Clinical features of drug-induced Parkinsonism

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Abstract

Drug-induced Parkinsonism is often reversible after withdrawal of the causative drug. Its clinical course, however, is not well understood, as the majority of cases are caused by drugs prescribed by departments outside of neurology. We reviewed 21 cases of drug-induced parkinsonism for several factors, including age, sex, causative drug and reason for prescription, department by which it was prescribed, and outcome. The age at onset ranged from 40 to 87 years, with an average Hoehn and Yahr Scale score of 4, indicating severe disability. Sulpiride was the most commonly observed causative drug (71.4%). All causative drugs were prescribed in non-neurological departments and over one half were prescribed in non-psychiatric departments; most were prescribed to treat depression or abdominal discomfort. Ten patients (48%) were previously diagnosed with a neuromuscular disease, including cerebrovascular diseases and Parkinson's disease. Recovery was observed in 15 cases (71%) after withdrawal of the causative drug, but lingering symptoms were observed in the remaining cases. It is suggested that physicians should be more cautious of Parkinsonian side effects when prescribing such drugs.

Introduction

Drug-induced Parkinsonism (DIP) is the second most prevalent cause of secondary Parkinsonism. Its symptoms, which include tremor, rigidity, bradykinesia, and gait disturbance, are very similar to those of Parkinson's disease (PD). Initially reported as a complication of antipsychotics, it was later recognized as a common complication of antidepressants, calcium channel antagonists, gastrointestinal prokinetics, antiepileptic drugs, and many other compounds.[1,2] DIP is particularly burdensome for the elderly and its management includes the recognition of symptoms and identification of risk factors and offending agents. Prompt discontinuation of the causative agent often leads to marked improvement, though the condition might persist or remit slowly in up to 10% of patients. These patients are often suspected of concomitantly developing PD.[3] DIP shows more rapid progress, symmetry of symptoms, relative absence of rest tremor, and coexistence of oro-mandibular dyskinesias compared with PD. However, differentiating DIP from PD in such cases is difficult.[2,4]

Additionally, DIP is frequently overlooked[5-7] and its clinical course is not well understood because the majority of cases are caused by drugs prescribed by departments outside of neurology. Therefore, we aimed to examine the clinical course of DIP.

Materials and Methods

We reviewed 21 cases of drug-induced Parkinsonism and gathered information on 13 different parameters to study the clinical course of the illness. These parameters included: age at onset, sex, whether the case was inpatient or outpatient, maximum Hoehn and Yahr Scale score, causative drug, reason for prescribing the drug, department by which the drug was prescribed, description of any involuntary movement, brain abnormalities (as determined by magnetic resonance imaging [MRI]), use of any anti-parkinsonism drugs, neuromuscular diseases before DIP onset, outcome, duration of causative drug use before DIP onset, time to recovery after withdrawal of causative drug and difficulties after drug withdrawal (Table 1).

Results

The age at onset ranged from 40 to 87 years, with 90% of patients over the age of 65 years and a male: female ratio of 2:5. The average Hoehn and Yahr Scale score was 4, which was indicative of severe disability. Two patients showed oromandibular dyskinesia (Table 1). Sulpiride was the most common causative drug (71.4%); other drugs included tiapride, metoclopramide, maprotiline, haloperidol, and risperidone (Figure 1). All causative drugs were prescribed in departments that did not specialize in neurology, with a large portion prescribed by psychiatric departments (eight cases; 38.1%). In the remaining 13 cases (61.9%), drugs were prescribed in a non-psychiatric department, which included seven by a general practitioner, three in a general hospital's surgical department, two in a general hospital's internal medicine department, and one in a nursing home (Figure 2A). Commonly cited reasons for prescription included depression (29%), other psychiatric symptoms (33%), abdominal discomfort (19%), and unknown (19%) (Figure 2B).

Based on clinical symptoms and neuroimaging (MRI and computed tomography) findings, neuromuscular diseases were not present in 11 of the cases (52%) before symptom onset. However, these diseases were present in the remaining 48%, which included cerebrovascular diseases (28%; five vascular dementia, one higher-order dysfunction due to multiple cerebral infarction, and one hemiplegia), three with neurodegenerative diseases (14.3%; Parkinson's disease, familial spastic paraplegia, and geriatric dementia), and one with depression (4.8%) (Figure 3A). After withdrawal of the causative medication, 15 of the patients (71%) were once again able to walk at home, but three were wheelchair-bound and one died from malignant syndrome (Figure 3B).

