

SHORT REPORT

Neuroleptic induced parkinsonism: MRI findings in relation to clinical course after withdrawal of neuroleptic drugs

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Abstract

Parkinsonism is a common complication of neuroleptic drug use; however, the pathophysiology of the persistence of parkinsonian symptoms after withdrawal of neuroleptic drugs is poorly understood. Twenty patients with neuroleptic induced parkinsonism were studied by high field MRI. Persistence of symptoms was associated with different findings depending on the age of the patients—namely, putaminal hypointensity in young patients and striatal hyperintensities in old patients. High field MRI may be useful in identifying patients at higher risk for neuroleptic induced parkinsonism.

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The clinical course of neuroleptic induced parkinsonism after withdrawal of neuroleptic drugs may be characterised by rapid remission of symptoms (within five to 60 days), by persistence of symptoms, or by further progressive deterioration.¹⁻⁶ Whereas it is generally agreed that the extrapyramidal symptoms are linked to the functional blockade of postsynaptic dopaminergic receptors, several mechanisms have been suggested to explain the pathophysiology of progressive or persistent forms. Studies using PET have shown a high degree of correlation between persistence or progression of symptoms and low putaminal uptake of ¹⁸F-dopa.⁷ Genetic factors,⁸ toxicity of neuroleptic drugs beyond dopaminergic

blockade,⁹ and acceleration of idiopathic Parkinson's disease¹⁰ have all been postulated. Functional age related changes in dopamine receptors and striatal concentrations of dopamine may play an important part. An MRI study has shown a high prevalence of focal hyperintensities in the caudate nucleus of aging patients with neuroleptic induced parkinsonism with respect to age matched controls.¹¹ We therefore studied MRI abnormalities in young and old patients with neuroleptic induced parkinsonism in relation to their clinical course after neuroleptic withdrawal.

Patients and methods

Twenty patients with a diagnosis of "chronic schizophrenic disturbance" (DSM-III) chronically treated with neuroleptic drugs consented to participate in this study. Patients were selected from about 100 inpatients admitted to the psychiatric facilities of Villa Pini (Chieti, Italy). Patients were subdivided into two groups based on their age. The first consisted of 10 patients with an age range of 18-45 years, and the second of 10 patients older than 60. Patients were selected only when there was no clear contraindication to the withdrawal of neuroleptic drugs in terms of behavioural disturbances and compliance with instructions, and when misuse of alcohol or other drugs could be excluded. Patients with a mini mental state examination score of less than 17 were also excluded. Table 1 describes the demographic and clinical characteristics of the two groups.

Patients were evaluated at baseline (t_0) for severity of extrapyramidal symptoms with a shortened version of the unified Parkinson's disease rating scale (UPDRS)¹² which considers six cardinal symptoms (bradykinesia, rigidity, tremor, postural instability, gait, posture) each scored on a scale from 0 (absent) to 4 (severe), with a total maximum score of 24. The presence of other movement disorders was evaluated by means of the abnormal involuntary movements rating scale (AIMS).

MRI studies were performed on all patients using a superconducting magnet (Magneton Siemens) operating at 1.5 Tesla, with T1 (TR/TE = 500/15 ms) and T2 (TR/TE = 2000/90 ms) weighted sagittal, coronal, and

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Table 1 Demographic and clinical characteristics of patients with neuroleptic induced parkinsonism (NIP)

	Young NIP (n = 10) (mean (SD))	Old NIP (n = 10) (mean (SD))
Age (y)	34.6 (6.9)	65.6 (3.9)
Education (y)	13.7 (3.4)	5.0 (4.0)
MMSE	25.6 (5.8)	22 (7.1)
Symptom duration (y)	9.8 (6.6)	28 (4.2)
Neuroleptic treatment (y)	7.1 (5.1)	15 (6.3)
Neuroleptic dose (mg eq chlorpromazine)	330 (97.7)	170 (74.4)
Anticholinergic drugs	10 (100%)	5 (50%)
Other treatments	0	4 (40%)

Table 2 Changes in UPDRS scores after neuroleptic drug withdrawal

	t_0	t_1
Young patients with NIP (n = 10)	11.8 (2.3)	5.3 (5.1)**
Old patients with NIP (n = 10)	8.6 (2.6)	7.1 (2.4)*

*P < 0.02; **P < 0.01.

Values are means (SD).

Scores were obtained at baseline (t_0) and 6 months after withdrawal of neuroleptic drugs (t_1).

