Probable progressive supranuclear palsy in a patient with chronic schizophrenia: A case report

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Abstract. Rare neurodegenerative disorders may be considered in the differential diagnosis of Parkinsonism in patients with schizophrenia who show worsening signs of Parkinsonism under treatment with antipsychotics. To the best of our knowledge, the present study is the first report describing probable progressive supranuclear palsy (PSP) in a patient with chronic schizophrenia. A 64-year-old man presented with hallucinations, delusions and asociality. He had received treatment with both typical and atypical antipsychotics for ~13 years. He began experiencing short-term memory impairment and bradykinesia two years before presentation, and then showed increased dysphagia, upper-limb muscle rigidity, extrapyramidal symptoms, vision loss and photophobia. Psychological manifestations included chronic depression, irritability and, occasionally, euphoria. His gait worsened, leading to repeated falls. Antipsychotics were discontinued, and the patient was almost completely dependent on a wheelchair in daily life. In a neurology consultation, he was diagnosed with probable progressive supranuclear palsy-Richardson's syndrome presenting as vertical supranuclear gaze palsy and prominent postural instability with falls. Brain magnetic resonance imaging (MRI) revealed atrophy of the mesencephalic tegmentum, and ^{123}I-ioflupane single-photon emission computed tomography (SPECT) revealed reduced bilateral striatal reuptake. Overall, PSP should be considered in patients with schizophrenia with worsening Parkinsonism, especially when it is accompanied by supranuclear ophthalmoplegia, pseudobulbar palsy, dysarthria and dystonic stiffness of the neck and upper body. In the present case, the combination of brain MRI and ^{123}I-ioflupane SPECT helped to discriminate PSP from other Parkinsonian syndromes, including drug-induced Parkinsonism, in the differential diagnosis.

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Abbreviations: DIP, drug-induced Parkinsonism; EPS, extrapyramidal symptoms; MDS, International Parkinson's and Movement Disorder Society; MRI, magnetic resonance imaging; MSA, multiple system atrophy; PD, Parkinson's disease; PSP, progressive supranuclear palsy; PSP-RS, progressive supranuclear palsy-Richardson's syndrome; SPECT, single-photon emission computed tomography

Key words: progressive supranuclear palsy-Richardson's syndrome, Schizophrenia, Parkinsonism, magnetic resonance imaging, case report

Introduction

The incidence of drug-induced Parkinsonism (DIP) increases with older age, and the most common cause is antipsychotic medication (1). In patients with schizophrenia who show exacerbation or progression of Parkinsonism under treatment with antipsychotics, rare neurodegenerative disorders may have to be considered in the differential diagnosis of Parkinsonism (2).

Progressive supranuclear palsy (PSP) is a rare progressive neurodegenerative disease characterized by vertical supranuclear gaze palsy, pseudobulbar palsy, dysarthria, early postural instability, and axial dystonia (3). An important advance was made in 2016 with the development of the new International Parkinson's and Movement Disorder Society (MDS) Criteria for the Diagnosis of PSP (4). In brief, essential features of PSP are required for all patients based on MDS criteria, where mandatory eligibility criteria indicate the presence of sporadic, adult-onset and, gradually progressive disease-related symptoms. Conversely, mandatory exclusion criteria indicate other neurological disease such as Alzheimer's disease, dementia with Lewy bodies, and severe leukoencephalopathy should be ruled out in clinical and neuroimaging manifestation for any patients. Furthermore, four core functional domains [i.e., ocular motor dysfunction (O), postural instability (P), akinesia (A) and cognitive dysfunction (C)] are proposed as diagnostic clinical symptom of PSP. Each of functional domains is stratified into three stages, which could contribute to diagnose different clinical subtypes of PSP in clinical practice. For instance, the combination of falls with vertical ocular motor dysfunction (O) and early onset postural instability (P) is generally referred to as progressive supranuclear palsy-Richardson's syndrome

(PSP-RS) (4). The prevalence of PSP-RS is ~5-7 cases per 100,000 individuals, the average age at onset in the mid-60s, and the disease duration is ~6 years (5-7).