In 13 patients from 15 patients who were again able to walk, we could examine the relationship between the length of time from first administration of the causative drug to the onset of symptoms and the length of time until recovery after drug withdrawal. It was found that the length of time from first administration of the drug

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Table 1. Summary of the characteristics of the 21 patients with drug-induced Parkinsonism.

Age at onset	Sex	Outpatient/ hospitalized	Maximum Hoehn-Yahl	Causative drug	Department by which the causative drug was prescribed	Reason for prescription	Involuntary movement	Brain MRI findings	Anti-Parkinsonism drug used	Neuromuscular diseases before symptom onset	Outcome	Duration of causative drug use before DIP onset (weeks)	Time to recovery after withdrawal of causative drug	Problems after withdrawal of the causative drug
84	F	Outpatient	V	Sulpiride 150 mg/day	General practitioner	Depression	Oromandibular dyskinesia	Lacunes in bilateral basal ganglia	None	None	Independent on activities of daily living	12	6	Oromandibular dyskinesia
80	F	Outpatient	IV	Sulpiride 150 mg/day	Nursing home	Abdominal discomfort	Rt. hand tremor	Lacunes in bilateral white matter	None	None	Independent on activities of daily living	64	8	Abdominal discomfort
68	F	Outpatient	III	Sulpiride 100 mg/day	Psychiatry	Depression	None	Lacune in left putamen	None	None	Independent on activities of daily living	40	4	None
78	F	Outpatient	V	Tiapride 75 mg/day	General hospital surgery	Hallucination	Oromandibular dyskinesia	Widespread white matter hyperintensities	L-DOPA 100 mg/day (discontinued)	Vascular dementia	Able to walk at home	24	16	Dementia
81	M	Outpatient	IV	Metoclopramide	General practitioner	Abdominal discomfort	Rt. hand tremor	Cortical infarct	L-DOPA 150 mg/day	None	Independent on activities of daily living	12	8	None
71	F	Outpatient	V	Tiapride 75 mg/day	General practitioner	Malaise	Limb and jaw tremor	Lacunes in bilateral white matter	None	None	Independent on activities of daily living	12	3	Malaise
83	F	Outpatient	IV	Sulpiride 150 mg/day	General practitioner	Unknown	None	Widespread white matter hyperintensities	None	Vascular dementia	Independent on activities of daily living	48	4	None
74	F	Outpatient	IV	Sulpiride 150 mg/day	General practitioner	Anorexia, abdominal discomfort	Rt. hand, jaw tremor	Lacunes in bilateral white matter, basal ganglia and thalamus	None	None	Unknown	Unknown	Unknown	Unknown
66	F	Outpatient	IV	Sulpiride 200 mg/day	Psychiatry	Depression	None	Unknown	None	None	Unknown	Unknown	Unknown	Unknown
66	M	Hospitalized	V	Haloperidol 5 mg/day	General hospital surgery	Insomnia	None	Normal	L-DOPA 100 mg/day	Parkinson's disease	Independent on activities of daily living	1	1	Parkinson's disease
86	F	Hospitalized	V	Sulpiride 100 mg/day	General practitioner	Hallucination	None	Widespread white matter	L-DOPA 100 mg/day	Vascular dementia	Able to walk at home	6	8	Dementia
40	F	Hospitalized	V	Sulpiride 300 mg/day	Psychiatry	Psychiatric symptoms	None	Normal	L-DOPA 200 mg/day (discontinued)	Hereditary spasticparaparesis	Independent on activities of daily living	10	4	Psychiatric symptoms
83	F	Hospitalized	V	Sulpiride 200 mg/day	General hospital internal medicine	Irritation, insomnia	Lt. hand tremor	Widespread white matter hyperintensities	None	None	Independent on activities of daily living	12	16	None
86	M	Hospitalized	IV	Sulpiride 100 mg/day	General hospital internal medicine	Anorexia, abdominal discomfort	None	Cortical infarcts	None	Multiple infarction	Independent on activities of daily living	4	4	None
59	F	Hospitalized	V	Risperidone 9 mg/day	Psychiatry	Depression, delusion	Hand tremor (lt.and rt.)	Normal in brain CT	L-DOPA 300 mg/day (discontinued)	None	Independent on activities of daily living	56	4	Insomnia
84	M	Hospitalized	IV	Maprotiline 10 mg/day	Psychiatry	Depression	Limb tremor	Bilateral temporal cortical atrophy	L-DOPA 100 mg/day	Senile dementia	Able to walk at home	Unknown	1	Wandering due to dementia
80	F	Hospitalized	V	Sulpiride 300 mg/day	Psychiatry	Depression	None	Lacunes in bilateral white matter	L-DOPA 100 mg/day	None	Wheel chair-bound at nursing	Unknown	Unknown	None
81	F	Hospitalized	IV	Sulpiride 100 mg/day	General practitioner	Unknown	Limb tremor	Lacunes in bilateral white matter and basal ganglia	None	None	Independent on activities of daily living	Unknown	8	None
78	F	Hospitalized	V	Sulpiride 150 mg/day	General hospital surgery	Unknown	None	Widespread white matter	None	Vascular dementia	Wheel chair-bound at nursing	Unknown	Unknown	None
84	M	Hospitalized	IV	Sulpiride 200 mg/day	Psychiatry	Depression	None	Periventricular lucency in brain CT	None	Depression	Able to walk at nursing home	Unknown	Unknown	Insomnia, dementia
87	M	Hospitalized	V	Sulpiride 100 mg/day	Psychiatry	Unknown	Limb tremor	Widespread white matter hyperintensities	Amantadine 400 mg/day, bromocriptine 7.5 mg/day	Vascular dementia	Died from malignant syndrome	8	Unknown	Died

