A MODERN PERSPECTIVE ON THE TOP 100 CITED JNNP PAPERS OF ALL TIME

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 collections of several British neuropa-
thologists with a clinical diagnosis of
Parkinson’s disease. They 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
correlative work led to the proposal of
prospective diagnostic criteria (step 3
OSBB 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. 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 clinico-
 pathological 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
delegated for the task will have wide
clinical experience of the malady and take
account of the heterogeneity of both the
clinical phenomenza 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
close the final clinical diagnosis of
Parkinson’s disease with the actual brain
pathological diagnosis. Andrew later
admited to me that he was sceptical that
such an elementary audit would produce a
publication. 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 referring
of our paper by clinical researchers.
During the study, Andrew was acutely
aware of the enormous 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
disappointing diagnostic accuracy for Parkin-
son’s disease was sent to JNNP (‘the green
gag’) as our rst choice and accepted with
minor revisions. When Andrew rst
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
misdiagnosis rate at the expense of
excluding large numbers of true Parkin-
son’s disease cases. The natural extension
of this study was to return to the liles and
collect as much clinical information as
possible on all 100 patients and examine
whether retrospectively applying estab-
lished diagnostic criteria or other com-
nbinations of clinical features could improve
this disappointing 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 sensitivity, 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 pathologic-clinical study of 100
cases of pathologically proven Parkinson’s
disease.4

Throughout the 1990s, many detailed
clinic pathological studies were carried out
on Parkinson’s disease and atypical
parkinsonian syndromes at the Queen
Square Brain Bank and a decade later
Andrew Hughes returned to do a sabbatical
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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