The pathological specificity of probable PSP is 95-100%, and the clinical distinction between genuine DIP and PSP is likely identifiable (4). However, in patients with newly developed DIP, the diagnosis of PSP may be overlooked. This is because symptoms such as different resting tremors [e.g., Parkinson's disease (PD)] on the left and right sides, which are less likely to occur in DIP, are more pronounced in PSP.

Here, we report a case involving a 64-year-old male inpatient with schizophrenia who had received long-term treatment with antipsychotic medication and likely developed PSP-RS.

Case report

The patient had no family history of psychiatric or neurodegenerative diseases. In 1980, at 27 years of age, he first presented with hallucination/delusions and was diagnosed with schizophrenia on the basis of the DSM-3 criteria in our hospital. In July 2002, at 49 years of age, he was admitted to the hospital for the third time because of frequent insomnia, hallucinations, a tendency to become excited, and increasing incidences of violence. Head computed tomography at the time of admission showed no atrophy of the midbrain tectum or frontal lobe (Fig. 1).

Since 2002, he received typical antipsychotic medications, such as levomepromazine (125 mg) and haloperidol (4.5 mg), for ~8 years. However, he could not be discharged home due to severe asociality, avolition, and the fact that he usually stayed in bed throughout the day. Since 2010, his motility worsened under management with atypical antipsychotic drugs [quetiapine (600 mg) and olanzapine (20 mg)], although he was never prescribed anticholinergic drugs.

In 2015, at 62 years of age, he began experiencing short-term memory impairment and bradykinesia. In April 2016, he showed increased dysphagia, upper-limb muscle rigidity, and extrapyramidal symptoms (EPS) and began experiencing vision loss and photophobia. However, his psychological symptoms included chronic depression and irritability with bouts of euphoric mood, which had never been observed before. DIP was suspected because he began to cough while eating. Therefore, biperiden was prescribed at a dosage of 2 mg/day starting in July 2016. However, his speech was difficult to comprehend because of the sialorrhea. Moreover, his inactivity, muscular rigidity, and slouching gait gradually worsened, following which he began to use a walking aid. In December 2016, he experienced repeated falls due to suspected DIP, and risperidone (from 9 mg) and olanzapine (from 20 mg) were gradually tapered off over 12 months. Although antipsychotic medications were completely discontinued, he showed persistent Parkinsonism symptoms with an apathetic mood, and he became mostly wheelchair-dependent in his daily activities, during which he had fallen at least five times. In December 2017, at 64 years of age, he was referred to the neurology department, where he presented with severe supranuclear vertical gaze palsy, retrocollis, mild limb muscle rigidity with little laterality, and total akinesia. Although standing was difficult due to severe retropulsion, no rapid eye movement sleep behavior disorder, autonomic symptoms such as orthostatic hypotension, illusion, or signs of upper and lower motor neuron disorders were noted. Based on the MDS-PSP criteria, this patient had presented severe supranuclear vertical gaze palsy (O1) and repeated falls with severe retropulsion within 3 years (P1) without gait freezing and speech disorder, which was most likely to meet a key requirement for diagnosis of probable PSP-RS. The bedside assessment of cognitive abilities using the Mini-Mental State Examination score was 16/30 points, indicating moderate cognitive decline. Further, while blood examination showed normal results, brain MRI showed features of PSP, such as atrophy of the mesencephalic tegmentum (hummingbird sign) and atrophy of the frontal lobe (Fig. 2 A-C). ^{123}I-ioflupane SPECT revealed decreased striatal uptake (Fig. 3). On the basis of these findings, the patient was finally diagnosed with probable PSP-RS by a neurologist (4).

In March 2018, a swallowing test indicated the need for an alternative mode of nutrition because of the aspiration of saliva. In May 2018, because of repeated aspiration pneumonia and hemophagocytic syndrome, the patient was transferred to another medical hospital, following which he died soon from worsening multi-organ failure.

Discussion

PSP is a rare neurodegenerative disorder. To our knowledge, this is the first report of an older male patient with chronic schizophrenia and probable PSP-RS.

