Neurochemical Basis of Dementia in Parkinson's Disease

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ABSTRACT: According to their mental status, patients with Parkinson's disease can be subdivided into three groups: (1) mentally normal patients; (2) patients with severe cognitive impairment and Alzheimer-type brain pathology (neuritic plaques, neurofibrillary tangles, granulovacuolar changes); and (3) demented patients without any evidence of Alzheimer changes. Neurochemically, irrespective of the presence or absence of Alzheimer-type brain pathology, demented Parkinson patients seem to have the same disturbance of cortical cholinergic neuron function as patients with Alzheimer-type dementia (Alzheimer's disease), namely, reduced levels of cortical acetylcholine esterase and choline acetyltransferase activity. At present, the question whether the "cortical cholinergic deficiency" is the only (or sufficient) neurochemical basis for the cognitive impairment in Parkinson patients with dementia cannot be answered with certainty; the additional role of other neurotransmitter changes known to occur in the Parkinson brain, especially loss of cortical, hippocampal and subcortical noradrenaline and/or dopamine cannot be ruled out.

RÉSUMÉ: Les patients Parkinsoniens peuvent constituer, en rapport avec leur état mental, trois groupes distincts: (1) patients mentalement normaux; (2) patients avec atteinte cognitive sévère et pathologie type Alzheimer (plaques, amas neurofibrillaires, modifications granulo-vasculaires); (3) patients déments sans évidence d'Alzheimer. Peu importe la présence ou non des modifications pathologiques de l'Alzheimer, les parkinsoniens déments ont tous un taux réduit cortical de l'activité de l'acéthyl-choline-estérase et de la cholineacetyl-transferase, comme dans la maladie l'Alzheimer. Nous ne pouvons donc pas dire se cette déficience cholinergique corticale est suffisante pour expliquer les troubles cognitifs. Ainsi nous ne pouvons exclure un role pour les pertes corticales, hippocampiques et sous corticales de nor-adrenoline et/ou de dopamine.

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Parkinson's disease (PD) as a disturbance of basal ganglia regulation is essentially a disorder of (extrapyramidal) motor function, and global dementia is not an obligatory symptom of this condition. However, it has long been known that patients with PD often present with signs of cognitive impairment of varying severity. A survey of the literature available to us shows that probably as many as 30 percent of PD patients may have disabling dementia, the severity of which probably satisfies DSM-III criteria (Table 1).

Only few studies seem to deal with the possible neuropathology underlying dementia in PD; in addition, all pertinent studies invariably include very small numbers of cases (and do not always have appropriate controls). However, a review of the literature indicates (Table 2) that a substantial number of PD patients with dementia whose brains underwent histological examination had all the neuropathological changes characteristic of Alzheimer's disease (AD) (Alvord et al., 1974; Hakim and Mathieson, 1979; Boller et al., 1980). From these observations it can be concluded that the dementia in PD patients who had all the neuropathological changes typical of AD was in fact due to the co-existence of PD with AD; global dementia is an essential symptom of the latter condition. In this context, it is certainly noteworthy that the incidence of AD in patients with PD seems to be higher than in the general population (cf. Table 2). This suggests that there may be a link between the (as yet unknown) disturbance underlying PD and that underlying the neuropathology of AD.

Table 1: Dementia in Idiopathic Parkinson's Disease

References	Number of Cases**	Mean Age	Control Group	% of Patients with Probable DSM-III Dementia (%)
Talland (1962)	45 PD	55	+	0 (PD)
	40 C	55		- (C)
Asso (1969)	61	55	−	0 (WAIS IQ test)
Danielczyk (1983)	21	73	−	0
Patrick & Levy (1922)	146	50	−	2
Pollock & Hornabrook (1966)	83	67	−	6
Sacks et al. (1972)	72	?	−	6
Marttila & Rinne (1976)	421	68	−	6-14
Celesia & Wanamaker (1972)	153	64-69	−	7-24
Ruberg et al. (1982)	14	70	−	14 (−50?)
Mindham et al. (1982)	40 PD	62	+	20-26 (PD)
	39 C	66		20-24 (C)
Heston (1980)	30	?	−	40
Boller et al. (1980)	29 PD	71	+	31 (PD)
	3182 "Control"	52-86		5 ("C")
Lieberman et al. (1979)	520 PD	66-70	+	32 (PD)
	407 Control	66		4 (C)

*Not included are many studies in which the diagnostic criteria of dementia are unclear, or do not appear to meet DSM-III standards (e.g. Mjones, 1949; Sweet et al., 1976) or in which patients with severe dementia were specifically excluded (e.g. Garron et al., 1972; Mayeux et al., 1981).

