Dementia in Movement Disorders

H. Teräväinen, M. Hietanen, J. Stoessl and D.B. Calne

ABSTRACT: Of all the movement disorders, Huntington's disease has been most consistently associated with dementia, while it is only over the last decade that intellectual and cognitive decline have been recognized as common features of Parkinson's disease. It is now known that the pathology in these two conditions reflects differential involvement of the striatum. The Huntington lesion is primarily in the caudate, while the Parkinson lesion preferentially affects the putamen. Both conditions have more diffuse pathology, and dementia may also occur in a wide range of other extrapyramidal diseases, such as progressive supranuclear palsy, the parkinsonism-dementia complex of Guam, and certain spinocerebellar degenerations. Clinicopathological correlations will be reviewed in these disorders of primarily subcortical pathology, and comparisons will be made with Alzheimer's disease, a disorder of predominantly cortical pathology.

RÉSUMÉ: La démence dans les désordres du mouvement. De tous les désordres du mouvement, la maladie de Huntington a été celle qui a été le plus fréquemment associée à la démence. Ce n'est que depuis la dernière décennie que le déclin intellectuel et cognitif est reconnu comme une manifestation fréquente de la maladie de Parkinson. Nous savons maintenant que la pathologie de ces deux affections reflère une atteinte différentielle du striatum. La lésion de la maladie de Huntington est principalement au niveau du noyau caudé, alors que, dans la maladie de Parkinson, elle atteint préférentiellement le putamen. Les lésions dans ces deux maladies sont plus diffuses et la démence peut aussi survenir dans une grande variété d'autres maladies extrapyramidales, comme la paralysie supranucléaire progressive, le complexe parkinsonisme-démence de Guam et certaines dégénérescences spinocérébelleuses. Nous revoyons les corrélations clinicopathologiques dans ces maladies impliquant principalement une pathologie sous-corticale et nous présentons des comparaisons avec la maladie d'Alzheimer, une affection dont la pathologie est située principalement au niveau du cortex.

Can. J. Neurol. Sci. 1986; 13:546-558

While dementia occurs in many diseases, there is a group of disorders of mainly unknown etiology characterized primarily by degenerative changes in the nervous system. Of all the movement disorders, Huntington's disease has been most consistently associated with dementia, it is only over the last decade that intellectual and cognitive decline have been recognized as common manifestations in Parkinson's disease. It is now known that the striatal pathology in these two conditions represents opposite poles, the Huntington lesion being primarily in the caudate, while the Parkinson pathology is predominantly in the putamen. Both conditions have more diffuse pathology, and dementia may also occur in a wide range of other extrapyramidal diseases such as progressive supranuclear palsy, parkinsonism dementia complex of Guam and certain spinocerebellar degenerations (Table 1). Clinicopathological correlations will be reviewed in these disorders of primarily subcortical pathology, and comparisons will be made with Alzheimer's disease, a disorder of predominantly cortical pathology. It is therefore necessary to start by considering the salient pathological and biochemical features of Alzheimer's disease, for comparative purposes.

Alzheimer's type dementia

We will first briefly review Alzheimer's disease[1,2] since it is the commonest and most extensively studied dementing illness. Until recently the use of the name Alzheimer's disease was limited to persons below 65, but now the term is included among the group of primary degenerative dementias (DSM III 1980) (Table 2), and the age is not considered relevant to etiology.[3] The disease shares numerous clinical features with Pick's disease[4] and these two diseases are frequently considered as one entity in the current literature, particularly since clinical separation is difficult. On the other hand, these two diseases still warrant differentiation since the pathological findings are regionally disparate and biochemical changes may be different.[5] In both diseases the neuropathological changes observed affect certain brain regions selectively and show important differences compared to the neuropathology accompanying movement disorders associated with dementia. In Alzheimer's disease the most evident alterations are observed in the frontal, temporal and parietal association cortex, and in the hippocampus. The primary motor, somatosensory and visual cortical areas are relatively preserved,[2,6,7,8,9,10,11,12] and these regional

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differences are reflected during life by comparable changes in cerebral glucose metabolism (Fig. 1) (c.f. also[13,14,15,16]). Alzheimer's disease differs from the various disorders of motor function that may be associated with dementia (Table 1) in that most subcortical cerebral structures are relatively well preserved, though in both categories of illness significant changes may occur in the nucleus basalis of Meynert,[17,18,19,20,21,22] amygdala[23] and locus ceruleus.[24,25,26,27] The subcortical structures are also relatively intact in Pick's disease occupying a somewhat intermediate position, in which the most significant changes are found in the frontal and anterior temporal cortex, although caudate atrophy does occur.

Disappearance of the large cholinergic neurones from the nucleus basalis of Meynert (a part of the substantia innominata) and the associated degeneration of their cortical projections have recently gathered interest because of the suggestion of a causal relationship with dementia.[22,28] This neuronal loss in the nucleus basalis in Alzheimer's disease contrasts with Huntington's disease, where the number of basalis neurons does not seem to be reduced in demented patients.[17,18,29] Significant depletion of the large neurones has recently been reported also in Parkinson's disease without concomitant Alzheimer changes.[20,30,31] Both decreased[32] and normal[33] numbers of cells have been reported in Pick's disease.

Ball et al[34] recently reported that decline in cognitive function correlates with changes in the hippocampus with or without cortical changes.

