

Short report

Confusion, dementia and anticholinergics in Parkinson's disease

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SUMMARY Among a population of 75 hospitalised Parkinsonian subjects, confusional states were observed in 46% of demented patients not receiving anticholinergic drugs and in 93% of demented patients under anticholinergic therapy. The sensitivity of demented Parkinsonians to anticholinergic drugs can be attributed to a cholinergic deficiency which has been detected in the cortex and hippocampus of Parkinsonian patients post-mortem. The observations suggest that anticholinergic medication should be avoided in Parkinsonians with intellectual impairment.

It has long been recognised that Parkinsonism is frequently accompanied by intellectual impairment. The incidence of dementia among Parkinsonians has been estimated to be about 30% on the basis of clinical^{1–6} and neuropathological evidence,⁷ although figures of over 50% have been advanced.^{8,9} It is not yet known, however, whether the dementing process is intrinsic to the pathology of the disease. On the assumption that lesions of the basal ganglia may be responsible for deficient intellectual performance as well as for the motor symptoms of the disease, the hypothesis was formed that Parkinsonians may suffer from a form of "subcortical dementia".¹⁰ This notion has found echo among a number of authors.^{13,4,6,8,11–14} The neuronal system involved, however, have not been identified. The implication of cortical structures in Parkinsonian dementia is also suggested by observations of cortical atrophy^{15,16} and neuropathological signs resembling those found in Alzheimer's disease and senile dementia in the brains of Parkinsonians.^{7,9} A recent biochemical study of Parkinsonian patients, performed post-mortem, has provided evidence as to nature of this lesion.¹⁷ It was observed that choline acetyltransferase activity, measured as an index of cholinergic innervation, was significantly lower in the frontal cortex of Parkinsonians as compared to controls. This biochemical deficiency, ordinarily associated with senile and Alzheimer type dementia^{18–21} was correlated in the Parkinsonian subjects studied with

clinical observations of intellectual impairment, as far as this could be determined by retrospective analysis of the patients' records. An increase in muscarinic cholinergic receptors was also observed in the frontal cortex of these patients and was correlated with the decrease in choline acetyltransferase activity; the group of subjects that had received anticholinergic therapy had receptor densities greater than the mean for the group as a whole.

Since the muscarinic receptor antagonists used in the treatment of Parkinson's disease have been reported to produce confusional states,^{12,22–24} we hypothesised that these episodes of confusion might be related to a pre-existing cholinergic deficit aggravated by receptor blockade. To confirm this hypothesis we attempted to determine clinically whether episodes of mental confusion corresponded to treatment with anticholinergic drugs and whether they were observed primarily in patients with impaired intellectual functions, that is with putative cholinergic deficits. To this end, the intellectual status, susceptibility to episodes of confusion, and treatment by anticholinergic drugs was determined for the 75 patients hospitalised during the year 1980 in the Neurology and Neuropsychology Clinic of the Salpêtrière Hospital.

Patients and methods

All the Parkinsonian patients admitted to our unit during the year 1980 were hospitalised either to attempt to improve their motor condition or because of adverse reactions to treatment (on-off phenomena, dyskinesias, mental disturbances and/or intercurrent infections). The patients, all of whom were treated with Levodopa plus a peripheral decarboxylase inhibitor, were

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divided into four groups: non-demented patients without anticholinergic medication; non-demented patients with anticholinergic medication; patients suffering from intellectual deterioration (demented) without anticholinergic medication; demented patients with anticholinergic medication.

Dementia, defined as progressive and irreversible impairment of intellectual functions was assessed retrospectively on the basis of bedside evaluations of memory and higher intellectual functions, as noted in the patients' records and reported by family members. Mental confusion was considered to be an acute and reversible impairment of temporo-spatial orientation, inability to act or speak coherently with delirium in certain cases.

Although it is possible that the study is biased by the choice of a population of hospitalised Parkinsonians, the proportion of demented patients (36%) is the same as reported by other authors for a more general population of Parkinsonians and the incidence of confusion in non-demented patients (8%) falls within the reported range¹² (table 1). These 75 patients may therefore be tentatively considered as a representative population.

Results

Among the 75 patients, 27 (36%) had some degree of intellectual impairment and were considered to be demented (table 1). Anticholinergic drugs had been administered to 21 (28%) of the patients. Confusional states were observed in 8% of non-demented subjects (groups I and II) but in 70% of the demented patients. Among the demented patients 46% of those not under anticholinergic medication were subject to confusional states, whereas 93% of the demented Parkinsonians receiving anticholinergic drugs became confused. Confusional states were, therefore, more prevalent among demented Parkinsonians and the administration of anticholinergic drugs to these patients produced

confusion in almost all cases.