until symptom onset ranged from 1 to 64 weeks (mean 23.2±42.7 weeks), while the period for recovery ranged from 1 to 16 weeks (average 13.2±4.7 weeks). There was no significant correlation between symptom onset and recovery (Figure 4).

Discussion

Examination of 21 cases of drug-induced Parkinsonism (DIP) from our department showed that DIP was more common in elderly women, which is consistent with the known risk factors for DIP.[3] Additionally, DIP progressed more rapidly than Parkinson's disease. Despite the patients having Hoehn and Yahr Scale ratings between 4 and 5, cessation of the medication resulted in relatively rapid recovery. The patients were able to fully recover and return to their baseline state; 15 of 21 cases (71.4%) had good outcomes in that they were able to walk at home after drug withdrawal. However, there were cases in which the patient entered a geriatric facility and became wheelchair-bound, as well as one case of death due to malignant syndrome.

These data suggest that prescription by departments outside of psychiatry accounts for more than 60% of DIP cases. It is possible that these medications are being prescribed by physicians with a minimal understanding of their dangerous side effects; therefore, more attention from the prescribing physician is required. Lopes-Sendon *et al.*[3] found that the risk factors for developing DIP included older age; female sex; cognitive impairment; potency, dose, and length of treatment; and pre-existing extrapyramidal signs. More attention should be paid to the risk factors of DIP.

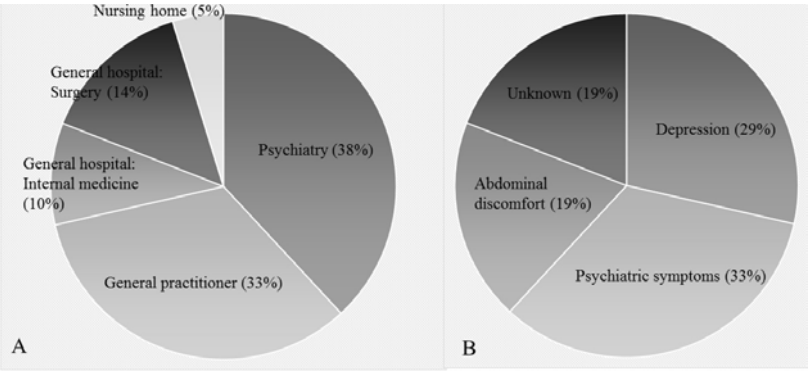

Figure 2. All causative drugs were prescribed in non-neurological departments. Drugs were prescribed in 8 cases (38.1%) in psychiatric and in 13 cases (61.9%) in non-psychiatric departments, which included prescriptions from seven general practitioners, three general hospital surgeons, two general hospital internal medicine physicians, and one nursing home physician. In total, over half of the causative drugs were prescribed in non-psychiatric departments (A). The main reasons for prescribing were listed as depression (29%), psychiatric symptoms (33%), abdominal discomfort (19%), and unknown (19%) (B).

