progressive supranuclear palsy
NFT parkinsonism = only substantia nigra and locus cereuleus neuronal loss, neurofibrillary tangles restricted to these regions
DIP = Drug-induced parkinsonism
Alzheimer's disease = cortical Alzheimer's pathology only
*other indicates two entities - a case of status cribrosus in the striatum and globus pallidus and a case of Alzheimer's disease with both cortical and subcortical pathology.

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