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Comorbid schizophrenia and Parkinson's disease: a case series and brief review

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Abstract

Traditionally, schizophrenia is considered to be a result of dopaminergic hyperactivity while dopaminergic deficiency underlies Parkinson's disease (PD). This opposing pathophysiology makes comorbid schizophrenia and PD seemingly impossible; however, they do coexist rarely in clinical practice. We present four patients with paranoid schizophrenia diagnosed in their youth who developed parkinsonian symptoms on a stable regimen of quetiapine or clozapine after several years. The diagnosis of comorbid schizophrenia and PD was made mainly according to clinical observation. In addition, dopamine transporter (DAT) imaging with ^{18}F-FP-CIT PET was done in two patients, which showed normal DAT density. It is believed that dopaminergic dysfunction in distinct dopaminergic pathways may explain the coexistence of these two disorders.

INTRODUCTION

Schizophrenia is a chronic mental disorder characterized by abnormal social behavior and failure to distinguish between what is real and what is imaginary. The clinical manifestations are largely divided into three categories: positive symptoms like delusions, auditory hallucinations and thought disorganization, negative symptoms like apathy and a lack of drive and motivation with social withdrawal, and cognitive symptoms like poor executive functioning, problems paying attention and with working memory. There are five subtypes in schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) – paranoid, disorganized, catatonic, undifferentiated, and residual subtypes. The paranoid subtype is the most common, which usually begins in the late adolescence or early adulthood. Traditionally, schizophrenia is attributed to hyperactive dopamine transmission (hyperdopaminergia) as its pathophysiology, which comprises an increase of dopamine synthesis capacity, higher synaptic dopamine levels, and augmented dopamine release.[1,2] The hypothesis of hyperactive dopamine transmission in schizophrenia is evidenced from clinical observations that dopamine receptor blockers improve psychosis[3,4] and that psychosis may develop after dopaminergic medications.[5]

Parkinson's disease (PD) is characterized by an array of motor features centered on the presence of bradykinesia and at least one additional motor symptom–rest tremor, rigidity or postural instability. Progressive loss of nigrostriatal dopaminergic neurons (hypodopaminergia) underlies PD.

Given this ostensibly opposing pathophysiology, it seems likely that schizophrenia and PD cannot coexist. However, schizophrenia and PD do coexist although it is rare. In 1987, a diagnosis of PD was presumed as a comorbid condition in a patient with schizophrenia[6], and subsequently, several case reports showed a coexistence of schizophrenia and PD based on clinical evaluation, dopamine transporter (DAT) imaging, or post-mortem neuropathological findings.[7,8] The pathophysiology underlying the coexistence of these two disorders is not entirely clear and still needs to be elucidated.

In this report, we present a case series that describes patents with both schizophrenia and PD and discuss how the dopaminergic system is affected in the coexistence of these two disorders.

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CASE REPORTS

We are taking care of five patients with comorbid schizophrenia and PD. One case of a juvenile-onset PD with PARK2 mutation, who developed schizophrenia several years after parkinsonian symptoms, had been previously reported.[9] In this report, remaining four cases are presented. All the four patients fulfilled the DSM-IV criteria for paranoid schizophrenia, presenting with predominantly auditory hallucinations and/or delusions, and began to be treated with antipsychotic medications since their youth (Table 1). During follow-up, initially administered antipsychotic drugs that were likely to induce parkinsonian symptoms or could not be tolerated due to other side effects had been discontinued for more than 6 months (See confounding drugs in Table 1). Then, low-dose quetiapine or clozapine, which have almost no risk of extrapyramidal symptoms (EPS), were administered as a maintenance antipsychotic regimen. Quetiapine and clozapine continually showed therapeutic benefits. However, several years later since this stable course, parkinsonian symptoms developed in these patients, including bradykinesia, rest tremor, rigidity and gait disturbance. Parkinsonian symptoms began with asymmetric onset, and progressed gradually. In two patients, a significantly decreased DAT density was observed in the striatum on F-18-N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl) nortropane positron emission tomography (^{18}F-FP-CIT PET) (Figure 1). Antiparkinsonian drugs were administered to control motor symptoms, and all patients showed sustained response. Quetiapine and clozapine were maintained with some dose adjustments for not only schizophrenia but also for psychiatric symptoms possibly ascribed to PD.

DISCUSSION

We contend that our patients have comorbid schizophrenia and PD and the parkinsonian symptoms are of genuine PD rather than antipsychotic drug-induced parkinsonism on the basis of the followings. First, the parkinsonian symptoms developed several years after antipsychotics with a substantial risk of extrapyramidal symptoms were discontinued. Based on the clinical course described above, the parkinsonian symptoms could be attributed to genuine PD rather than drug-induced parkinsonism, considering that the symptom of drug-induced parkinsonism improves to varying degrees within months after the offending drugs are withdrawn and it is not likely to persist for several years.[10] Second, the decreased DAT density on ^{18}FP-CIT PET indicates nigrostriatal dopaminergic degeneration of PD rather than pure drug-induced parkinsonism, which shows no abnormalities in the DAT density.[11] Although just two patients underwent ^{18}FP-CIT PET, the other two patients exhibited sustained response to antiparkinsonian drugs, implying damage to the nigrostriatal dopaminergic pathway. Of note is the