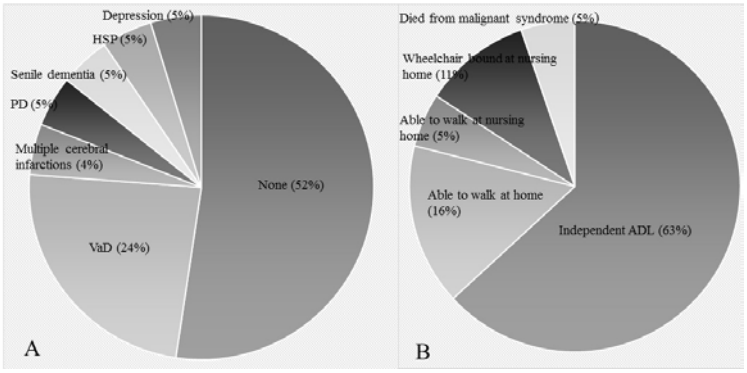

Figure 3. Based on clinical symptoms and neuroimaging findings, 11 of the 21 cases (52%) had no presence of neuromuscular diseases before DIP onset. The remaining 48% did, which included cerebrovascular diseases (28%; five vascular dementia, one higher-order dysfunction due to multiple cerebral infarction, and one hemiplegia), neurodegenerative diseases (14.3%; one Parkinson's disease, one case of familial spastic paraplegia, and one case of geriatric dementia), and depression (4.8%) (A). Fifteen of the patients (71%) had a good outcome in that they were able to walk at home after withdrawal of the causative drug, but three were wheelchair-bound and one died from malignant syndrome (B).

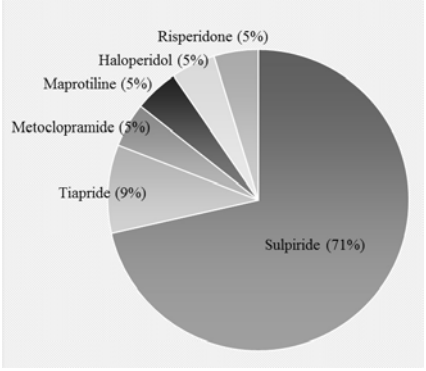

Figure 1. Sulpiride was the most common causative drug (71.4%). The other causative drugs were tiapride, metoclopramide, maprotiline, haloperidol, and risperidone.

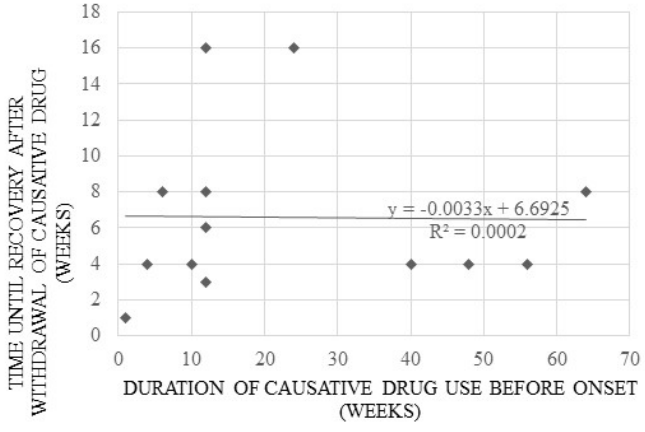

Figure 4. There was no significant correlation between duration of use of the causative drug before DIP onset and time to recovery after drug withdrawal.

We also found there to be some difficulties associated with drug withdrawal because some cases experienced side effects after withdrawal of the causative drug. For example, some patients experienced abdominal discomfort, psychiatric symptoms, insomnia, or behavioral and psychological symptoms of dementia following withdrawal. In these cases, the symptoms experienced following withdrawal were the main reasons for the prescription. If the medication cannot be withdrawn, the dose should be lowered or the medication switched to reduce the risk of DIP. Additionally, another problem experienced following withdrawal of the causative drug is oromandibular dyskinesia. Shin *et al.* found that levosulpiride-induced movement disorders are often severe, and are irreversible even after withdrawal of the drug.[8] In our study, there was a patient who still showed oromandibular dyskinesia after drug withdrawal. Physicians should be also cautious of such symptoms.

Conclusions

In our study, all of the causative drugs were prescribed in non-neurological departments, and more than 60% were prescribed in non-psychiatric departments. Approximately 70% of patients recovered after drug withdrawal; however, the remaining patients did not. We suggest that neurologists pay closer attention to the Parkinsonian side effects of these commonly prescribed drugs.

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