In addition to neuronal loss in the regions noted, Alzheimer's disease is characterized by the accumulation of large numbers of neurofibrillary tangles and lipofuscin, notably in neocortex, hippocampus, basal forebrain and amygdala, senile or neuritic plaques (especially in cortex and amygdala), as well as astrocytic hyperplasia and, particularly in the hippocampus, granuovacuolar degeneration.[2,8,9,10,12,34,35,36] Neurofibrillary tangles comprise argyophilic fibers consisting of paired helical filaments, each about 100 Å wide.[2,12,37] Senile plaques consist of the remnants of neuronal degeneration surrounding a dense central amyloid core. Their number seems to correlate with the severity of dementia,[34,38,39,40] whereas the amount of lipofuscin does not.[41] Although the constellation of pathoiogical features is characteristic, the individual components are nonspecific and can be found in the brains of aged non-demented persons,[9,42] Down's syndrome,[43] in various extrapyramidal syndromes including Parkinson's disease,[44,45] progressive supranuclear palsy,[46] parkinsonism-dementia complex of Guam,[47] subacute sclerosing panencephalitis[48] and dementia pugilistica.[43,48,49,50]

Neurochemical alterations reflect the structural changes. The loss of hippocampal and cortical cholinergic neurons and of cholinergic axons ascending from the nucleus basalis of Meynert, lead to significant declines in acetycholine and the activity of cholinergic enzymes (choline acetyltransferase and acetycholinesterase); changes in other neurotransmitters are less profound.[51,52,53,54,55,56,57,58,59] Muscarinic acetycholine receptors are normal.[58,60,61,62]

Indices of noradrenaline, dopamine and serotonin may be decreased in cerebral cortex and hippocampal noradrenaline, dopa-

Table 1. Diseases accompanied by dementia

- Primary degenerative
  - Cortical dementias
    - Alzheimer's disease
    - Pick's disease
  - Extrapyramidal disorders
    - Huntington's disease
    - Multiple system atrophies
    - Parkinson's disease
    - Spinocerebellar degenerations
    - Progressive supranuclear palsy
    - Wilson's disease
- Vascular
  - Binswanger's disease
  - Multi-infarct dementia
- Infectious
  - General paresis
  - Slow-virus infections
- Toxic and metabolic
  - Alcoholism
  - B12 vitamin deficiency
  - Drug intoxications
  - Heavy metal poisoning
  - Hypothyroidism
- Miscellaneous
  - Anoxic
  - Hydrocephalus
  - Neoplastic and Paraneoplastic
  - Traumatic

Table 2. Clinical criteria for dementia (Modified DSM III, reference 227)

1. Loss of intellect sufficient to impair social or occupational function.
2. Memory impairment.
3. One of the following:
   - — impaired abstraction
   - — impaired judgement
   - — aphasia
   - — agnosia
   - — constructional difficulties
   - — personality change
4. Alert state of consciousness

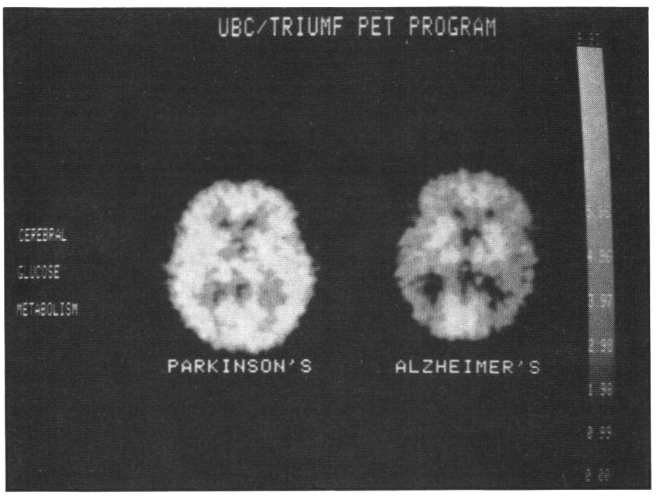

Figure 1 — Fluorodeoxyglucose (FDG) PET scans of patients with Parkinson's disease and Alzheimer's disease. The Parkinson scan is normal (see figure 2 for comparison) but in the Alzheimer scan, there is hypometabolism in temporoparietal cortex, with preservation of subcortical structures and occipital cortex.

https://doi.org/10.1017/S031716710003729X Published online by Cambridge University Press

mine and serotonin activity is diminished.[26,27,56,63,64,65,66,67] There is a loss of noradrenergic and serotonergic projections from the brain stem, particularly the locus ceruleus.[25,27,63,68] Comparable changes have also been reported in the hypothalamic nuclei and caudate[26,65,69] in postmortem material. Reduced levels of striatal dopamine have also been noted[56,57] but the reports have been variable,[71] and striatal MAO-B activity is increased.[56] Homovanillic acid concentrations are reported to be low in striatum[72] and CSF.[73,74] The concentration of dopamine-beta-hydroxylase is decreased in cortex and hippocampus.[75] The number of striatal dopamine receptors is claimed to fall,[76] particularly D2 receptors.[62,77] Serotonin (S1 and S2) receptors are reduced in the cerebral cortex, hippocampus and amygdala but not in the basal ganglia or in the basal forebrain.

Somatostatin-like immunoreactivity is reduced in the cortex[78] and somatostatin receptors are also decreased.[79] Neuronal tangles have been demonstrated within somatostatin neurons[80] and somatostatin immunoreactivity has been demonstrated within neuritic plaques.[81] Significant alterations in peptide concentrations seem to be limited to somatostatin,[78,81] and possibly substance P[34,54,82,83,84] and the GABA system seems also to be relatively spared.[64,82,83,85] Diminished GABA has been reported in the temporal cortex,[82,83] but this finding was not substantiated by another investigator.[86]

Analyses have mainly been performed on postmortem samples with the exception of the work of Francis et al,[87] who reported a correlation between reduced acetylcholine synthesis measured in vivo (in cortical biopsy samples) and cognitive function. There were less significant changes in serotonin, noradrenaline and 5-HIAA. Furthermore, the Alzheimer biochemistry may be different in early onset disease compared to late. These various neurotransmitter alterations are likely to reflect neuronal loss and their significance in clinical dementia remains to be shown. Perhaps further insight will emerge by taking heterogeneity into account. For example, Mayeux et al[88] divided patients into subgroups: 1. Benign with no or little progression, 2. myoclonic with severe intellectual decline, 3. extrapyramidal with severe intellectual and functional decline, 4. typical.