**PD = Parkinson's disease; C = Controls

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Table 2: Alzheimer-type Neuropathology and Dementia in Parkinson's Disease

References	Number of Patients		% of Patients with Dementia		% of Patients with Alzheimer-type Neuropathology	
	PD	C	PD	C	PD	C
Hakim and Mathieson (1979)	34	34	56%	6%	68%	6%
Boller et al. (1980)	36 (29)	34	31 (−55%)	5%	31-42%	5%
Heston (1980)	30	2174	40%	13%	0	—
Perry et al. (1983)	10	—	70%	—	10%	—

PD = Parkinson's disease; C = Controls

However, the data shown in Table 2 demonstrate that AD brain changes are apparently not the only precondition for the expression of dementia in all demented PD patients; evidently, there also exists a group of PD patients with disabling dementia who did not have any significant AD brain pathology (cf. especially Heston, 1980; Perry et al.,1983). These patients represent a subgroup with "pure" PD and dementia. Thus, according to the data in the literature it is possible to subdivide patients with PD into three subgroups: (1) PD with no cognitive impairment; (2) PD with dementia and co-existing AD; and (3) PD with dementia but no AD brain pathology ("pure" PD with dementia). Due to the small number of cases so far studied, at present it is impossible to know the exact size of these three subgroups in relation to the total PD population.

Based on the above clinical and neuropathological information, the following discussion of the neurochemical basis of dementia in PD will be divided into two sections: (1) neurochemical basis of dementia in PD with evidence of AD; and (2) neurochemical basis of dementia in PD without any evidence of AD neuropathology.

Neurochemical Basis of Dementia in Parkinson's Disease with Evidence of Alzheimer Neuropathology

Dementia of AD is the only type of dementia for which there exists some solid knowledge as to the underlying neurochemical pathology. A brief discussion of the neurochemical changes in AD dementia is essential for the understanding of dementia in PD.

Alzheimer's disease

The neuropathology of AD is dominated by the occurrence of large numbers of (a) neuritic plaques (most commonly in cortex and amygdala); (b) neurofibrillary tangles (NFT) (in hippocampus, amygdala, neocortex and several basal forebrain nuclei); and (c) granulovacuolar cell changes (in hippocampus), as well as nerve cell loss in hippocampus, amygdala, several cortical regions and, most significantly, the nucleus basalis of Meynert (a component of the substantia innominata) (cf. Terry and Davies, 1980).

The most characteristic neurochemical change so far detected in AD is a marked reduction in the activity of acetylcholine esterase as well as choline acetyltransferase (CAT), the marker enzyme for cholinergic neurons, in cortex and (especially pronounced) in hippocampus of AD patients as compared to age-matched controls (biopsy and postmortem material) (Pope et al., 1965; Davies and Maloney, 1976; Perry et al., 1977a; Richter et al., 1980; Sims et al., 1980; Rossor et al., 1982; and many others, cf. Bartus et al., 1982). The changes in cortical CAT activity are accompanied by (usually less severe) loss of neurons in the nucleus basalis of Meynert (Whitehouse et al., 1981;' 1982, Perry et al., 1982; Candy et al., 1983; Nagai et al., 1983). This nucleus has recently been shown to be the main source of a widespread cholinergic innervation of the cerebral cortex (Shute and Lewis, 1967; Johnston et al., 1979; cf. Coyle et al., 1983). These cholinergic neurons seem to subserve several important cognitive functions, including memory (cf. Bartus et al., 1982). Since the reduction in cortical CAT activity has been shown to be correlated with the degree of cognitive impairment (as well as incidence of neuropathological changes) of AD (Perry et al., 1978), it seems justified to conclude that the massive loss of forebrain cholinergic innervation is directly related to the symptoms of dementia in AD.

