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■ CASE REPORT ■

Quetiapine: The Possibility of Quetiapine as a Cause of Neuroleptic Hypersensitivity in Dementia with Lewy Bodies

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The clinical manifestations of dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) overlap and differential diagnosis may be difficult. However, among the diagnostic criteria of DLB, severe neuroleptic sensitivity is strongly suggestive of DLB. We report a case of a 79-yr-old woman who developed with acute confusion state after low dose quetiapine medication.

Key Words: *Neuroleptic hypersensitivity, Parkinson's disease dementia, Dementia with Lewy bodies*

INTRODUCTION

The cardinal symptoms of dementia with Lewy bodies (DLB) include progressive cognitive decline, visual hallucinations, and parkinsonism [1]. It is difficult to distinguish between DLB and Parkinson's disease dementia (PDD) because DLB patients may present with parkinsonism around the same time as the cognitive symptoms, and early cognitive change is also identified in patients with PD without dementia. Additionally, there is no standard that can absolutely differentiate DLB from PDD, as both may have psychiatric symptoms, autonomic insufficiency, and rapid eye movement (REM)-sleep behavioral disorder [2].

However, some differences in clinical features have been described in studies of DLB and PDD patients characterized by consensus criteria. In particular, adverse reactions to antipsychotic agents may be more severe and frequent in DLB than PDD. In DLB patients, high morbidity and mortality are associated with neuroleptic sensitivity reactions, which are characterized by the acute onset or exacerbation of parkinsonism and impaired consciousness. Approximately 50% of patients with DLB receiving typical or atypical antipsychotic agents react adversely, and a positive history of severe neuroleptic sensitivity is strongly suggestive of DLB [1, 3]. We

present a case of DLB who developed an acute confusional state after quetiapine medication even though we prescribed low dose quetiapine.

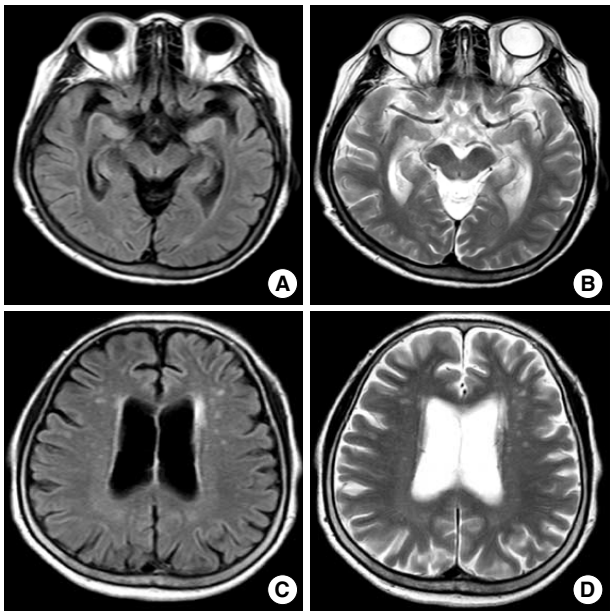

Fig. 1. Brain magnetic resonance imaging (MRI) shows diffuse brain atrophy and scattered ischemic lesions in periventricular white matter on fluid-attenuated inversion recovery (FLAIR) images (A, C) and T2-weighted images (B, D).

CASE REPORT

A 79-yr-old woman visited our outpatient clinic due to recurrent visual hallucinations for 6 months. She had experienced well-formed and vivid visual hallucinations, which were related to her deceased mother-in-law. Her family reported that she sometimes talked to her mother-in-law who passed away several years ago. She had also been complaining of frequent forgetfulness and difficulty in finding words that were getting worse gradually. She had been diagnosed with Parkinson's disease 3 yr ago and treated with an anticholinergic agent (trihexyphenidyl, 1mg twice a day) and a dopaminergic agent (L-dopa, 125 mg twice a day) until now. On neurological examinations, she showed hypomimia and hypophonia, resting tremor of the right hand, slightly increased arm rigidity in the right side, mild bradykinesia, and short-stepped gait with decreased arm swings of both arms. However, she did not show postural instability. The other neurological examinations were unremarkable. The laboratory data including thyroid function tests were within normal limits. Brain magnetic resonance imaging (MRI) showed diffuse brain atrophy and scattered ischemic lesions on bilateral periventricular

Table 1. Results of Seoul Neuropsychological Screening Battery (SNSB)