The most important symptom in the Alzheimer's disease is the relentless decline in intellectual functions, that occurs much more rapidly than during normal aging. Short of brain biopsy, there is no specific test available for diagnosis during life so other dementing diseases (Table 1) must be excluded. One usable set of criteria is given in Table 3.[89] The first symptom of the disease is almost always a decline in memory with impaired ability to learn new and recall old information.

The general physical and neurological examination is unremarkable at early phases of the illness, contrasting clearly with the abnormal neurological findings related to movement disorders which may or may not be accompanied by a decline in mental functions (Table 4). With more advanced disease, the dementia may frequently be accompanied by extrapyramidal signs comparable to parkinsonism: hypokinesia, rigidity, postural changes and tremor.[90] These may be associated with primitive reflexes, myoclonus, seizures and incontinence. There seem to be atypical cases of Alzheimer's disease combined with pyramidal and extrapyramidal signs early in the illness.[91]

Huntington's Disease

Huntington's disease[92,93,94] is characterized by chorea, dementia and a history of similar symptoms in relatives, the mode of inheritance being autosomal dominant. The adult type has its onset between 30 and 40 years of age. Both the earlier age of onset and the clinical features distinguish Huntington's disease from Alzheimer's disease. Involuntary movements usually begin at about the same time as patients begin to experience difficulties in their memory function. Early in the disease the choreic movements may be intermittent and localized but they later become generalized, involving facies, head, trunk and legs. Dystonic postures are evident in advanced cases and the end stage of the disease is characterized by fixed flexed posture. A few subjects may have pyramidal signs and some may have disturbed oculomotor function.[93,95,96,97,98] Close to 15% of the patients have the rigid (Westphal) variant of the disease.[99,100] This often begins in the second decade and is frequently accompanied by grand mal epilepsy.[101,102] Cases with the Westphal variant at an older age could be confused with parkinsonism.

Unlike idiopathic Parkinson's disease, the memory decline in Huntington's disease is usually evident early and personality

Table 3. Criteria for clinical diagnosis of Alzheimer's disease (Modified from reference 89)

Probable

Dementia established by clinical evaluation and verified by neuropsychological examination.

Deficits in at least two cognitive areas.

Progressive worsening of memory and other cognitive functions over a period of months.

Alert state of consciousness.

Onset between ages of 40 and 90 years.

Absence of systemic disorders that could account for progressive deterioration of intellectual function.

Diagnosis is supported by progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia), impaired activities in daily living and altered behaviour, normal cerebrospinal fluid, normal or non-specific changes in EEG and CT evidence of cerebral atrophy.

Definite

Clinical criteria for probable Alzheimer's disease fulfilled.

Histopathological evidence obtained from biopsy or autopsy.

Table 4. Clinical characteristics of primary degenerative dementias (Modified from reference 220)

	Alzheimer	Subcortical Dementias
Verbal Output		
Language	Aphasic	Normal
Speech	Normal	Dysarthric, hypophonic
Mental Status		
Memory	Amnesic: learning deficit	Forgetful: retrieval deficit
Cognition	Abnormal: poor judgement	Abnormal: slow processing
Affect	Unconcerned or disinhibited	Apathetic or depressed
Motor System		
Posture	Normal*	Stooped, extended
Gait	Normal*	Abnormal: usually slow
Involuntary movements	None*	Tremor, chorea, dystonia
Muscle tone	Normal*	Usually increased

*Non-specific abnormalities in late stages of the disease.

https://doi.org/10.1017/S031716710003729X Published online by Cambridge University Press

changes, such as apathy, anxiety, irritability, impaired concentration and bizarre behaviour[103] are frequent and often profound. About 50% of the Huntington patients show significant depression, sometimes alternating with mania,[104,105,106,107] and about 25% have psychotic symptomatology resembling schizophrenia.[106,107,108] Unlike the depression of Parkinson's disease, that of Huntington's disease often conforms to the DSM-III criteria for major depression with frequent suicides.[104,108] Personality changes and psychiatric symptoms are usually present in the early stages of the disease; in about one third of subjects they precede the chorea.[109,110,111,112]

The profile of dementia in Huntington's disease seems to differ from that in Alzheimer's disease: the verbal linguistic abilities are relatively spared, with no aphasia or agnosia in Huntington's disease, and short term memory is significantly more severely affected than long-term memory. In contrast, intellectual decline in Alzheimer's disease is characterized by early impairment of language, prominent loss of long term memory with relative preservation of immediate recall in many early cases.[113,114,115,116,117,118,119] Later, more global intellectual disintegration occurs.[120]

Extensive degeneration of the caudate nucleus is the pathological hallmark of advanced cases of Huntington's disease but caudate atrophy also occurs in other choreatic diseases.[118,121,122,123] Loss of neurons also occurs in the putamen[8,124,125] and thalamus;[126,127] the ventroanterior putamen is relatively spared.[128] Macroscopic changes include slight to moderate subcortical-fronto-parietal brain atrophy rather than cortical atrophy. The most significant microscopic change is preferential loss of small neurons both in striatum and thalamus; the large neurons may be selectively spared in the rigid variant.[129] Neurons are lost in the cerebral cortex and hippocampus.[8,124,130] Unlike Alzheimer's disease, there is no significant decrease in the number of cholinergic neurons in the nucleus basalis of Meynert.[17,18,29]

Profound declines of GABA and its biosynthetic enzyme glutamic acid decarboxylase take place in both striatum and substantia nigra.[131,132,133,134,135,136,137] The CSF GABA content may be reduced.[138,139,140] The number of GABA receptors is decreased in putamen and caudate but increased in substantia nigra.[141] Significant depletion of acetylcholine transferase occurs,[132,143,142,143] while monoamine oxidase and tyrosine hydroxylase levels are normal.[142] Changes in dopamine are controversial. Spokes[144] observed significant increases in dopamine in striatal nuclei, nucleus accumbens and substantia nigra pars compacta. Birds and Iversen[134] found increased putamenal dopamine in rigid patients but most of these were advanced cases, rather than juvenile forms. Melamed et al[145] reported normal levels of dopamine in the caudate nucleus and an increase in putamen, but the HVA-dopamine ratio was unchanged.