Parkinson's disease

From the observations in AD brains, it seems logical to expect that, in addition to the typical brain dopamine (and noradrenaline) changes, PD patients with evidence of AD brain pathology also will have characteristic neurochemical pathology of AD, that is marked cortical cholinergic deficiency. Judged from the single such case so far examined (Perry et al., 1983), this seems to be indeed the case (Table 3). Since in AD the dementia correlates, as mentioned, with cortical (and hippocampal) reduction in CAT activity (Perry et al., 1978), there is good reason to assume that in those demented PD patients who have a co-existing AD neuropathology (that is, greatly above-normal plaque counts, NFT, etc.) the dementia is, as would be expected, due to an Alzheimer-type derangement of the forebrain cholinergic function. This conclusion is supported by a neuropathological study (Table 3) showing that a group of demented PD cases (two of whom had evidence of AD pathology) had markedly reduced cell counts in the nucleus basilis of Meynert (50-75% neurons lost) as compared with non-demented age-matched PD cases or control cases (Whitehouse et al., 1983).

Neurochemical Basis of Dementia in Parkinson's Disease without Evidence of Alzheimer's Disease

In a recent study, Perry et al. (1983) examined the behaviour of cortical cholinergic neurons in six demented and three non-demented PD cases; both of these PD groups did not have any evidence of AD (neuritic plaque counts within the normal range). The authors compared the results with the data obtained in one demented PD case with co-existing AD (highly above-normal cortical plaque counts) and a group of typical AD cases. Whereas the non-demented PD cases had CAT values (measured in frontal and temporal cortex) within the control range, the six PD cases with marked cognitive impairment (but no AD changes) had highly reduced cortical CAT levels which were identical with the values found in AD brains and the single case of PD with Alzheimer-type brain pathology (Table 3).

The results of this important study are in accord with similar observations made earlier by Ruberg et al. (1982). These authors found significantly reduced CAT levels in (frontal) cortex of eight PD cases with dementia, ranging in degree from mild to severe (Table 3). However, since no AD related histology was performed in the PD brains, it is impossible to know whether the cases studied were "pure" PD with dementia or PD cases with co-existing AD. In addition, the mental status of the PD

cases does not seem to have been assessed clinically according to a standardized score system.

The morphological basis for the reduced cortical CAT in the demented PD cases without AD neuropathology seems to be a selective loss of neurons in the nucleus basalis of Meynert which, as mentioned, is the main source of the cholinergic innervation of wide parts of the cortex. This is indicated by a recent study of Whitehouse et al. (1983) who have observed that idiopathic PD cases with accompanying signs of (clinically unqualified) dementia had highly reduced cell density in the nucleus basalis as compared with controls or non-demented PD cases (Table 3). However, since two of the four demented PD cases examined had (some) evidence of AD, it is rather uncertain whether any of these demented PD patients actually belonged to the group of "pure" PD with dementia.

Taken together, the above neurochemical and neuropathological observations indicate that the basis for dementia in cases with "pure" PD may be a marked "cortical cholinergic deficiency" due to neuronal loss in the nucleus basalis of Meynert. This suggests that despite the different neuropathology, from the neurochemical point of view all PD cases with dementia would appear to have a common basic neurochemical disturbance.

Open Questions

Is dementia a "cortical cholinergic deficiency" symptom?

Although it would be tempting to consider dementia, regardless of its neuropathological basis, as a "cortical cholinergic deficiency symptom", caution seems to be in order. First, to date there have been too few studies performed in PD (with too few appropriate cases and controls) that would satisfy rigorous clinical, neuropathological and neurochemical criteria, so as to permit any such far-reaching conclusions. Second, other conditions with disabling dementia, such as Huntington's disease, multi-infarct dementia, renal encephalopathy, have usually much milder or no cortical cholinergic or nucleus basalis changes (Perry et al., 1977b; Perry and Perry, 1980; Parhad et al., 1982). Third, clinical differences have been noted between dementia in PD and AD (demented PD patients having less agnosia, aphasia, and apraxia) and the suggestion of a "subcortical" dementia in PD, distinct from the cortical dementia in AD, has been made (cf. Albert, 1978).

Is cell loss in nucleus basalis of Meynert a sufficient explanation of dementia in PD without AD changes?