Tests	Response	Tests	Response
K-MMSE	21	Memory	
Attention		SVLT 1st/2nd/3rd	1/4/4
Digit span: forward/backward	4/3	Delayed recall	2
Letter cancellation	AB	Recognition: TP/FP	9/4
Language and related function		Recognition score	17
Spontaneous speech	Fluent	RCFT immediate recall	2.5
Contents	NL	RCFT delayed recall	3
Comprehension	NL	RCFT recognition: TP/FP	12/3
Repetition	15/15	RCFT recognition score	21
S-K-BNT	11/15	Frontal executive functions	
Reading	NL	Motor impersistence	NL
Writing	NL	Contrasting program	20/20
Praxis	NL	Go-no-go test	16/20
Finger naming	NL	Fist-edge-palm	NL
Right-left orientation	NL	Alternating hand movement	NL
Calculation	NL	Alternating square and triangle	NL
Body part identification	NL	Luria loop	
Visuospatial functions		Word fluency animal/supermarket	7/5
Interlocking pentagon	AB	Word fluency ㄱ/o/ㄱ	1/2/2
RCFT	21.5/36	K-CWST word/color reading	AB

S-K-BNT, short form of Korean version of the Boston Naming Test; RCFT, Rey-Osterrieth Complex Figure Test; SVLT, Seoul Verbal Learning Test; K-CWST, Korea-Color Word Stroop Test; K-MMSE, Korean version of Mini-Mental State Examination; AB, abnormal; D, deformed; NL, normal; TP, true positive; FP, false positive.

white matter (Fig. 1). The Korean version of the Mini-Mental State Examination resulted in a score of 21/30, and her Clinical Dementia Rating was 1 [4, 5]. The Seoul Neuropsychological Battery (SNSB) revealed impairment in visuospatial function, verbal and visual memory, and frontal executive functions (Table 1) [6]. We diagnosed her with PDD and prescribed low dose quetiapine (12.5 mg per day) to control the recurrent visual hallucinations. Several days later, she was admitted to our hospital via the emergency room for impaired consciousness. Her daughter reported that confusion had suddenly developed after taking the quetiapine and tended to fluctuate. On the day of admission the patient was deeply drowsy and could not fully respond to verbal stimuli. Her speech was disorganized. Arm rigidity was slightly increased bilaterally but other extrapyramidal symptoms had not worsened. The body temperature was 36.8℃. There was no tachycardia, tachypnea, or diaphoresis. Laboratory findings, including serum creatine kinase, were within normal limits. We considered her state to be caused by quetiapine-induced hypersensitivity reactions. We decided to discontinue the quetiapine and conducted intravenous hydration. Her mentality gradually improved and became normalized to the previous level. We performed brain ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET), which showed decreased glucose metabolism in the right parietal and posterior temporo-occipital areas and the left parietal area (Fig. 2). We made a diagnosis of probable DLB according to consensus guidelines for the clinical diagnosis of DLB [1].

DISCUSSION

Patients with dementia in the context of parkinsonism, with either PDD or DLB, frequently experience various neuropsychiatric symptoms, in particular, visual hallucinations. These symptoms cause increased burden of patients and caregivers [7]. Therefore, antipsychotic drugs are commonly prescribed as part of the clinical management of these patients. Many studies have demonstrated that atypical neuroleptics are a suitable first-line treatment for psychiatric symptoms of dementia and several psychiatric disorders in place of conventional neuroleptics because there is less likelihood of adverse reactions. Among atypical neuroleptics, quetiapine is relatively unlikely to increase plasma prolactin concentrations and shows a low frequency of extrapyramidal symptoms. Quetiapine is currently considered a good choice for management