Changes in morphology and biochemistry of the cerebral cortex are less than those in the subcortical structures.[142,143] These differences are reflected in the pattern of glucose utilization, which is decreased more in the striatum than in cortical areas.[146,147] We have found decreased cortical glucose metabolism in the cortex of patients with Huntington's disease,[148] particularly in the frontal lobes, which are relatively spared in Alzheimer's disease. Others have reported[149] decreased coupling between various cortical regions in Huntington's disease.

In Huntington's disease there is a significant increase in somatostatin[150] and a loss of substance P, met-enkephalin and cholecystokinin.[151,152,153] The activity of the peptide metabolizing enzyme proline endopeptidase activity is abnormally low in striatal nuclei.[154] The number of somatostatin containing neurons seems to be decreased in striatum but not in the substantia nigra.[155]

Parkinson's disease

Parkinsonism has many possible causes (Table 4). We will focus on idiopathic parkinsonism or Parkinson's disease, with emphasis on memory and cognitive functions, comparing these with Alzheimer's disease and Huntington's disease.

Parkinsonism is a motor disorder, characterized by a stooped posture, relative immobility, and tremor at rest. Speech may be monotonous and the voice may lose its volume. A slow gait with short steps is associated with loss of normal arm swings; progression is interrupted by brief periods of 'freezing', and there may be difficulty in negotiating doorways, turning, and maintaining balance. Rigidity is elicited during examination of passive movements but there are no pyramidal signs and sensory examination is normal (even though sensory symptoms varying from paresthesiae to pain may occur). Parkinson's disease is not solely a disorder of motor system, however; autonomic and higher mental functions are also involved. Autonomic symptoms include constipation and urinary retention. Parkinson's disease is some 20 times more common than Huntington's chorea. The disease is sporadic in most cases, with increasing frequency after the age of 40 years, although juvenile forms exist[156] and there are occasional hereditary forms.[157] Unlike Alzheimer's disease and Huntington's disease, regional glucose utilization (Figure 1) is not grossly disturbed,[158] although interregional metabolic relationships may be altered.[149,159]

Recently it has been recognized that cognitive decline occurs in idiopathic Parkinson's disease though this feature was either neglected or even denied in some earlier studies. The estimated frequency of cognitive decline varies widely. Clinical studies without formal psychological examination in 1354 unselected patients with Parkinson's disease have led to estimates of dementia in 8 to 56% of patients.[45,160,161,162,163,164,165,166]

The most extensive of the above surveys included a total of 964 patients and it was concluded that the prevalence of demen-

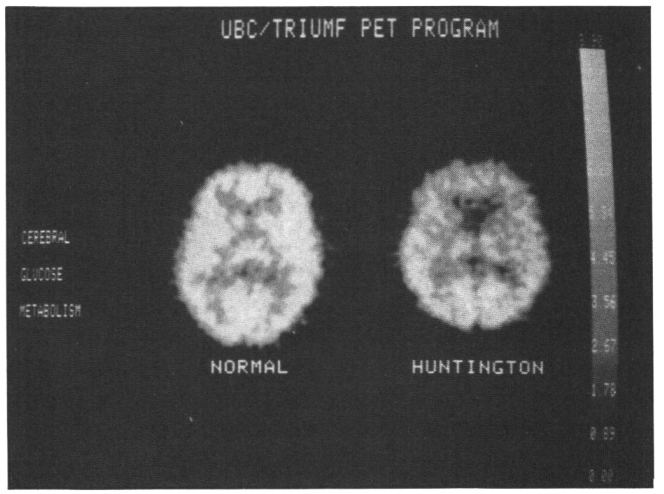

Figure 2 — FDG PET scan of a patient with early Huntington's disease, who had normal caudate nuclei as assessed by CT. There is obvious hypometabolism in the caudates compared to a normal scan at the same level, as well as a decrease in cortical metabolism, particularly in the frontal lobes.

tia was 29-32%.[106,107,163] It seems probable that the prevalence of dementia at the time of diagnosis of Parkinson's disease is higher (about 10%) than in the normal population of comparable age.[167]

Studies employing formal psychological tests report cognitive declines between 3%[168] and 93%[169] of patients (Table 5). It is difficult to compare the results (Table 5) since patients had varied durations of disease, were on varying medications and some had undergone stereotactic surgery. It is also possible that earlier literature included patients with Shy-Drager syndrome and Steele-Richardson-Olszewski syndrome prior to their general recognition as separate entities.

In spite of the wide range of observations, it is certain that dementia is a significant cause of disability in Parkinson's disease, and dementia is more common in patients with more severe motor deficits;[170] cognitive function and memory declines as the disease advances.[171,171a] However, the extent of dementia in various phases of the illness is still controversial,[172,173] and its profile is only now being characterized.[173a] Declines have been reported to occur in memory, concept formation, solving of complex problems, visuospatial processing and perceptual motor function. Information processing is slow, but there is generally no aphasia or agnosia. Depression is common (about 50%), and reported to be more frequent in subjects with cognitive impairment.[174]

One of the most confounding aspects of evaluating the dementia in Parkinson's disease is assessing the impact of medications (Table 5). It is well known that anticholinergic agents and dopaminomimetics can have adverse mental effects, including confusion and psychosis. It was recently reported[175] that after one month of treatment with small doses of trihexyphenidyl, a mean decrease of about 30% occurred in recent recall but not in immediate memory tests; the score for associative learning decreased from 12.7 to 10.7.

To obtain further information on the mental profile of Parkinson's disease, we analyzed the neuropsychological performance of 130 patients with Parkinson's disease (mean age 62.2 years, mean disease duration 4.7 years, mean clinical disability 3.3 on Hoehn and Yahr[176] scale).