In addition to the psychiatric symptoms of chronic schizophrenia, our patient presented with EPS as an exacerbation of PSP. Komatsu *et al* recently reported a case of multiple system atrophy (MSA) in a 60-year-old female patient with chronic schizophrenia who developed possible MSA with predominant Parkinsonism (2). Her Parkinsonism was reported to be unremedied, although antipsychotic medication was switched from typical to atypical antipsychotics and tapered off. In our case, a 64-year-old male patient developed PSP-RS with chronic schizophrenia when his antipsychotics were discontinued for several months. However, his Parkinsonism was exacerbated and he was mostly wheelchair-dependent in his daily activities. Parkinsonism that appears in patients taking antipsychotics for chronic schizophrenia can be generally considered a drug-induced syndrome. However, the combination of MRI and ^{123}I-ioflupane SPECT plays a critical role in the differential diagnosis of DIP in these cases, suggesting that the comorbidity of schizophrenia and other degenerative disorders such as PSP and MSA should be taken into consideration in clinical practice.

In Boxer's previous review, the most frequently reported symptoms of PSP-RS at onset were unexplained falls, unsteady gait, bradykinesia, subtle personality changes (apathy, disinhibition), cognitive slowing (bradyphenia), executive dysfunction (difficulty planning or multitasking), slow, ataxic, spastic, and hypophonic speech, dysphagia, and impaired ocular movement (i.e., slowing of vertical saccades, difficulty reading, or apraxia of eyelid opening) (8,9). In the MDS criteria, a diagnosis of probable PSP-RS requires O1 (ocular motor dysfunction, vertical supranuclear gaze palsy) and P1 (postural instability, repeated unprovoked falls within three years) (4). In addition to the diagnostic criteria (supranuclear ophthalmoplegia and repeated falls) for MDS, our patient also showed unsteady

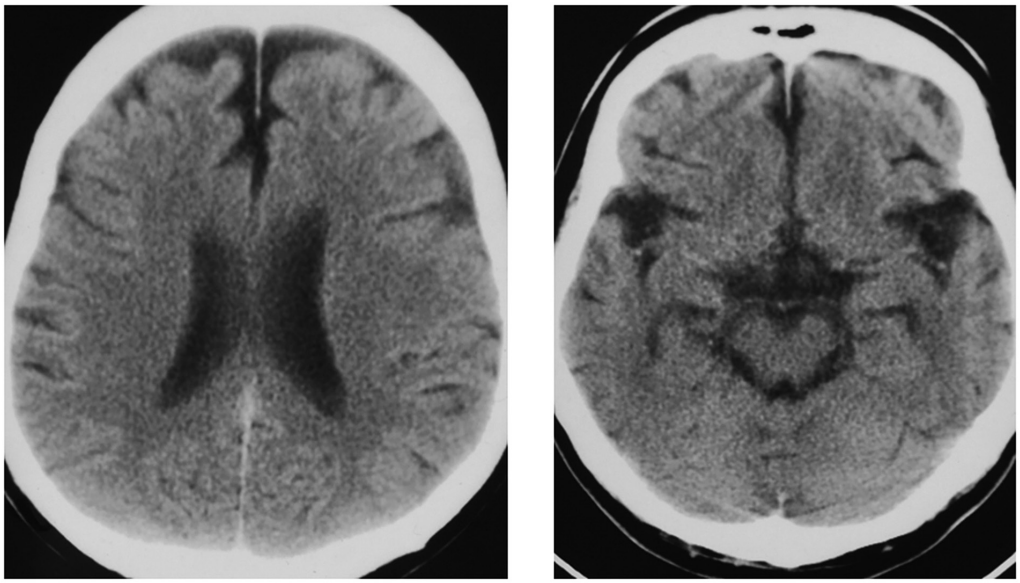

Figure 1. Brain computed tomography images of the patient at 49 years of age (July 2002). No atrophy of the frontal lobe or midbrain tectum can be observed.

