Attentional and Perseverative Impairment in Two Cases of Familial Fatal Parkinsonism with Cortical Sparing

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ABSTRACT: The neuropsychological findings in twin brothers with familial fatal Parkinsonism are reported. Post-mortem examination had shown extensive pathology in basal ganglia and brainstem, but not in the cerebral cortex. Although both showed average intelligence three months prior to death, they had impairment on a sorting task and in serial attention span. Some possible neural mechanisms are discussed.

RÉSUMÉ: Déficit de l'attention et de la persévération chez deux patients souffrant de Parkinsonisme familial, sans atteinte corticale, dont l'issue a été fatale. Nous rapportons les observations neuropsychologiques notées chez des frères jumeaux atteints de Parkinsonisme familial dont l'issue a été fatale. L'autopsie a révélé des lésions extensives des noyaux gris centraux et du tronc cérébral, sans atteinte du cortex cérébral. Même si tous deux démontraient un niveau d'intelligence moyen trois mois avant leur décès, ils manifestaient un déficit aux épreuves de découverte d'un code et à l'épreuve d'attention en sériée. Nous discutons des mécanismes neurologiques sous-jacents possibles.

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This paper reports the neuropsychological findings in two cases, twin brothers, with a familial form of fatal Parkinsonism. The neurological, pathological and neurochemical findings were reported in detail some years ago.[1] The present report is concerned with a retrospective consideration of the neuropsychological assessment, since there are few cases in the literature in which post-mortem findings show sparing of the cerebral cortex, and in whom a psychometric assessment has been carried out.

The neurological symptoms in both cases began in their 40's, progressed rapidly and led to death before the age of 50. The Parkinson-related signs were primarily bradykinesia and depression, but the disorder which led to death was a failure of automatic respiration. The mother had died at age 50 with similar symptoms, and other members of the family were affected as well.

Methods and Results

One brother was assessed only once, and the other three times. Both had fairly complete assessments approximately 3 months before death, and these are the assessments which will be emphasized, because they a) provide a good picture of abilities fairly close in time to the post-mortem findings, but before general fatigue was an acute problem, and, b) permit comparisons to be made between the two cases, thus providing a more reliable picture of which abilities were affected in this disorder.

Patient 1 (deceased 20 October, 1976). This patient was first seen by the Neurology service at University Hospital when he was 46 years old. He was diagnosed as having Parkinson's disease and was started on L-Dopa therapy.

He was first assessed by the neuropsychology service at age 47, on 5 December, 1975, about 9 months prior to his death. His intelligence at this time, measured by the Wechsler Adult Intelligence Scale,[2] was in the average range, with no significant discrepancy between the Verbal IQ (97), measuring verbal skills, and the Performance IQ (91) measuring nonverbal skills. Memory function, as measured by the Wechsler Memory Scale (Form I),[3] was above average, and all subtests were at least average. Tests of attention span (described below) were also satisfactorily performed at this time. In fact, the only significant deficit on this occasion was a difficulty with the Wisconsin Card Sorting Test,[4,5] on which the patient achieved zero categories (maximum = 6). He sorted all 128 cards according to matching forms, and thus received a perseverative error score of 95. This is remarkably poor performance in a person otherwise so intellectually intact.

The second (and last complete) assessment took place on 16 July, 1976, three months before death (see Table 1). By this time the Parkinson signs had accentuated, as had the shortness of breath and erratic breathing. He was nevertheless still co-operative and testable.

At this second assessment, the Full Scale IQ of 99 (tested by the alternate form of the WAIS, the Wechsler-Bellevue Scale, Form II)[6] was still in the Average range. The Verbal IQ was 93, and the Perfor-

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Table 1: Neuropsychological Test Findings Approximately 3 Months Prior to Death

	Patient 1	Patient 2
Intelligence Quotient	99	97
Verbal IQ	93	98
Performance IQ	105	96
Memory Testing:		
Memory Quotient	90	101
Recurring Verbal Score	14	31
Attention Span:		
*Digit Span Raw Score	8	8
*Digit Span Forwards	5	5
*Digit Span Backwards	3	3
*Modified Knox Cubes		
Immediate	3	3
Delay	0	4
Sorting Task:		
*Card Sorting Task	[0 categories, 95 perseverations /95 total errors]	3 categories, 53 perseverations /62 total errors