We employed subtests (similarities, picture completion and block design) of the Wechsler Adult Intelligence Scale (WAIS) and Wechsler Memory Scale (WMS-1) with digit span, logical memory, associative learning and visual reproduction subtests. The level of depression was assessed using Beck Depression Index. The subjects were tested at their first visit.

The memory scores, arranged by ascending order of performance of individual patients in each of the four tests, are shown in Figure 4. It is evident that the variation between individual patients was large. Furthermore, the number of patients with abnormally low scores was much larger in the more complex subtests (such as logical memory and associative learning) that required processing of material, than in a less demanding test (digit span) based upon immediate retrieval of numbers.

The cognitive profile (subtests of WAIS) is shown in Figure 3. Again a large range was observed in the performance of individual patients. The number of subjects with relatively good performance in the picture completion subtest was larger than in the block design or similarities subtests.

Comparison of the present results with the figures published for Alzheimer's and Huntington's disease indicates that the memory profile in our patients resembled Alzheimer's disease more than Huntington's disease.

The mean Beck Depression Index (+SD) was 5.18 (+4.9) and the depression scores of individual patients are shown in Figure 5. In some 50% of the patients the score was 5 or more, indicating some degree of depression. There was a small group of patients (8%) who could be considered to be significantly depressed, although only two fulfilled the DSM III criteria for major depression. The subjects with more significant depression might differ from the general parkinsonian population who showed relatively linear and gradual increases of the Beck index (Figure 3). It seems evident that the level of depression in Parkinson's disease is only rarely comparable to that seen in Huntington patients, and may be more comparable to the depression that occurs in Alzheimer's disease.

To evaluate the memory and cognitive performance of patients free from drug effects and to compare their performance with normal controls, we analyzed 67 patients who had not received any antiparkinson medications, and 43 control subjects (mean age 59.4 years). The mean age of the patients was 59.1 years and mean disability[176] was 2.3. None of the subjects had other

Table 5. Psychological studies evaluating cognitive performance in Parkinson's disease

Reference	N	Age (mean years)	Control group	Drug Treatment	Disease Duration	Cognitive decline present	%
221	55	54	Yes	Anticholinergic	NR	Yes	NR
179	50	54	No	Varied	NR	Yes	NR
22 2	61	54.5	No	Varied	NR	No	—
183	74	55.3	Yes	NR	5.1	—	—
223	25	50.9	Yes	NL	NR	Yes	NR
180	47	63.5	Yes	NL	5.5	Yes	45
182	63	64	No	Anticholinergic	7.2	Yes	37
171	42	58	No	Anticholinergic	No	—	—
224	79	57.5	Yes	NL	7.6	Yes	NR
170	60	62.3	No	Levodopa	9.4	Yes	NR
169	60	62.7	Yes	Levodopa	9.4	Yes	93
225	20	65	Yes	Levodopa & Anticholinergic	NR	Yes	55
178	30	59.4	Yes	None	2.4	Yes	NR
226	10	69	Yes	Levodopa & Anticholinergic	12.7	Yes	NR
171a	203	67	No	Levodopa	12.6	Yes	29
173a	28	67	Yes	NR	6.0	Yes	53

NR = not reported
NL = no levodopa, other treatment not reported

https://doi.org/10.1017/S031716710003729X Published online by Cambridge University Press

neurological diseases. The patients and the controls received the same test battery as already described. The data were submitted to statistical analysis using Chi-square test, Student's t-test, Pearson's product-moment correlation, canonical correlation and discriminant analysis. The clinical neurological disability (Columbia score) and the psychometric performance of the two groups is shown in Table 6 and Figure 6. The patients scored lower than the controls in all the memory tests except the digit span subtest, confirming the less rigorously obtained data from the general population shown in Figure 4. The cognitive performance of the patients was inferior to the controls only in the block design subtest of WAIS, which necessitates the use of both motor capabilities and visuospatial abilities. Critical flicker fusion frequency was analyzed since the test is said to correlate with the level of attention;[177] the results in the two groups were not significantly different.

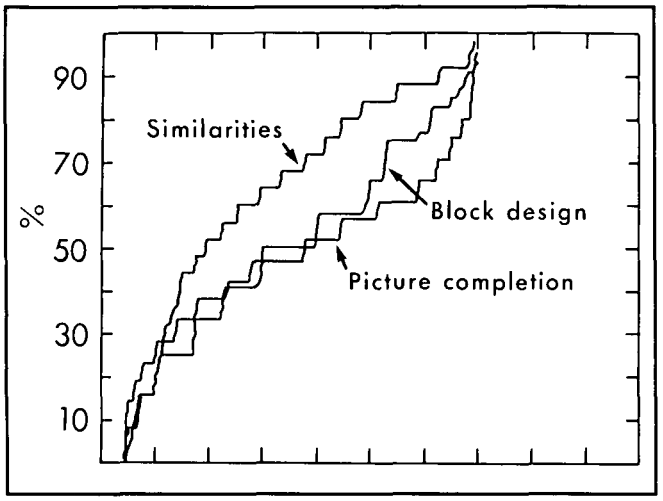

Figure 3 — Subcores for cognitive (WAIS) tests in 140 unselected patients with Parkinson's disease at their first visit expressed as percent of maximum obtainable score and arranged in ascending order. The cognitive score obtained by individual patients show large variations as did the memory score (Fig. 4). The number similarities of patients with relatively good performance in the subtest was larger than in the subtests of block design and picture completion: 75 patients out of 140 scored less than 50% of maximum possible in the picture completion and 59 in the block design test compared with 38 patients in the subtest of similarities.