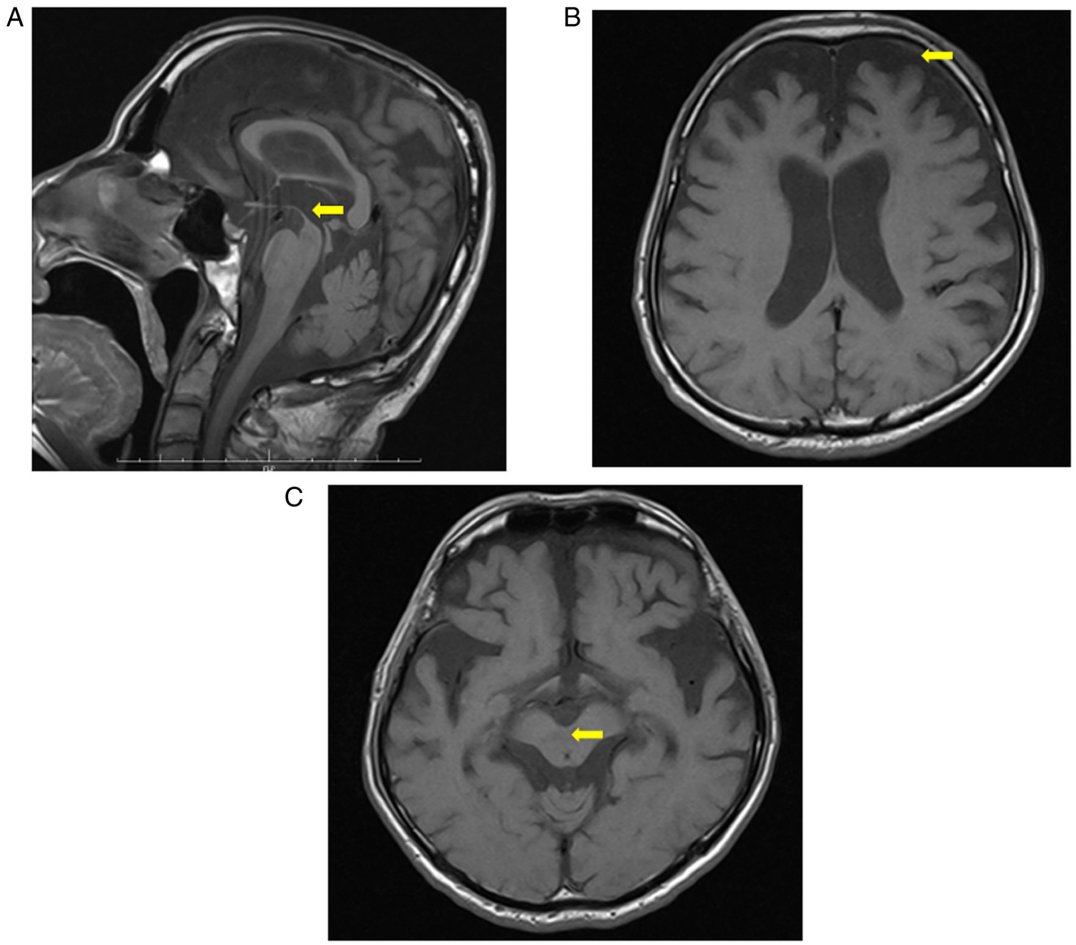

Figure 2. Brain MRI of the patient at 64 years of age (December 2017). Brain MRI shows (A) atrophy of the mesencephalic tegmentum (hummingbird sign), (B) atrophy of the frontal lobe and (C) atrophy of the mesencephalic tegmentum, which are characteristics of progressive supranuclear palsy-Richardson's syndrome. Arrows indicate the noted features. MRI, magnetic resonance imaging.

gait, bradykinesia, slowness, ataxia, dystonic stiffness of the neck and upper body, personality changes, cognitive decline, dysarthria, and dysphagia (pseudobulbar palsy), and he was diagnosed as having probable PSP-RS.

