The relevance of the Lewy Body to the pathogenesis of idiopathic Parkinson’s disease

Accuracy of clinical diagnosis of idiopathic Parkinson’s disease

Andrew John Lees

During my undergraduate training at the London Hospital, Whitechapel, the teaching autopsy was an eagerly anticipated ritual. The whole medical firm would troop across the road from the hospital to the mortuary where a clinician, often the consultant, would present the history and physical signs of the deceased and then the morbid anatomists would reveal the macroscopic pathological findings. Henry Urich perched on a ledge next to the cadaver would, with his exotic Eastern European accent, lead the discussion on all the neurological cases while we remained transfixed looking down in awe from the gallery. The naked eye appearances of the sliced brain allowed him to suspect diagnoses such as Parkinson’s disease and exposed other pathologies, such as tumours and haemorrhage. These demonstrations taught me the rudiments of the classical anatomo-clinical neurological method, the great level of uncertainty relating to the cause of death that existed in so many cases, the frequency of multiple pathologies in an individual case and most of all the need for humility. A decade later autopsy rates began to tumble in the UK and the teaching autopsy was on its last legs; but for a few dissenting voices, nobody seemed to care. The opportunities to do careful clinicopathological studies were dwindling fast as neurochemistry and imaging took centre stage as neurological research priorities.

Shortly after I had become a consultant at University College Hospital, London, and Queen Square, I was flying to a meeting on Parkinson’s disease in Vienna and had the good fortune to sit next to the late Professor David Marsden. Over a couple of drinks I told him that I wanted to set up a brain bank dedicated to Parkinson’s disease and that the pathologist at Maida Vale Hospital, Dr Robin Barnard, was supportive of the idea. David, who had carried out important anatomical studies on the substantia nigra in animals as a medical student, was enthusiastic and on our return we obtained a 5 year programme grant from the Parkinson’s Disease Society of the UK and the UK Parkinson’s Brain Bank was born. The first frozen half brains were dispatched to the Institute of Psychiatry for neurochemical studies in Peter Jenner’s laboratory while Bill Gibb, a MRC funded research fellow, and I worked on the formalin fixed tissue under Dr Barnard’s direction at Maida Vale Hospital.

Bill and I started to review together the surprisingly limited and largely conflicting literature on the neuropathological findings in Parkinson’s disease. Early revelations were that the substantia nigra lesion, first described in 1917 in the doctoral thesis of Konstantin Tretiakoff, a young Russian émigré working in Pierre Marie’s laboratory, did not gain general acceptance for another 40 years and much more remarkably that the characteristic macroscopic bleaching of the midbrain, although described in post-encephalitic Parkinsonism, was also not recognised in Parkinson’s disease until the mid-1950s. The clinical data provided in the best histopathological reports were skimpy at best and the natural history in each case ignored.

Based on the available published data and expert opinion, we constructed tentative clinical operational criteria to use in a retrospective review of the available case notes of the early brain bank material to try to determine if we could predict whether an individual brain was likely to have severe loss of nigral pars compacta cells with brain stem Lewy bodies. Although our occasional review paper published in 1988 in JNNP focused primarily on the importance and relative selectivity of the Lewy Body for Parkinson’s disease and the notion that individuals with incidental Lewy Body pathology might have been at greater risk of developing Parkinson’s disease in life than age matched controls without Lewy bodies, this landmark paper has been mainly remembered and quoted for the first reference to the Queen Square Brain Bank criteria (the full details of which were published a year later in a little quoted paper: Gibb WRG, Lees AJ. Neuropath and Applied Neurobiology 1989; 15:27–44). In this study of 269 patients generously provided from the

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Professor Andrew Lees of the National Hospital for Neurology and Neurosurgery, Queen Square describes the clinico-pathological studies at the Queen Square Brain Bank that have led to improved diagnostic accuracy of Parkinson’s syndromes in neurological practice

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Title: THE RELEVANCE OF THE LEWY BODY TO THE PATHOGENESIS OF IDIOPATHIC PARKINSON’S DISEASE
Authors: W R G Gibb, A J Lees
Published: 1988;51:745—52