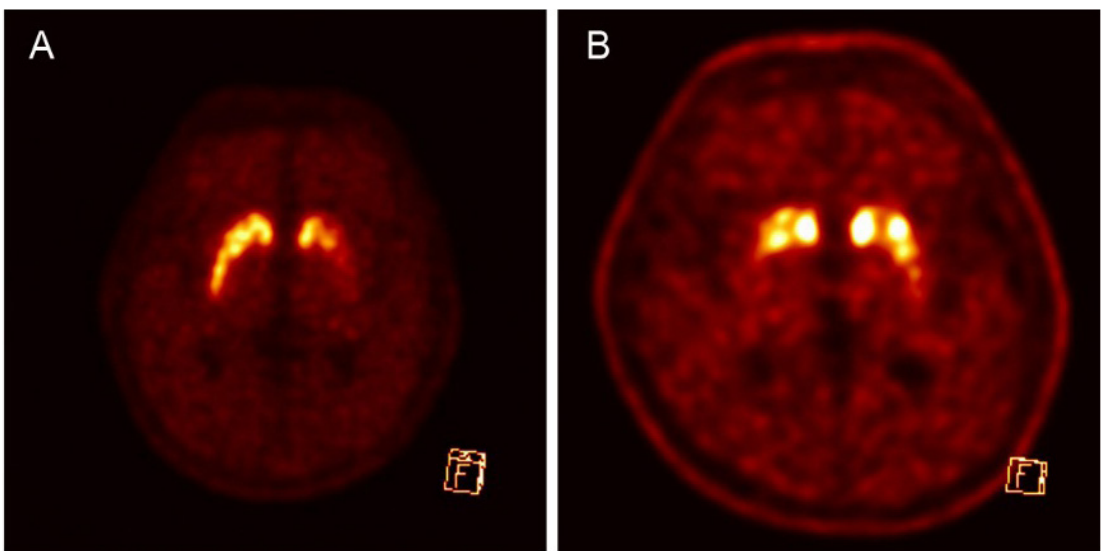

Figure1. Brain^{18}FP-CITPET images at the striatal level in patients with comorbid schizophrenia and Parkinson's disease. Note the markedly decreased uptake in the left putamen (A) and in the bilateral putamen with the more affected right side (B).

Table 1: Clinical findings of the patients

Gender	Age at Dx (SCZ)	†Subtype (symptoms)	Confouding drugs (*duration)	Stable antipsychotics (daily dose)	Age at Dx (Pism)	Pism (symptoms)	^{18}FP-CIT-PET	PD meds (daily dose)
M	34	Paranoid (delusions)	Olanzapine Paliperidone Aripiprazole (6m)	Quetiapine (25mg) Diazepam (5mg)	58	bradykinesia, tremor, rigidity(Rt)	unilateral↓↓‡ putamen (Lt)	Levodopa(300mg) Amantadine(300mg) Rasagiline(1mg)
M	21	Paranoid (delusions)	Risperidone Aripiprazole Paliperidone (2y)	Clozapine (150mg)	41	bradykinesia & rigidity(Lt>Rt), tremor(Lt), gait disturbance	bilateral↓↓‡ putamen (Rt>Lt)	Levodopa(300mg) Rasagiline(1mg) Rotigotine(8mg)
F	28	Paranoid (AH)	Haloperidol (6y)	Quetiapine (100-400mg) Clonazapam (0.5mg)	60	bradykinesia, tremor, rigidity(Rt) gait disturbance	Not done	Levodopa(300mg) Amantadine(150mg) Rasagiline(1mg)
F	30	Paranoid (AH & delusions)	Risperidone Olanzapine Perphenazine Aripiprazole (3y)	Quetiapine (150-300mg) Lorazepam (1mg)	56	rigidity & bradykinesia (Lt≈Rt), gait disturbance	Not done	Levodopa(300mg)

SCZ, schizophrenia; AH, auditory hallucinations. †Subtype of schizophrenia according to DSM-IV criteria . ‡^{18}FP-CITPET revealed markedly decreased uptake.
* Duration of neuroleptic withdrawal.

possibility that neuroleptics can cause nigrostriatal damage, which has been raised recently and need to be explored further.[12]

All our patients had been diagnosed with paranoid schizophrenia in accordance with the DSM-IV criteria. Schizophrenia is usually identified when a first-episode of positive symptoms appears in the late adolescence or early adulthood. During the course, the positive symptoms relapse and remit alternately. The negative and cognitive symptoms may precede the positive symptoms, which is commonly overlooked, and persist during the whole course of disease; in the advanced stage of schizophrenia, the negative and cognitive symptoms become predominant manifestations. It is hypothesized that an evolution of symptoms in schizophrenia may be related to alterations of dopamine transmission; decreased tonic activity is associated with the negative and cognitive symptoms, and this alteration in turn results in a hypersensitive dopamine system, leading to phasic release associated positive symptoms.[13]

Dopamine is produced in the substantia nigra (SN) and ventral tegmental area (VTA). Dopamine activities in schizophrenia and PD rely on distinct dopaminergic pathways projecting from VTA or SN, respectively. In our patients, schizophrenia may result from the hyperactive dopamine transmission in the mesolimbic dopaminergic pathway projecting from the VTA, while dopamine deficiency in the nigrostriatal dopaminergic pathway projecting from the SN brings about PD. Thus, the schizophrenia and PD have ostensibly opposing pathophysiology; however, dysfunction in these distinct dopaminergic pathways may explain the coexistence of these two disorders.[14]

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