Short report

Dementia associated with Parkinson's disease: a genetic study

LEONARD L HESTON

From the Psychiatry Research Unit, University of Minnesota, Minneapolis

SUMMARY Relatives of 12 probands who had severe dementia associated with Parkinson's disease were studied. A high risk for Parkinson's disease was found among relatives but only one instance of dementia. The high risk to relatives and the dementia of the probands appeared to be related to the overall severity of the Parkinsonian illness.

Parkinson's disease appears clustered in some families which suggests that genetic factors are important in aetiology.^{1–3} Although this conclusion may be questioned because an ongoing twin study has so far discovered no concordant pairs, the other evidence favoring some aetiological involvement of genetic factors is substantial. This report describes a family study of a subset of Parkinson's disease, selected because the probands had severe dementia and Parkinson's disease. While some degree of intellectual impairment is common in Parkinson's disease, the dementia of the probands in this study dominated their clinical course. Study of the probands and their families produced data that may help begin to unravel the relationship among Parkinson's disease, dementia, and genetics.

Methods

The probands came from a series of 2204 necropsies done in Minnesota State Hospitals between 1952 and 1972. The material is regarded as unselected. Using the necropsy report, which included a neuropathological section prepared by University of Minnesota neurologists or neuropathologists, and the clinical record compiled by the hospital, 304 cases were found where dementia was present. Dementia was defined as a progressive decline in memory for recent events, abstract thinking and judgment which had become sufficiently severe as to require custodial supervision. Also required was the absence of

systemic disease or condition known to be associated with diffuse impairment of brain and the absence of cerebral vascular disease judged significant by the examining pathologists. Among the 304 demented cases, at necropsy 12 had evidence of Parkinson's disease; decreased pigmentation of the substantia nigra and the locus ceruleus was present in all cases; free melanin pigment and gliosis in those areas was present in most cases; Lewy bodies were described in nine cases. The clinical record of the same 12 cases recorded tremor, rigidity, and bradykinesia and offered Parkinson's disease as a diagnosis. All 12 were of North European extraction. None was thought to be a post-encephalitic case and there were no recorded episodes of oculogyric crises. In the whole series of necropsies, there were 18 additional cases of Parkinson's disease where dementia was not prominent. These cases provided controls for some estimates as will be described. The 12 families were followed up as part of a genetic study of all 304 cases of dementing illness. At least one informant was interviewed in each family and all medical records including death certificates were reviewed. A reasonably complete medical history was obtained for all first and second degree relatives of each proband. Further details of follow-up methods can be found in Heston and Mastri.⁴

Results and discussion

The pathologists found occasional senile plaques and neurofibrillary tangles in cortical areas of eight of the 12 proband brains, but in no case in numbers large enough to warrant consideration of a

Address for reprint requests: Leonard L Heston, Professor of Psychiatry, Psychiatry Research Unit, Box 392 Mayo, University of Minnesota, Minneapolis, Minnesota 55455 USA

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dementia of the Alzheimer's type. Thus, contrary to the suggestion of Hakim and Mathieson⁵ it seems unlikely that the dementia in these Parkinson's cases can be associated with Alzheimer's neuropathological changes. Also, this systematically collected group of probands did not include any examples of a rare or unexpected syndrome such as the Parkinsonism-dementia complex found among the Chamorros of Guam or the occasional familial Alzheimer's case where Parkinsonism is prominent.

There were seven secondary cases of Parkinson's disease among first degree relatives in six families: a father, two mothers, a sister and three brothers, two of the latter in one family. Few children were in the ages at risk and none was affected. One secondary case was found in a second degree relative. The age corrected risks estimated by the Weinberg mortality method⁶ were $24 \pm 13\%$ for parents and $23.3 \pm 9\%$ for siblings. One secondary case, a mother, was demented. Otherwise, no relative, whether affected with Parkinson's disease or not, had a dementing course. Thus, there was no independent genetic segregation of Parkinson's disease and dementia as would be expected if the two conditions were associated with different unlinked genes. A sibling had amyotrophic lateral sclerosis, a condition associated with the Parkinsonism-dementia complex of Guam, but regarded as coincidental in this study. There was no excess of affective illness which is consistent with the negative result of Stern *et al.*⁷

Kondo *et al.*² and Young *et al.*⁸ conclude that Parkinson's disease, though genetically transmitted, is multifactorial and that its appearance in families is not explained by simple genetic models. In such situations, the number of unfavourable factors may vary among families and therefore some families will be more severely afflicted than others. Increasing severity is associated with earlier onset, rapid course, and greater frequency of disease among relatives. That such considerations are relevant to Parkinson's disease is shown by differences in the risk of Parkinson's disease to siblings of two groups of probands from Martin *et al.*¹ One group of Martin's probands were either relatively young at the onset of their illness or had an affected parent and so presumably had relatively severe illness. Their siblings were affected at rates of 20 to 30%. In contrast, the morbid risk to siblings of probands from the same study who became ill later in life and who did not have an affected parent was only 3 to 4% (approximately). The same conclusion follows from the demonstration by Mjones³ that increases in small but consistent steps in proband's average age of onset was associated with decreasing risk to siblings; Mjones found that the greater the estimated genetic risk, the earlier the onset of illness

and the greater the proportion of affected siblings.

Demonstrating such relationships between the twelve families in this study and those reported by others is complicated because investigators have grouped and reported their data in different ways making it hard to find directly comparable estimates. However, three comparisons seem defensible and suggest that the probands in this study had relatively severe illness:

(1) The siblings of probands in this study were affected with Parkinson's disease at an estimated rate of $23.3 \pm 9\%$ which is comparable to the highest risk groups of Martin *et al.*¹ that is, the siblings of probands who were affected at youngest ages ($20.5 \pm 5.3\%$) and the siblings of probands who had affected parents ($29.7 \pm 9.1\%$). Mjones³ divided his probands into groups which make direct comparison impossible. However, it is possible to use his table XX plus data in his text to calculate a risk to siblings of unselected probands of $11.1 \pm 2.0\%$ which is decidedly lower than that found in this study.

(2) The probands in this study had an average age at onset of 53.5 years (range 21–60) compared to estimates from the literature for comparable groups of 55.3 years⁹ and 59 years.^{10 11} The 18 non-demented Parkinson's cases from the same autopsy series as the probands in this study provide a reasonable comparison group. Their average age at onset of illness was 62.4 years. The probands appear to have become ill while relatively young.

(3) The probands in this series survived an average of 7.1 years of illness. Hoehn and Yahr⁹ reported an average survival of 9.7 years and Pollock and Hornabrook,¹⁰ 9 years in groups of their subjects comparable to this group of probands. The 18 non-demented Parkinson's cases survived 13.4 years on average after onset. Thus, the proband group in this study survived a relatively short time.

Although numbers are small and standard error large, the results of this study are consistent in all respects with the conclusion that the probands had relatively severe Parkinson's disease. In turn, this suggests that the dementia which distinguished their course was associated with relatively severe Parkinson's disease; no other explanation for the dementing course was found and no other explanation seems needed.

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