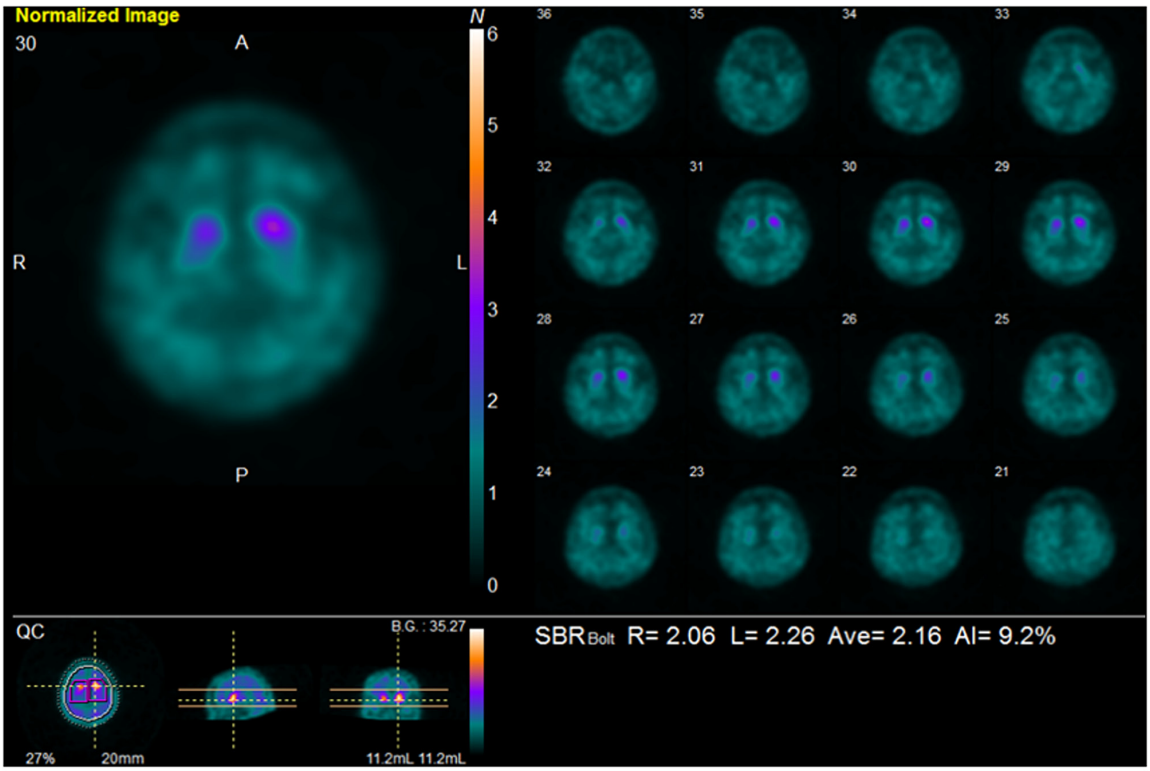

Figure 3. ^{123}I-ioflupane SPECT results from December 2017. ^{123}I-ioflupane SPECT data show reduced bilateral striatal uptake. Specific binding ratio: 2.16 (right, 2.06; left, 2.26); asymmetric index: 9.2 (%). SPECT, single-photon emission computed tomography.

During the course of the illness, patients with PSP typically exhibit psychotic symptoms. Behavioral abnormalities were common in Gerstenecker's cohort of patients with PSP, with more than half experiencing apathy, depression, and sleeping problems, and approximately one-third displaying agitation, irritability, disinhibition, and eating problems (10). Neuropsychiatric symptoms such as hallucinations and delusions, however, were only observed in 5-10% of patients (10). The patient in the present report showed cognitive impairments, apathy, depression, sleeping problems, irritability, and hallucinations as psychiatric symptoms of PSP during 2 years after onset, however, he had positive symptoms (i.e., hallucination/delusion, insomnia, agitation) and negative symptoms (i.e., asociality, avolition) of schizophrenia for 35 years.