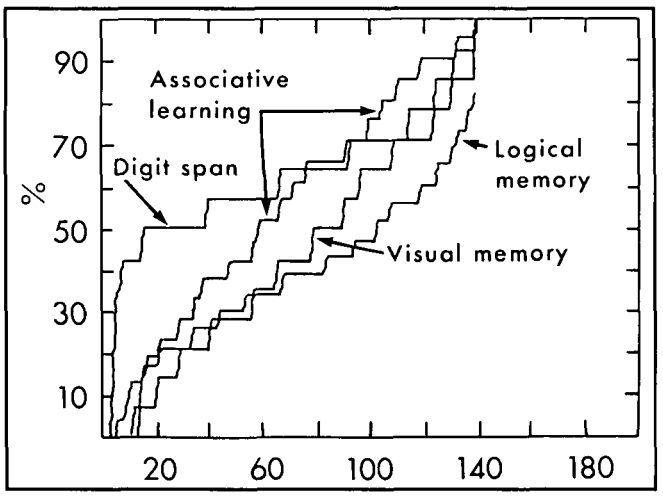

Figure 4 — Subscores of WMS-1 memory texts obtained in 130 unselected patients with Parkinson's disease at their fist visit. The scores are expressed as per cent of maximum possible score for the test in ascending order of performance. The number of patients with low scores is much larger in more complex subtests requiring processing of material, than in the digit span subtests which only required immediate retrieval. Out of the 140 patients, 102 patients scored less than 50% of the maximum possible in the test for logical memory, as did 78 in the test for visual memory, 58 in the test for associative learning and less than 15 in the digit span test.

Examination of untreated patients allowed a unique possibility to evaluate the relationships between mental function and motor disability. There was no significant association between the Columbia score or its subscores and either cognitive function or memory; the correlation coefficients are shown in Table 7. The results were verified by canonical correlation analysis. Lees and Smith[178] reported difficulties in shifting conceptual sets and perseverative errors in a group of untreated parkinsonian patients, whereas there was no significant memory decline. Their patients were somewhat less disabled but perhaps of greater importance, they used a memory test (two choice recognition test) that measured recognition mainly. Our results also indicated that immediate retrieval was not significantly inferior to the performance of the controls whereas more complex subtests involving mental processing showed a small but definite impairment.

This mean Beck Depression Index was somewhat higher in these untreated patients than in the general parkinsonian population (5.9); it did not correlate with neurological disability or with the memory or cognitive scores. A possibility thus exists that the depression, cognitive decline and the motor disability are separate biological phenomena in Parkinson's disease even if they often occur together. Impaired cognitive functions have previously been reported to be associated with rigidity,[163,179] akinesia,[180] bradykinesia,[163,170,181] all of these[182] or none of

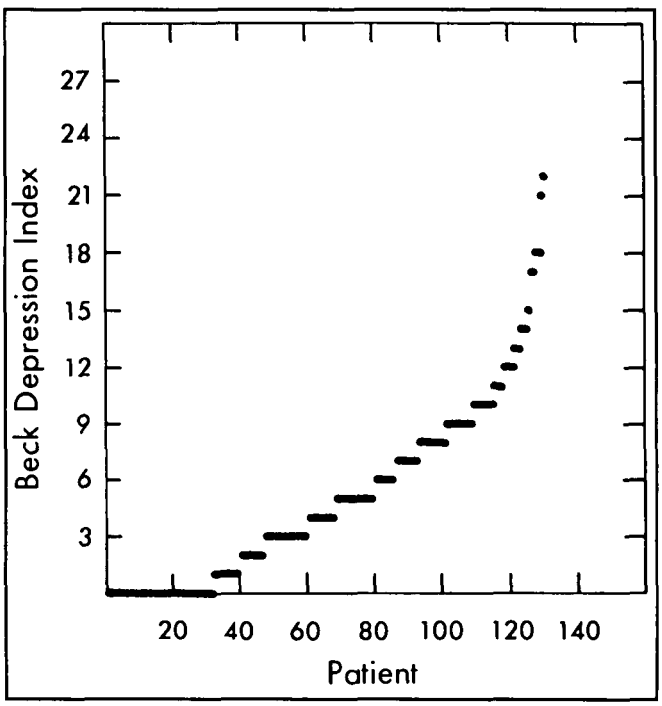

Figure 5 — Beck Depression Index (BDI) of 130 unselected patients with Parkinson's disease at their first visit arranged in ascending order. The mean BDI was 5.18 indicating that about 50% of the patients were at least mildly depressed. The BDI was less than 12 in about 120 patients; only two patients obtained BDI scores comparable to those observed in major depressions.

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these.[183] Some of the discrepancies may be explained by the drug therapy used in the previous studies, which may have had significant effects on the clinical scores. In addition, larger studies have included a more severely disabled population of patients.

By dividing the untreated parkinsonian subjects arbitrarily into two groups, over 60 years (mean 67.2) and 60 years or younger (mean 49.1), it was possible to study the relative effect of aging on cognitive functions in a population of patients with similar clinical disability. (Columbia total score for 'young' = 20.0 - 9.1 and 'old' 24.2 - 9.7). An age-related decrease of about 15% in psychomotor and cognitive performance occurred between ages 50 and 70 related to aging (Figure 7) except for logical memory, which did not decline.

From our observations (Figures 3 and 4), some 20% of the total population of parkinsonian patients studied obtained a score less than 30% of maximum possible on formal psychological examination, indicating impairment of memory and cogni-