In the largest series known to us, Buttlar-Brentano (1955) found definite cell loss and reduced cell density in the nucleus basalis of Meynert in 15 of the 16 histologically confirmed idiopathic PD cases which were examined. Since it is unlikely that all these cases were demented, cell loss in the nucleus basalis may occur more frequently than dementia in PD. This conclusion seems to be strengthened by the report of Candy et al. (1983) who examined histologicaly three PD cases with no clinical evidence of dementia (and no cortical AD changes): in all three cases, the authors found a markedly reduced cell density in nucleus basalis (see Table 3). Do these observations indicate that cell loss in nucleus basalis is a necessary but not sufficient reason for dementia in "pure" PD? In contradiction to this possibility, Whitehouse et al. (1983) did not observe any cell loss in the nucleus basalis in three non-demented PD patients (see Table 3). It is evident that only much more extensive clinical-neuropathological correlations can provide an answer to this question.

Is the cortical cholinergic deficiency in PD without AD changes sufficient to produce severe dementia?

As mentioned above, Perry et al. (1983) found in non-demented PD cases cortical CAT levels to be within the range of controls (see Table 3). In contrast, Ruberg et al. (1982) measured significantly subnormal CAT activity in frontal cortex of six non-demented PD cases; as a matter of fact, the mean CAT level in these patients was as much reduced as in the group of five "highly demented" PD cases they examined (see Table 3). Do these observations indicate that the cortical cholinergic deficiency by itself is not a sufficient neurochemical alteration to produce symptoms of severe dementia? Again, it seems that more extensive clinical-neuropathological-neurochemical correlations are needed.

Is dementia due to cortical cholinergic deficiency a threshold phenomenon?

It is very likely that there is a critical threshold for the loss of the cholinergic nucleus basalis innervation of the cortex above which—due to the large compensatory capacity of the remaining

Table 3: Dementia in Parkinson's Disease: Neurochemical-Pathological Correlations

Subgroups of Patients with Parkinson's Disease (PD)	Cortical CAT in % of Control		Neuritic Plaque Count (% of Control)	Cell Density in N. basalis of Meynert (% of Control)
	Temporal	Frontal		
Study 1 (Perry et al., 1983)				
PD — Mentally normal (3)	76*	66*	132*	—
— Cognitive impairment				
— without AD changes (6)	15**	28**	126*	—
— with AD changes (1)	13	28	719	—
Study 2 (Ruberg et al., 1982)				
PD — Non-demented (6)	—	60***	—	—
— "Highly demented" (5)	—	52‡	—	—
Study 3 (Whitehouse et al., 1983)				
PD — Non-demented (3)	—	—	—	106
— Demented (4)	—	—	(above-normal in two cases)	24-47**
Study 4 (Candy et al., 1983)				
PD — Non-demented (3)	—	—	normal	greatly reduced

*Not significantly different from controls; **$p < 0.001$; ***$p < 0.02$; ‡$p < 0.01$ (vs controls)
Abbreviations: AD = Alzheimer's disease: CAT = choline acetyltransferase; PD = Parkinson's disease

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neurons—there will be no clinically overt symptoms (dementia). This phenomenon, which is well known to occur in PD within the nigrostriatal dopamine system (Hornykiewicz, 1982) may explain some of the morphological as well as neurochemical differences in the literature (see above).

Do brain neurotransmitter changes other than acetylcholine contribute to the dementia in PD?

Although at present there is no reason to doubt the primary role played by the cortical cholinergic changes in the production of the symptom of dementia in PD (or AD), the possibility has to be kept in mind that some of the other cortical and subcortical neurotransmitter changes known to occur regularly in PD may significantly contribute to the "cholinergic deficiency" dementia. Of these non-cholinergic neurotransmitter changes, the changes in noradrenaline and dopamine seem to be most conspicuous in relation to dementia in PD.

Noradrenaline

Reduction in the concentration of noradrenaline (Adolfsson et al., 1979; Mann et al., 1980; Gibson and Ball, 1983) and the noradrenaline synthesizing enzyme, dopamine-ß-hydroxylase (Cross et al., 1981) has been observed in cortex and hippocampus of AD brain. Consistent with this finding is the observation of substantial neuronal loss in the locus caeruleus in AD cases (Mann et al., 1980; Bondareff et al., 1981; Tomlinson et al., 1981); the locus caeruleus is the source of widespread non-adrenergic innervation of most regions in the brain and spinal cord (cf. Moore and Bloom, 1979). Although Perry et al. (1981) did not find any statistically significant correlation between loss of cortical dopamine-ß-hydroxylase activity and plaque counts (usually a reliable neuropathological marker of AD dementia), this question requires further more extensive studies.