Title: ACCURACY OF CLINICAL DIAGNOSIS OF IDIOPATHIC PARKINSON’S DISEASE: A CLINICO-PATHOLOGICAL STUDY OF 100 CASES
Authors: Andrew J Hughes, Susan E Daniel, Linda Kilford, Andrew J Lees
Published: 1992;55:181—4
collections of several British neuropa-
thologists with a clinical diagnosis of
parkinsonism, 78 were selected on the
basis of the proposed operational criteria
and 73 of these were found to fulfil
accepted pathological criteria (severe
nigral cell loss and brainstem Lewy
bodies). This 6% mismatch was the start
of the diagnostic accuracy work, which
would follow. In devising the criteria, our
aim was always to construct positive
criteria from a basic starting point of
exclusion criteria and this preliminary
work led to the proposal of
prospective diagnostic criteria (step 3
QSBB criteria), that included unilateral
onset, coarse pill rolling rest tremor,
persistent limb asymmetry of signs,
excellent response to L-dopa lasting more
than 5 years and a disease duration of
more than 10 years.1 The criteria were
simple to use and started from a clinical
perspective. They contrast strikingly with
the detailed and frequently unwieldy
consensus diagnostic criteria that are now
so much in vogue in neurology and
psychiatry. They were not intended for
routine clinical use but we hoped that
they might prove helpful for clino-
copathological correlative research. The fact
that they have been widely adopted and
used in research projects all over the
world for more than 20 years is both
ironic and a pleasant surprise. The
clamour for revised more inclusive criteria
is now mounting as the diagnosis of
Parkinson’s disease especially in the first
years of disease remains difficult. Let us
hope that whichever panel of experts is
debated for the task will have wide
clinical experience of the malady and take
account of the heterogeneity of both the
clinical phenomena and disease course.
Andrew Hughes, a neurologist from
Melbourne, then came to work at the
Middlesex Hospital with Gerald Stern and
me, and after he had got to know all about
apomorphine therapy I set him a ‘little side
project’ at the Queen Square Brain Bank.
The idea was simply to compare the final
clinical diagnosis of Parkinson’s disease
with the actual brain bank pathological
diagnosis. Andrew later admitted to me
that he was sceptical that such an
elementary audit would produce a pub-
clication. Much of the work was done in
the evening by Andrew working alone in
the brain bank where he followed sometimes
late into the night the course of a patient’s
life from the general practitioner case notes
describing childhood illnesses and later to
the first subtle emerging features of
neurological disease and finally in the
hospital case notes, the long increasingly
emotional journey of Parkinson’s disease.
The project was straightforward and
although the ‘final’ diagnosis of the first
hundred brains did require a detailed
review of the clinical notes rather than
accepting what was recorded in the
brain bank file, within a month Andrew had
come up with a figure of 76%. Twenty-four
of the patients considered by neurologists
to have Parkinson’s disease at the time of
death did not have the histopathological
changes in the brain generally recognised
to be associated with Parkinson’s disease.
When after clinic Andrew reported the
figures to Gerald and me in our weekly
research meeting on Thursday evening, I
could hardly contain my excitement.
The orientation of the brain bank with
the emphasis on the clinical findings of
the donor in life made it a unique resource.
‘The gift that keeps on giving’ later proved
to be the ongoing referencing of our paper
by clinical researchers. During the study,
Andrew was acutely aware of the enor-
mous privilege it was to have access to the
personal details of patients who had so
generously donated their brains, and by
piecing together their medical history
from the notes at times it almost felt like
some of them were coming back to life.
The 1992 paper describing the disap-
pointing diagnostic accuracy for Parkin-
son’s disease was sent to JNNP (‘the green
rag’) as our first choice and accepted with
minor revisions. When Andrew first
presented the data at the Association of
British Neurologists meeting in London,
he received a frosty and intimidating
questioning from several eminent senior
neurologists. Surely this level of inac-
curacy referred to general practitioners not
neurologists? In North America and parts
of Continental Europe, the poor figures
were blamed on the relative dearth of
neurologists in the UK and poor training.
Perhaps fortunately for the longstanding
success of our paper, a well respected
movement disorder specialist Ali Rajput
simultaneously reported in the Canadian
Journal of Neurological Sciences identical
figures from his own practice.2
Our study looked at clinical variables,
which might improve the diagnosis of
Parkinson’s disease, including a retrospec-
tive application of the Queen Square Brain
Bank criteria to the case notes and exposed
the shortcomings of too stringent criteria,
which only slightly reduced the misdiag-
nosis rate at the expense of excluding large
numbers of true Parkinson’s disease cases.
The natural extension of this study was to
return to the files and collect as much
clinical information as possible on all 100
patients and examine whether retrospec-
tively applying established diagnostic
criteria or other combinations of clinical
features could improve this disappoin-
ting figure. This second phase required
the perspective of a clinical epidemiologist, and
Andrew and I were indoctrinated with the
novel concepts, at least for us, of sensi-
tivity, specificity and positive and negative
predictive values.3 These studies suggested
there may well be a broader clinical
phenotype to Parkinson’s disease than was
generally appreciated, and prompted a third study—a pathologico-clinical study
of 100 cases of pathologically proven
Parkinson’s disease.4
Throughout the 1990s, many detailed
clinical pathological studies were carried out
on Parkinson’s disease and atypical parkin-
sonian syndromes at the Queen Square
Brain Bank and a decade later Andrew
Hughes returned to do a sabatical when
he found gratifyingly that our pioneering
work had led to a significant improvement
in clinical accuracy in the diagnosis of
Parkinson’s disease in the UK.5 6

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