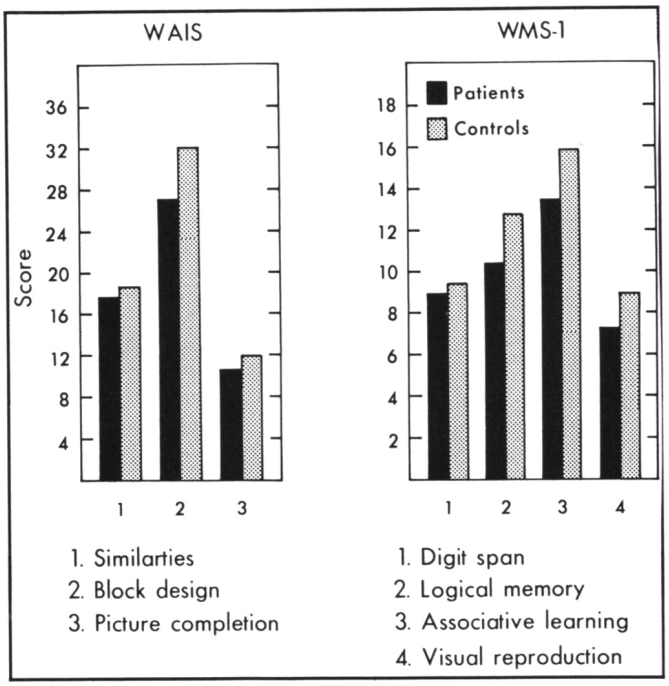

Figure 6 — Mean scores of cognitive (WAIS) and memory (WMSI) performance in 67 untreated patients with Parkinson's disease (solid bars) and 43 age-matched controls (dotted bars). The patients performed worse than the controls in the WAIS similarities (1), block design (2) and picture completion (3) subtests. This difference had statistical significance ($p<0.05$) only in the block design subtest (2). The inferior memory performance (WMSI) of the patients compared to the control subjects reached statistical significance in the subtests of logical memory (2, $p<0.01$), associative learning (3, $p<0.01$) and visual memory (4, $p<0.05$) but not in the digit span (1, $p>0.05$).

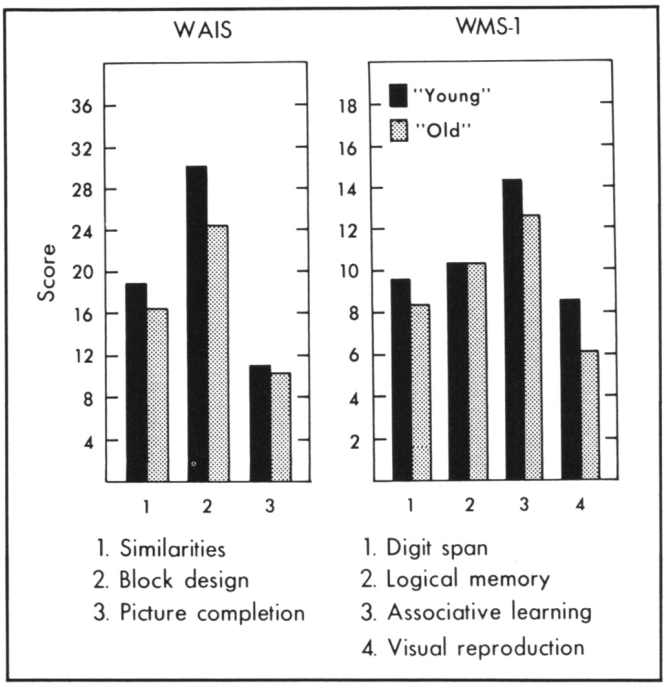

Figure 7 — Mean cognitive (WAIS) and memory (WMSI) scores of untreated patients with Parkinson's disease less than 60 (49.1 + 7.0, mean + SD, N = 30) and 60 or more (67.2 + 6.1, mean + SD, N = 37) years of age. The older patients (dotted bars) performed worse than the younger (solid bars) in the WAIS similarities (1) and block design (2) subtests, but the difference was small in the picture completion (3) subtest. There was no difference in the WMSI logical memory (2) subtests whereas the performance of the older patients was inferior to that of the younger ones in the WMSI subtests of the digit span (1), associative learning (3) and visual memory (4).

Table 6. Cognitive and memory functions in untreated Parkinsonian patients and controls (mean + SD)

	Parkinsonian patients	Controls	Significance
N	67	46	
Age (years)	59.1 + 11.1	59.4 + 12.5	NS
Disease Duration (years)	2.3 + 1.4	—	
Clinical disability*	2.5 + 0.7	—	
Columbia score			
— Temor	2.0 + 2.1	0.0 + 0.3	
— Rigidity	6.0 + 3.0	0.2 + 0.6	
— Hypokinesia	14.3 + 7.4	1.6 + 2.0	
— Total clinical score	22.3 + 9.6	1.8 + 2.3	
WAIS			
— Similarities	17.5 + 5.2	18.5 + 4.4	NS
— Block design	26.9 + 10.5	31.9 + 9.6	$p<0.05$
— Picture completion	10.5 + 3.6	11.8 + 3.7	NS
WMS I			
— Digit span	8.9 + 1.8	9.4 + 1.6	NS
— Logical memory	10.3 + 4.4	12.7 + 3.7	$p<0.01$
— Associative learning	13.4 + 5.2	15.8 + 4.3	$p<0.01$
— Visual reproduction	7.2 + 3.4	8.9 + 3.2	$p<0.01$
Critical flicker fusion frequency	37.9 + 3.6	38.2 + 3.5	NS

https://doi.org/10.1017/S031716710003729X Published online by Cambridge University Press

tive ability. These findings do not emerge in the early years of disease. The patients with Parkinson's disease differ from those with Alzheimer's disease in that their memory loss is relatively small in comparison with the control population and they do not seem to have a sufficient variety of other cognitive deficits to justify the term dementia.

Diffuse cerebral atrophy is commonly observed in neuroradiological and post mortem studies of Parkinson's disease,[184,185,186] but the striatal changes are usually slight,[187] in contrast to Huntington's disease. Similarly, minor changes are frequently present in hippocampus, ventral tegmental, and hypothalamic nuclei.[188,189] Histological changes are characterized by profound degeneration in the substantia nigra pars compacta. Significant but less severe loss of neurons is found in other catecholamine containing nuclei, such as locus ceruleus, and dorsal vagal nucleus.[190,191] The presence of Lewy bodies may be found in the involved structures.