The four groups of patients were also analysed for other factors which might be related to mental disturbance in Parkinsonian subjects, such as the doses of levodopa and anticholinergic drugs administered, age of the patients and stage and duration of the disease (table 2). The doses of levodopa did not differ among the groups; thus the prevalence of confusional states was not related to levodopa therapy itself. There was no difference between the doses of anticholinergic drugs administered to demented (group IV) or non-demented (group II) patients, but only the former became confused. Thus, while anticholinergic drugs increase spectacularly the incidence of confusion in Parkinsonian patients, the essential element in the appearance of confusion is the presence of dementia. Demented patients were significantly older than non-demented patients, but within these two groups those receiving anticholinergic drugs were not significantly older than the others. Since dementia in Parkinsonian patients has not been found to be correlated with age,⁵ the appearance of confusion is related rather to the presence of dementia in these patients than to their age. The disease was of significantly longer duration in both groups of patients receiving anticholinergic drugs (groups II and IV) than in nondemented subjects with anticholinergic therapy (group I) but was the same for all demented patients regardless of treatment. It again appears that the presence of dementia is the essential factor and not the duration of the disease; indeed, the disease was of longer duration in non-demented patients receiving anticholinergic medication than in demented patients not receiving anticholinergic drugs, but none of the former manifested

Table 1 Confusional state in Parkinsonian patients

Groups of patients	Number of patients	No confusional state	Confusional state
Group I : Non demented without Ach	41	37	4
Group II : Non demented with Ach	7	7	0
Group III : Demented without Ach	13	7	6
Group IV : Demented with Ach	14	1	13
Total	75	52	23

Ach = Anticholinergic drugs

Table 2 Patients' parameters (mean \pm sem)

	Non-demented patients		Demented patients	
	Group I without Ach	Group II with Ach	Group III without Ach	Group IV with Ach
Age (years)	60.7 \pm 1.3	56.4 \pm 3.4	67.3 \pm 3*	65.4 \pm 2.7†
Stage	2.7 \pm 0.1	2.7 \pm 0.2	2.8 \pm 0.2	3.3 \pm 0.1‡
Duration (years)	5.5 \pm 0.6	11.3 \pm 5*	7.0 \pm 1.4	8.8 \pm 1.6*
Levodopa (mg, + DCI)	625 \pm 52	407 \pm 115	479 \pm 53	491 \pm 86
Ach (mg)	—	6.6 \pm 4	—	7.7 \pm 1

* : p < 0.05 between Group III and Groups I and II. † : p < 0.05 between Groups IV and Group

‡ : p < 0.05 between Group IV and Groups I, II and III.

* : p < 0.05 between Group I and Groups II and IV.

|| see reference (3)

Ach = anticholinergics drugs

confusion. Finally the disease was significantly more advanced in the demented subjects receiving anticholinergic therapy (group IV). While this factor is not essential for the appearance of confusion in demented subjects, as evidenced by group III, it cannot be excluded that this factor is involved in the increased incidence of confusion among the patients of group IV.

Discussion

We conclude that the presence of dementia in Parkinsonians favours the appearance of confusional states and that the administration of anticholinergic medication to an intellectually impaired Parkinsonian will almost certainly result in mental confusion. Although these results must be confirmed in a prospective and quantified study, we feel that this "clinical picture" of a hospitalised Parkinsonian population gives two kinds of practical and pathophysiological information. Firstly episodes of confusion have been shown to be present almost exclusively in patients with intellectual deterioration and particularly in those patients who are taking cholinergic antagonists. The drug-induced confusion in demented Parkinsonians seems thus to be related to the exacerbation of a pre-existing or latent dementia. It is understandable then, that confusional states should be considered characteristic of severe dementia in Parkinsonians, according to the classification of certain authors.^{3,5} Anticholinergic drugs should be avoided in demented Parkinsonian patients. Disappearance of the confusion and return to the previous mental state should be obtained after interruption of the anticholinergic therapy. Secondly the cortical deficiency which was observed post-mortem in Parkinsonian subjects, especially those showing signs of intellectual impairment, would explain the particular sensitivity of Parkinsonians to anticholinergic drugs which can only aggravate the already reduced central cholinergic transmission.¹⁷ More recently, it has been shown that the reduction in cholinergic neurons in the cortical areas might be the consequence of the degeneration of the cholinergic system originating in the substantia innominata and projecting to the cerebral cortex,²⁵ a lesion which has recently been reported in Alzheimer's disease.²⁶ It seems clear, then, that the lesion of a non-dopaminergic subcortico-cortical cholinergic system, the extent of which is currently under investigation, is implicated in Parkinsonian as well as in Alzheimer type dementia, although the relationship between the two diseases has not yet been defined. It cannot, however, be affirmed that this lesion is uniquely responsible for the intellectual deterioration of Parkinsonians; the psychopathology of these patients is extremely complex²⁷ and a number of biochemical deficiencies have been observed in subcortical structures of Parkinsonians post-mortem.²⁸ It is of particular

interest that the mesocorticolimbic dopaminergic system is affected in Parkinsonians.²⁹ This lesion may explain the symptoms of bradyphrenia in untreated Parkinsonians,²⁷ the improvement of some intellectual functions as well as some of the psychic disturbances observed after levodopa treatment³⁰⁻³⁵ and may indeed underlie the group of symptoms which Albert defined as "subcortical dementia". The other aspects of intellectual deterioration in Parkinsonians, which escape this definition may be related to the mesocortico-cortical cholinergic lesion described here.

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