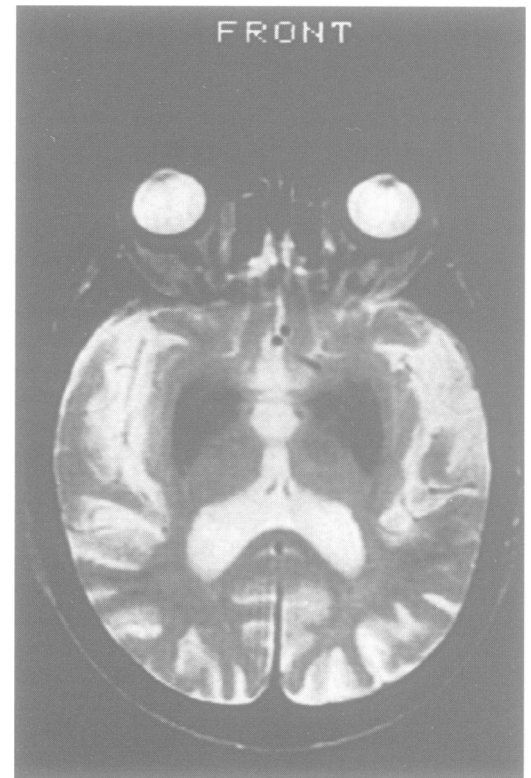
axial planes and a slice thickness of 5 mm. Images were analysed by a radiologist blind to the purpose of the study for the presence or absence of focal signal alterations, white matter abnormalities, cortical or subcortical atrophy, or other signal alterations. Putaminal hypointensity was defined as the intensity which was equal or less than that of the globus pallidus. Areas of relative comparison were chosen on constant regions of interest (0.2 pixels) localised on the tail of the putamen and on the corpus of the globus pallidus.

Neuroleptic drugs were then slowly tapered over three successive weeks to complete withdrawal; weekly visits allowed us to recognise the reappearance of psychotic symptoms and to treat these eventually with clozapine; motor symptoms were checked monthly; the final visit was scheduled six months (t_1) after neuroleptic withdrawal.

Statistical analysis was performed by Wilcoxon sum ranking test (within group between t_0 and t_1) and with a Mann-Whitney U test (between groups). Correlation between variables was calculated by Spearman's test.

Results

Clinical presentation differed between young and old patients with neuroleptic induced parkinsonism. Among the 10 young patients, eight had bradykinesia as the predominant symptom associated with postural tremor or rigidity, and two complained mainly of tremor. None of these patients had vascular risk factors. Among the old patients, eight complained chiefly of tremor (rest tremor in five and postural tremor in three) with associated rigidity in five and bradykinesia in three. Two patients had only a rigid-akinetic syndrome without tremor. In seven patients symptoms were bilateral and symmetric. Three of these patients had high blood pressure and two had



Putaminal hypointensity in a young patient with neuroleptic induced parkinsonism and slow remission of symptoms after withdrawal of neuroleptic drugs.

stable ischaemic cardiopathy. No correlations between UPDRS scores, years of psychiatric symptoms, and dose of neuroleptic drugs were found. None of the young patients exhibited other abnormal movement disorders. On the other hand two old patients had concomitant moderate buccolingual dyskinesiae alone, and two had concomitant mild buccolingual and upper arm dyskinesiae. Brain MRI of these patients was no different from that of the other old patients.

After withdrawal of neuroleptic drugs, mean total UPDRS scores decreased in both groups of patients (table 2). However, the clinical course differed between individual patients. In young patients four had rapid remission of extrapyramidal symptoms, four had slow remission, and two showed persistence of symptoms. In old patients with neuroleptic induced parkinsonism none showed rapid remission, five had a slow remission, and in the remaining five parkinsonian symptoms persisted throughout the follow up. Clozapine was needed in four young patients for reappearance of psychiatric symptomatology. No correlation between pattern of clinical presentation and evolution of parkinsonian symptoms after neuroleptic drug withdrawal was found. In old patients the persistence of parkinsonian symptoms after neuroleptic withdrawal was associated with a high incidence of white matter and striatal hyperintensities in T2 weighted images (table 3). In young patients, slow remission and persistence of symptoms were associated with putaminal hypointensity (figure), by contrast with patients showing a rapid and complete remission who had a normal MRI (table 4).