In addition to clinical features, brain MRI may help distinguish PSP from other Parkinsonian syndromes. Atrophy of the midbrain and superior cerebellar peduncles is a useful marker in differentiating PSP-RS from other Parkinsonian syndromes (11). Conventional structural MRI is more specific but less sensitive than a clinical diagnosis of PSP, and the hummingbird and morning glory flower signs each showed 100% specificity for PSP (11). The presence of frontal atrophy and hypometabolism are also prominent features of PSP-RS and they may improve diagnosis when considered together with midbrain atrophy (12). The current case showed MRI characteristics of PSP-RS: the hummingbird sign and frontal atrophy.

DIP should be considered in the differential diagnosis because it is one of the few reversible causes of the disorder (13). The management of DIP involves identifying and discontinuing the contributing medications, which usually resolves the symptoms, although the symptoms may linger for a few months or up to a year or two in some cases (14). Hayes' review suggests that dopamine active transporter imaging using ^{123}I-ioflupane SPECT may be useful in diagnosing DIP, as it is normal in those cases (15,16). The present case showed significantly reduced bilateral striatal reuptake on ^{123}I-ioflupane SPECT, and was not diagnosed as DIP.

Traditionally, schizophrenia is considered to be a result of dopaminergic hyperactivity, whereas dopaminergic deficiency underlies the pathology of PD (17). This conflicting pathophysiology makes coexisting schizophrenia and PD seemingly impossible. However, they have been shown to coexist in clinical practice, and comorbidity of idiopathic PD and schizophrenia represent a rare scenario that is often difficult to manage (17,18). These findings support the hypothesis that the nigrostriatal and mesolimbic dopaminergic pathways largely function independently, or time- and site-dependent variations in the severity of dysfunction within a common cortical-striatal-thalamocortical neuronal network results in the development of idiopathic PD in patients with schizophrenia as they age (19). Moreover, there is renewed interest in the motor aspects of schizophrenia's neurodevelopmental disorders, including spontaneous Parkinsonism, which appears to be independent of antipsychotic treatment (20). By examining a small number of cases of schizophrenia combined with degenerative disorders such as PD, PSP, and MSA, it may be possible to approach the neurodevelopmental disorder hypothesis for the pathophysiology of schizophrenia.

This case report had some limitations to make a diagnosis of PSP. First, a definite diagnosis of PSP could not be confirmed because of a lack of qualified pathologists capable

of performing an autopsy in a terminal hospital. Second, other brain imaging modalities (e.g., ^{123}I-meta-iodobenzylguanidine scintigraphy) could not be sufficiently investigated at other time points. Third, genetic analyses that can help to support the clinical diagnosis of PSP describing in context dependent exclusion criteria were not examined in this case (4).

In conclusion, this is the first known report to describe probable PSP-RS in an older patient with chronic schizophrenia. The comorbidity of PSP-RS in patients with schizophrenia is extremely rare, but PSP should be considered when such patients present with worsening symptoms of Parkinsonism, especially when accompanied by supranuclear ophthalmoplegia, pseudobulbar palsy, dysarthria, and dystonic stiffness of the neck and upper body. In this case, the combination of ^{123}I-ioflupane SPECT, brain MRI, and the patient's clinical features, helped us to discriminate PSP-RS from other Parkinsonian syndromes. Future research examining subjects with schizophrenia comorbid with neurodegenerative disorders such as PD, PSP, and MSA may provide a greater insight into understanding the shared common mechanisms that may contribute to overlapping pathophysiological and clinical features between the disorders, leading to an avenue for the novel drug discovery and development.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

AK, TT, MY, YS and HI contributed to the patient treatment. JK performed neurological examinations and treatment. AK, TT, MY, YS, HI and JK collected data and wrote the first draft of the manuscript. AK, TT, ST and SK supervised the project, were critically involved in its design, and assisted in editing the final manuscript. All authors contributed toward drafting the paper and agree to be accountable for all aspects of the work. AK and SK confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval was obtained from the Medical Ethics Commission for Clinical Studies in the Wakayama Medical University (approval no. 3428 on 21/02/2022).

Patient consent for publication

Patient consent for publication could not be obtained because of his death; however, consent in written form was provided by his family on 18/05/2018.

Competing interests

The authors declare that they have no competing interests.

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