Alzheimer-type neuropathological changes, such as neurofibrillary tangles and senile plaques, are present to variable degrees in Parkinson's disease but their significance is controversial. The severity of the motor deficits correlates with the neuronal loss in the substantia nigra,[44] but the reported association of parkinsonian dementia with Alzheimer-type changes in the neocortex[45,192] is far from established. Hakim and Mathieson[165] observed more Alzheimer changes in parkinsonian brains than controls but more recent studies indicate that the number of neuritic plaques and neurofibrillary tangles in Parkinson's disease may not be significantly different in patients with or without dementia, nor do their numbers differ from those observed in a normal age-matched population.[193,194] Furthermore, dementia may exist in parkinsonian patients without concomitant Alzheimer neuropathology.[195,196,197] The evidence does not allow any firm conclusion on whether cognitive decline is related to decreased neurons in the nucleus basalis of Meynert. In one report, loss of these neurons was seen in demented parkinsonian patients whereas no change was observed in patients without dementia.[198] In contrast, Candy et al[199] reported significant reduction of the neurons in the nucleus basalis without Alzheimer neuropathology in three parkinsonian patients without dementia; this clinicopathological finding may be more frequent than previously recognized.[31]

Neurochemical studies have given more consistent results relating to catecholamine pathways than cholinergic systems. Profound decreases in striatal dopamine have been observed with significant but less marked reductions in the hippocampal and limbic regions,[200,201,202] and others cf,[203,204] Depletion of serotonin and noradrenaline occurs in the basal ganglia, limbic system and neocortical areas, in accord with the histological findings.[137,202,205,206,207] While dopamine is thought to play a crucial role in motor function, decreases in serotonin may be related to depression.[208]

A plausable concept of cholinergic dysfunction has not yet emerged and its relationship to memory and cognitive decline in parkinsonism remains to be elucidated. There are reports that nondemented patients with parkinsonism may have normal choline acetyltransferase activity (CAT) in the cortex,[30,196] but subnormal CAT activity has equally been claimed to occur in parkinsonian patients whether or not they were demented.[209] A recent study[59] reported a high degree of correlation between mental impairment and reduction in temporal neocortical CAT activity. These changes were correlated with cell counts in the nucleus basalis, but not with plaque or tangle formation. Also reminiscent of Alzheimer's disease is the observation of Epelbaum et al[210] that hippocampal somatostatin is decreased in demented parkinsonians.

Finally, Kuhl et al[158,211] found severe temporoparietal hypometabolism in PET studies on demented subjects with Parkinson's disease, the pattern usually associated with Alzheimer's disease. More studies combining clinical, neuropsychological, histopathological and biochemical observations are needed, taking into account that there are subgroups in Parkinson's disease[170,212] as in Alzheimer's disease,[213,88] and that combinations of both diseases must exist.

Table 7. Correlations of cognitive and memory functions with extrapyramidal symptoms (Columbia score) in untreated Parkinsonian patients

	Tremor	Rigidity	Hypokinesia	Total Score
WAIS				
— Similarities	0.23	0.01	0.08	0.02
— Block design	0.05	0.13	0.10	0.13
— Picture completion	0.11	0.04	0.13	0.11
WMS I				
— Digit span	0.20	0.05	0.02	0.05
— Logical memory	0.10	0.07	0.03	0.01
— Associative learning	0.04	0.04	0.00	0.00
— Visual reproduction	0.01	0.03	0.09	0.06

Other movement disorders

In progressive supranuclear palsy,[46] conjugate gaze palsy, facial spasticity, pseudobulbar palsy and parkinsonian features are frequently associated with dementia.[214,215] Neuronal loss, neurofibrillary tangles and plaques affect nuclei of the striatum, brainstem and cerebellum. Glucose hypometabolism in prefrontal cortex has recently been reported,[216] and the authors considered that this might reflect disturbed innominatocortical projections. There is indeed loss of large cells of the nucleus basalis in this disorder.[217]

Striatonigral degeneration[218] may be clinically indistinguishable from Parkinson's disease. Mild cognitive changes may occur, but these are poorly characterized and brain biochemistry has not been studied. Nevertheless, a subcortical basis for the clinical features is probable, because cortical pathology is minimal.

In both multiple system atrophy (Shy-Drager syndrome) and olivopontocerebellar atrophy, dementia can occur in combination with bradykinesia, rigidity, tremor, ataxia or autonomic dysfunction.

The combination of rapidly progressive dementia, parkinsonism, ataxia and myoclonus is suggestive of Creutzfeldt-Jakob disease.

Corticodentatonigral degeneration[219] is a rare disorder characterized by hypertonia, involuntary movements and a profound degree of apraxia. The characteristic pathological feature is the presence of neuronal achromasia with neuronal degeneration affecting the cerebral cortex, substantia nigra and dentatoolivothalmic system. Although dementia was not a prominent feature in the original report, we have seen patients in whom the characteristic clinical features (pathologically unverified) have been associated with varying degrees of dementia and aphasia.

Finally, dementia can occur in conjunction with dystonia and/or tremor in a variety of uncommon degenerative disorders, including Wilson's disease, Hallervorden-Spatz disease and various lipid and ganglioside storage diseases.

Conclusion

We have compared the dementia of Alzheimer's disease with various extrapyramidal disorders in which there is a deterioration in intellectual function, in particular Huntington's disease and Parkinson's disease. In contrast to Alzheimer's disease, Huntington's disease is characterized by substantial impairment of memory at a stage when dysphasia is not evident. In Parkinson's disease the prevalence and nature of dementia are controversial. Studies are generally complicated by pharmacotherapy. From our own observations we conclude that dementia occurs in 15-20% of patients, the rate being lower in early disease and higher as motor deficits become substantial. The early pattern of parkinsonian intellectual difficulty involves mental processing rather than memory, and in contrast to Alzheimer's disease, dysphasia is not prominent. In both Huntington's disease and Parkinson's disease the predominant morphological and biochemical pathology are concentrated in the striatum, and in both of these disorders there is no conclusive evidence of major changes in the nucleus basalis. These features are all distinct from Alzheimer's disease, where deterioration in memory is associated with dysphasia, and the main pathology involves the cerebral cortex and substantia innominata.

Acknowledgement

We wish to thank the Dystonia Medical Research Foundation and the MRC of Canada for supporting this work.

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