Table 3 MRI findings in old patients with neuroleptic induced parkinsonism in relation to clinical course after withdrawal of neuroleptic drugs

	Rapid remission of symptoms (5-60 days)	Slow remission of symptoms (> 60 days) (n = 5)	Persistent symptoms (n = 5)
Age	—	66.6 (4.9)	64.6 (2.8)
Symptom duration (y)	—	27 (5.1)	29 (3.4)
Neuroleptic dose (mg eq chlorpromazine)	—	196 (79.2)	144 (67)
Baseline UPDRS	—	9.2 (3.3)	8.0 (2.0)
MRI			
Normal		1	1
Atrophy		4	4
White matter hyperintensities		1	4
Striatal hyperintensities		0	3
Putaminal hypointensity		1	0

Value are mean (SD) or number of patients.

Table 4 MRI (1.5 tesla T2 weighted) findings in young patients with neuroleptic induced parkinsonism in relation to clinical course after neuroleptic withdrawal

	Rapid remission of symptoms (5-60 days) (n = 4)	Slow remission of symptoms (> 60 days) (n = 4)	Persistent symptoms (n = 2)
Age (y)	31.5 (6.1)	38 (5.7)	34 (14.3)
Symptom duration (y)	5.7 (4.4)	11.2 (6.2)	15 (11.3)
Neuroleptic dose (mg eq chlorpromazine)	275 (95.7)	375 (104)	350 (70.7)
Baseline UPDRS	10.2 (1.7)	13 (2.6)	12.5 (2.1)
MRI:			
Normal	4	0	1
Atrophy	0	1	0
White matter hyperintensities	0	0	0
Striatal hyperintensities	0	1	1
Putaminal hypointensity	0	3	2

Values are mean (SD) or number of patients.

Discussion

Neuroleptic induced parkinsonism is a common disorder often clinically indistinguishable from idiopathic Parkinson's disease. The onset is within one month of treatment in 50%–70% of patients and within three months in 90%. Mean cumulative incidence is estimated to be 20%–50% of patients treated with neuroleptic drugs.^{13–15} Although the fact that the direct block of dopaminergic receptors is the primary cause for the appearance of parkinsonism is generally accepted, less is known as to why these rapidly wear off in some patients and persist in others. The results of the present study suggest that MRI may be a useful tool in the study of neuroleptic induced parkinsonism, indicating that the susceptibility to develop parkinsonian signs during neuroleptic treatment may have different pathophysiological mechanisms depending on the age of the patients. As expected, old patients had significantly more MRI abnormalities (striatal and white matter hyperintensities) than young patients, and this was more evident in those showing persistence of symptoms. The meaning and clinical relevance of these lesions is still a matter for debate. Previous studies have shown a high degree of correlation with vascular risk factors, dementia, stroke, and aging. Striatal hyperintensities have been variably associated with atherosclerotic parkinsonism^{16,17} and with gait disorders which characterise subcortical arteriosclerotic encephalopathy.^{18,19} Vascular risk factors may therefore clearly have a role in older patients, even though age related changes in striatal dopamine concentrations and receptors may be relevant considering that no patients of this age group showed rapid remission of symptoms.

On the other hand, in younger patients rapid remission of symptoms was seen only in those with normal MRI; in the ones showing an unfavourable clinical course MRI was characterised by the finding of putaminal hypointensity. This finding might be due to a direct toxic effect of neuroleptic drugs. Putaminal hypointensity seems to be correlated with the paramagnetic properties of iron accumulation. An increase in iron concentration is associated with an increased likelihood that oxidative reactions will occur and that free radicals will be produced.²⁰ Iron is a transition metal which catalyses oxidative reactions lead-

ing to damage of biological molecules and finally to cell degeneration.²¹ Changes in the concentration of transition metals have been implicated in several basal ganglia disorders, including Wilson's disease, Parkinson's disease, multiple systems atrophy, and Hallevorden-Spatz disease.^{22,23} Accumulation of iron with changes in iron metabolism have also been observed in the cortex of patients with Alzheimer's disease, in the white matter of patients with multiple sclerosis or spastic paraplegia.²³ Neuroleptic drugs may also induce iron accumulation in cerebral tissues, and may modify iron turnover.^{24,25} Post-mortem studies and MRI^{26,27} have shown an increased accumulation of iron in striatal structures of patients chronically treated with neuroleptic drugs. Increased iron in striatal structures has also been shown in patients with tardive dyskinesia after prolonged neuroleptic use,^{28,29} a report, however, not confirmed by other authors.³⁰

In conclusion, even though the results of this study must be considered as preliminary and need to be confirmed on a larger number of patients, techniques such as MRI may be useful in identifying patients at higher risk for developing neuroleptic induced parkinsonism.

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