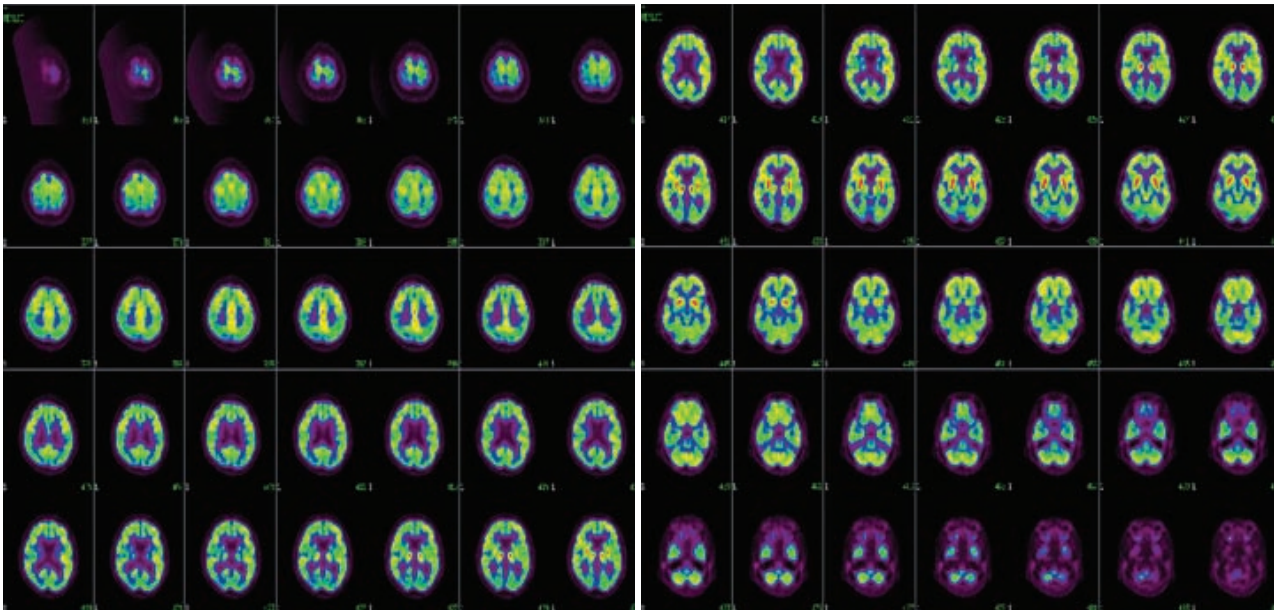

Fig. 2. Brain ^{18}F-FDG-PET demonstrates decreased glucose metabolism in the right parietal and posterior temporo-occipital areas and left parietal area.

of psychiatric symptoms in patients with dementia including DLB [8, 9].

However, neuroleptic hypersensitivity is one of suggestive features in the consensus criteria for the clinical diagnosis of probable and possible DLB [1]. The atypical antipsychotics are relatively less severe neuroleptic reactions than typical antipsychotics, but Kobayashi et al. reported a patient with probable DLB who developed neuroleptic malignant syndrome following quetiapine administration [10]. In our case, the patient experienced confusional mentality with increased rigidity immediately with quetiapine medication and recovered after discontinuation of quetiapine administration. We thought that the patient had a severe hypersensitivity reaction to antipsychotics, even though we administrated low dose quetiapine. The mechanism underlying this vulnerability to neuroleptics in DLB patients suggests that a reduction of dopaminergic innervations in the substantia nigra and striatum and a dysfunctional dopamine D2 receptor might account for this neuroleptic hypersensitivity [11]. However, the dopamine blockade hypothesis alone cannot fully explain occurrence of neuroleptic hypersensitivity symptoms, imbalance between dopaminergic systems and others, such as the cholinergic and serotonergic systems, may contribute to severe neuroleptic reactions as well as [10, 12].

We recommend that DLB patients who are sensitive to neuroleptics be considered at high risk for further adverse reactions, and special attention is needed, even upon treatment with atypical neuroleptics. In fact, severe neuroleptic sensitivity reactions not only occur in patients with DLB but could occur in other Lewy body disorders such as Parkinson's disease and PDD. However, the frequency of severe neuroleptic sensitivity reactions has not been described in PD or PDD patients, although these patients are at increased risk of exacerbation of extrapyramidal symptoms with neurolpetics due to nigrostratal dopaminergic deficiency. Low dose atypical antipsychotics such as clozapine and quetiapine may be reasonably well tolerated from the perspective of exprapyramidal symptoms, but the issue of severe sensitivity reactions has not been addressed [12].

The third report of the DLB consortium made a brief statement about PDD and DLB that reinforces the need to make a clinical distinction using the timing of cognitive symptom onset in relation to motor symptoms (I year or less=DLB; more than I year=PDD) as the basis [1]. Based on this, we considered PDD for our patient at first because she had parkinsonian symptoms for several years before the cognitive decline and visual hallucinations. While the 1-yr rule is applied to many studies for DLB, we believe that additional prospective studies are needed to clarify the differential diagnostic criteria of the clinical features in these disorders. There are many opinions on the differential diagnosis between PDD and DLB, but patients with severe neuroleptic sensitivity reactions are more strongly suggestive of DLB than PDD [1, 2]. Finally, we diagnosed this case with probable DLB because she had recurrent visual hallucinations, parkinsonism, and neuroleptic hypersensitivity, based on the guideline from the third report of the DLB consortium [1].

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