*Indicates significant impairment in both cases.

mance IQ 105. The pattern of abilities was similar to the first assessment, with the exception of Digit Span, a subtest measuring immediate attention span, which was now poor. Memory recall function, as indicated by a Wechsler Memory Quotient (Form II)[3] of 90, was lower than on previous testing, but was still compatible with the IQ level. Recognition of previously presented words, as measured by the score on a Recurring Words task,[7] was also affected in this patient.

The most striking deficit, however, was the very poor performance on a test of attention span, the Modified Knox Cubes Test.[7] Five simple black cubes are placed in a row in front of the patient. The examiner taps the 5 blocks in a particular order, and the patient is required to repeat the sequence correctly. Whereas, on the first testing occasion, the patient tapped 8 out of 10 sequences correctly, on this occasion he repeated only 3 out of 10 without error. (We must stress that the patient was not generally intellectually impaired.) When a 5-second delay was introduced before the patient could tap the sequence, performance fell to 0 out of 10.

The card sorting test was not administered again, apparently because he had been maximally impaired on the first occasion.

A final very abbreviated assessment, limited to Verbal IQ, was attempted over several days at the end of August — beginning September 1976, about six weeks before death. At this time the patient was having difficulty speaking and he fatigued very quickly. Despite this, he achieved a WAIS Verbal IQ of 87, which is just below the Average range.

Patient 2 (deceased 22 March, 1977). This patient had been diagnosed elsewhere 3 years previously as having Parkinson's disease, and was first admitted to University Hospital in December, 1976, with profound respiratory problems.

He had his only neuropsychological assessment at this time (14 and 15 December, 1976), approximately 3 months prior to his death (see Table 1).

The IQ measured in the Average range, with no significant discrepancy between the Verbal IQ of 98 and the Performance IQ of 97. Memory function, as measured by the Wechsler Memory Scale (Form I), was appropriate to the IQ level. Recognition of previously presented words (Recurring Verbal score) was good. However, on a comparable test employing designs (not shown in Table 1 because it was not administered to the other brother), performance was extremely poor.

The other salient finding was that attention span was affected. Digit Span was the lowest subtest score of the intelligence subtests, and the Modified Knox Cubes score was very low (3 out of 10, immediate). Finally, he achieved 3 categories on the card sorting test, but with 53 perseverative errors, showing an extreme perseverative tendency.

Summary of the Neuropsychological Assessment

Table 1 is a summary of all the tests administered to both brothers, approximately three months before death. It also includes the performance on the card sorting task in Patient 1, done at the time of the first assessment.

There are clearly no gross intellectual impairments. Intelligence measures in the Average range, and there is no reason to suspect that the prepathological condition was very different from average (occupations were an instrument handyman, and barber). It is noteworthy that even the Performance IQ, which samples primarily non-verbal intelligence and is very sensitive to generalized cerebral pathology, was intact in both patients.

Memory function is variable, but on any one test is not consistently impaired in both brothers.

The consistent findings in both cases are 1) impaired performance on tests of serial attention span (Modified Knox Cubes, Digit Span) and 2) highly perseverative behaviour on the card sorting task.

Summary of Neuropathological and Biochemical Findings

These were reported in detail in the original paper,[1] and will therefore be reviewed only briefly.

Post-mortem examination of the brains in both cases revealed a severe neuronal loss in the substantia nigra and the head of the caudate nucleus, with milder loss in the globus pallidus. The brainstem showed gliosis of the motor nucleus of X, n. tractus solitarius and adjacent reticular formation, with lesser gliosis in n. ambiguus. The cortex and cerebellum showed no abnormalities. Thus, there were extensive changes in the corpus striatum and in the medulla, but minimal changes elsewhere.