In PD loss of locus caeruleus neurons is a regular neuropathological change accompanying the (usually more severe) loss of substantia nigra (dopamine) neurons (Hassler, 1938; Greenfield and Bosanquet, 1953). In accord with this neuropathological observation are findings that in PD brain, the levels of noradrenaline are reduced in many brain regions, including basal ganglia and limbic forebrain nuclei, as well as neocortical and cerebellar cortical areas (Ehringer and Hornykiewicz, 1960; Farley and Hornykiewicz, 1976; Rinne and Sonninen, 1973; Kish et al., 1984; Scatton et al., 1983).

Although at present there is no direct evidence linking the reduction in cortical and subcortical levels of brain nonadrenaline in PD with the occurrence of dementia in this disorder, it may be significant that brain nonadrenaline has frequently been implicated in higher brain function, including memory (Kety, 1970). In this respect it is noteworthy that in patients with Korsakoff's psychosis, the degree of reduction in the concentration of the noradrenaline metabolite 3-methoxy-4-hydroxyphenyl glycol in CSF was highly correlated with the extent of memory impairment in this disorder (McEntee and Mair, 1978; Mair and McEntee, 1983).

The occurrence of brain noradrenaline deficiency in both AD and PD may not, therefore, be a mere coincidence. However, the fact that brain noradrenaline changes are a regular finding in PD brains, although not all PD patients present with dementia, shows that the relationship between brain noradrenaline reduction and cognitive impairment may not be a simple one.

Table 4: Reduction in Cortical Noradrenaline and Dopamine in Patients with Alzheimer's and Parkinson's Disease

	Percent of Control			
	Noradrenaline		Dopamine	
Brain Region	AD	PD	AD	PD
Frontal Cortex	30[a]	10-70[b-d]	54[a]	40-80[b]
Parolfactory gyrus	—	<10[c]	—	<10[e]
Hippocampus	40-60[a, f]	10-40[b, c]	20-40[f]	10-40[b, c]

[a]Adolfsson et al., 1979
[b]Scatton et al., 1983
[c]Hornykiewicz and Shannak (unpublished data)
[d]Rinne and Sonninen, 1973
[e]Price et al., 1978
[f]Gibson and Ball, 1983

Dopamine

The marked deficiency of dopamine in the nuclei of the basal ganglia in PD has been well documented (cf. Bernheimer et al., 1973; Hornykiewicz, 1981). In addition, in PD there also is a loss of dopamine in several cortical regions including the hippocampus (Scatton et al., 1983) and the parolfactory gyrus (Price et al., 1978). In this respect it is noteworthy that: (1) similar changes in cortical dopamine have been reported in patients with AD dementia (Adolfsson et al., 1979; Gibson and Ball, 1983); and (2) there seems to exist a type of dementia with normal neocortical plaque counts and acetycholine synthesis (biopsy material) but very low CSF levels of the dopamine metabolite homovanillic acid (Bowen et al., 1981). Although no direct correlation between dementia and forebrain dopamine changes in PD (or AD) has so far been established, surprisingly, a significant relationship has been determined, in PD patients, between the motor symptomatology and the intellectual deficits (Mortimer et al., 1982). Since in PD the severity of the motor symptomatology also correlates with the degree of dopamine loss in the basal ganglia nuclei (Bernheimer et al., 1973), the existence of a relationship between brain dopamine changes and certain aspects of intellectual impairment cannot be dismissed.

In conclusion, although the role of the cortical cholinergic deficiency in PD with dementia seems indisputable, it may be that a concurrent reduction in cortical (and subcortical?) noradrenaline and/or dopamine function is needed for the expression of the clinically overt picture of disabling dementia. The present state of our knowledge makes it obvious that much work has to be done in this area to permit a more comprehensive answer to the question regarding the neurochemical basis of dementia in PD.

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