Biochemical assays revealed no deficiency in GABA, some deficiency of glutamic acid decarboxylase relative to normal, but not relative to other Parkinson patients. There were extremely low levels of tyrosine hydroxylase in all areas of the brain, but particularly in the caudate, putamen and substantia nigra. Patient 1 was on L-dopa medication at the time of death, but dopamine levels were nevertheless subnormal in both brothers, and in Patient 2 was low even relative to other Parkinson patients. Thus, there was clear evidence of degeneration of the nigrostriatal dopaminergic systems. No assays for noreprinephrine were done.

Discussion

The most salient findings in both cases were the presence of perseverative responding on a sorting task, and the presence of an attention-span deficit. Perseverative tendencies have been previously reported on category tasks in patients with Parkinson's disease,[8,9] with one exception.[10] Perseverations have generally been attributed to associated pathology, in such patients, of the caudate nucleus or the frontal lobes.[11,12] Since there is no report of neuronal loss in the frontal lobes in our two cases, direct frontal pathology may not be a prerequisite for the perseverative responding which Sandson & Albert call "stuck-in-set perseveration".[13]

The two patients presented here were even more perseverative (100% and 85% perseverative errors) than our other Parkinson patients who had been given the card sorting task (N = 8, mean perseverative errors — 45.4/60.5 errors or 75.6%). They are also more perseverative than our comparably-aged patients with frontal damage (n = 16, mean perseverative errors — 33.7/47.7 errors or 71%).

Our data would be compatible with suggestions that caudate damage itself may mimic the effects of frontal-lobe damage,

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through frontal-caudate connections,[14] but since striatal damage was extensive in our two patients, the evidence for specific caudate contribution is not strong. Moreover, in reviewing four of our cases with Huntington's chorea and with CT scan evidence of caudate atrophy, who had been administered the card sorting task, performance was characterized by perseveration in only one case of the four. The perseverative behaviour previously reported in Parkinson cases may therefore be attributable to damage to other parts of the basal ganglia.

It is difficult to evaluate the effects of the periodic apnea. The original report on these patients stated that no anoxic changes were seen in the brains. Lasting hypoxia is reported to result in disorders of learning and memory,[15] yet the two cases reported here have Memory Quotients comparable to their intelligence level. Delayed recall of material from the Wechsler Memory Scale, which is even more sensitive to memory disorders than is the initial recall,[16] is not consistently impaired either.

The other major finding of interest was that the serial attention span was impaired in both patients, and this was true for both verbal and nonverbal material. Thus, digit span was considerably lower than would be expected at this age level, and repetition of the cubes sequence was poor. This is despite normal memory function in one case, and only moderate disturbance in the other. The presence of deficits in immediate attention span in the absence of other memory difficulties has been previously documented in patients with idiopathic epilepsy.[17,18] In contrast, patients with severe global amnesia often have intact immediate span.[19] Patient 1 in fact showed some spike-and-wave activity on the electroencephalogram, similar to that seen in idiopathic epilepsy, but Patient 2 had merely a generalized dysrhythmia. It seems unlikely, therefore, that the attentional deficit is directly attributable to subclinical episodes of the "absence" variety. Impairment of serial attention span has been attributed to dysfunction of upper brain stem or other non-specific neural systems presumptively involved in "attention".[20] The latter is usually assessed by the immediate store of serially-ordered material.

The impairment of serial span in the present two cases is parallelled by a deficit in other patients we have seen with Parkinson's disease and in Huntington's chorea. It is therefore possible that the serial attention span deficit is related to neuronal loss in either the basal ganglia or the brainstem. It has been suggested that another aspect of attending, akin to vigilance, may be dependent on norepinephrine systems, and is consequently reduced in patients with Parkinson's disease.[21] Unfortunately, we have no information about norepinephrine levels in the brains of our two subjects.

The significant contribution of these two cases lies in the fact that the cortex appeared to be spared, while basal ganglia and other subcortical structures were extensively affected. They provide strong support for a subcortical contribution to serial attention span mechanisms, and cast doubt on suggestions that primary frontal-lobe pathology is a necessary prerequisite for perseverative responding.

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