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Short Communications

Delirium-onset prodromal Lewy body disease: A series of 5 cases

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ABSTRACT

Background: Delirium-onset prodromal Lewy body disease (LBD) has been proposed as one of the primary phenotypes of prodromal stages of LBD. The detailed clinical features and biomarker profiles of delirium-onset prodromal LBD have not been well characterized.
Methods: Five consecutive cases of delirium-onset prodromal LBD were documented. The diagnosis of prodromal LBD was made based on neuroimaging biomarkers, including dopamine transporter single-photon emission computed tomography (SPECT), cardiac ^{123}I-metaiodobenzylguanidine scintigraphy, and/or brain perfusion SPECT, as well as clinical findings in the post-delirium follow-up periods.
Results: In all cases, one or more of the core or supportive clinical features of dementia with Lewy bodies, including rapid eye movement sleep behavior disorder, minor hallucinations, hyposmia, or autonomic dysfunction, were present prior to the onset of delirium. The precipitating factors for delirium were diverse, including surgery, radiation therapy, chemotherapy, and infection. The duration of delirium was prolonged for several months in two cases, whereas it was resolved within a few weeks in the other cases. In most cases, persistent mild cognitive or behavioral symptoms were observed, which were improved with donepezil.
Conclusions: Our observations suggest that delirium-onset prodromal LBD may represent the later stages of the prodromal LBD rather than its initial stages. It is possible that delirium in the prodromal stages of LBD may represent subthreshold cognitive fluctuations that are transformed into clinically detectable states by a variety of precipitating factors.

1. Background

The current diagno stic criteria for dementia with Lewy bodies (DLB), which include fluctuating cognition, visual hallucinations, parkinsonism, and rapid eye movement sleep behavior disorder (RBD) as core clinical features, have a high specificity, but their sensitivity is fair and unsatisfactory for the earliest stage of the disease [1,2]. In the prodromal stages of the disease, a wide variety of phenotypes may be present without overt dementia or any of the core clinical symptoms, making early diagnosis challenging. To overcome such situations, clinical research criteria for prodromal DLB has recently been proposed, which includes 1) mild cognitive impairment-onset, 2) psychiatric-onset, and 3) delirium-onset subtypes as the three primary phenotypes [3].

Previous epidemiological studies demonstrated that incidence of delirium before diagnosis of dementia is a 3–5 times higher in patients with DLB than those with Alzheimer's disease (AD) [4,5]. Although delirium associated with systemic disease or surgery is an important opportunity for early diagnosis of Lewy body disease (LBD), it is precluded by the current paucity of information on diagnostic clinical features for delirium-onset prodromal LBD [6,7]. Here, we present five cases of delirium-onset prodromal LBD to provide information on their precipitating factors, behavioral and other clinical features, and clinical course after resolution of delirium.

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2. Case presentation

Clinical features and biomarker findings of the 5 cases are summarized in Table 1 and Fig. 1.

2.1. Case 1

A man in his 50 s was admitted to the pulmonary unit for preoperative radiation and chemotherapy for lung cancer. He had no past cognitive problems and was working just prior to his hospitalization. He had a 15-year history of abnormal nocturnal behavior indicative of RBD, including getting out of bed and punching the wall during sleep. Otherwise, he had no significant past medical history or substance misuse. His family history was unremarkable. During his hospital stay, he experienced visual hallucinations and wandered around the ward. He was diagnosed with delirium and improved with zolpidem 5 mg/day. Two months later, he was readmitted for surgery and developed pneumonia postoperatively. He was severely agitated and complained frequent visual hallucinations. With a diagnosis of delirium, he was treated with haloperidol 5 mg IV, which successfully resolved his agitation. He was then maintained with quetiapine 75 mg/day and ramelteon 8 mg/day, but his delirium had not completely resolved. Five months after surgery, he was discharged to his home.

The patient was followed up in the psychiatric outpatient clinic. His cognitive function remained impaired and fluctuating, and he continued to experience occasional visual hallucinations. He complained occasional orthostatic dizziness. His Mini-Mental State Examination (MMSE) scores were 25/30 and 28/30 at nine and fifteen months after the surgery, respectively (Table 1). Neurological examinations revealed no parkinsonism or other sensorimotor abnormalities. Cardiac ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy showed decreased myocardial uptake (Fig. 1). Sixteen months after the surgery, the patient was started on donepezil 10 mg/day, and his cognition and visual hallucinations improved. However, feeling of presence and mild visual hallucinations persisted. Forty-one months after the onset of delirium, he continued to be employed with support.

2.2. Case 2

A man in his 70 s was admitted for surgery for appendicitis with peritonitis. He had no prior history of cognitive impairment and was actively employed just prior to his hospitalization. His medical history included pulmonary emphysema and being a liver transplant donor. He was a heavy drinker, consuming 9 units of alcohol daily. His family history was unremarkable. He had been hyposmic since his 50 s. Six months prior to the admission, he began to complain of visual illusions and minor difficulties with his daily activities. Following the surgery, he developed severe agitation with visual hallucinations. With a diagnosis

Table 1
Clinical features and biomarker findings.

	Case 1		**Case 2**		**Case 3**		**Case 4**		**Case 5**	
Age, sex	50 s, M		70 s, M		70 s, F		60 s, F		70 s, M	
Length of follow-up timeafter delirium onset	3y5m		2y2m		2y11m		1y8m		1y2m	
MMSE in post-delirium period										
1st assessment	25		23		25		22		22	
follow-up assessment	28		27		21		25		26	
after donepezil treatment	NA		30		27		NA		NA	
Core clinical features	Before delirium onset	After delirium onset	Before delirium onset	After delirium onset	Before delirium onset	After delirium onset	Before delirium onset	After delirium onset	Before delirium onset	After delirium onset
Fluctuating cognition	−	+	−	−	−	+	−	−	+	+
Visual hallucinations	−	+	±	−	−	+	−	−	±	+
REM sleep behavior disorder	+	+	−	−	+	+	−	−	+	+
Parkinsonism	−	−	−	−	−	−	−	−	−	−
Supportive clinical features before delirium onset	Orthostatic dizziness		Constipation, hyposmia, visual illusions		Constipation		Orthostatic dizziness		Passage hallucinations	
Indicative biomarkers										
Decreased DAT uptake (SBR right/left)	NA		Grade 0 (7.05/6.14)		Grade 2 (5.11/4.34)		Grade 1 (4.22/3.96)		NA	
Decreased MIBG uptake (HMR early/delayed)	+ (1.73/1.36)		+ (1.46/1.22)		NA		NA		+ (1.59/1.35)	
Supportive biomarkers										
Relative preservation of MTL on MRI/CT	+		+		+		+		+	
Generalized/occipital low uptake or posterior cingulate island sign on perfusion SPECT	+		+		−		+		NA	
Posterior slow-wave EEG activity	−		−		NA		−		NA	
Delirium										
Triggers	① Radiation and chemotherapies ② Surgery, pneumonia		Surgery, peritonitis		Surgery		Surgery		Coronavirus infection	
Visual hallucinations during delirium	+		+		+		+		−	
Duration	① 2w ② 3 *m*		2 *m*		10d		2w		1w	

DAT-SPECT was graded visually according to the previously published method (11).
CT, computed tomography; DAT, dopamine transporter; EEG, electroencephalogram; HMR, heart-to-mediastinum ratio; MIBG, metaiodobenzylguanidine; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; MTL, medial temporal lobe; NA, not assessed; SBR, specific binding ratio; SPECT, single-photon emission computed tomography.

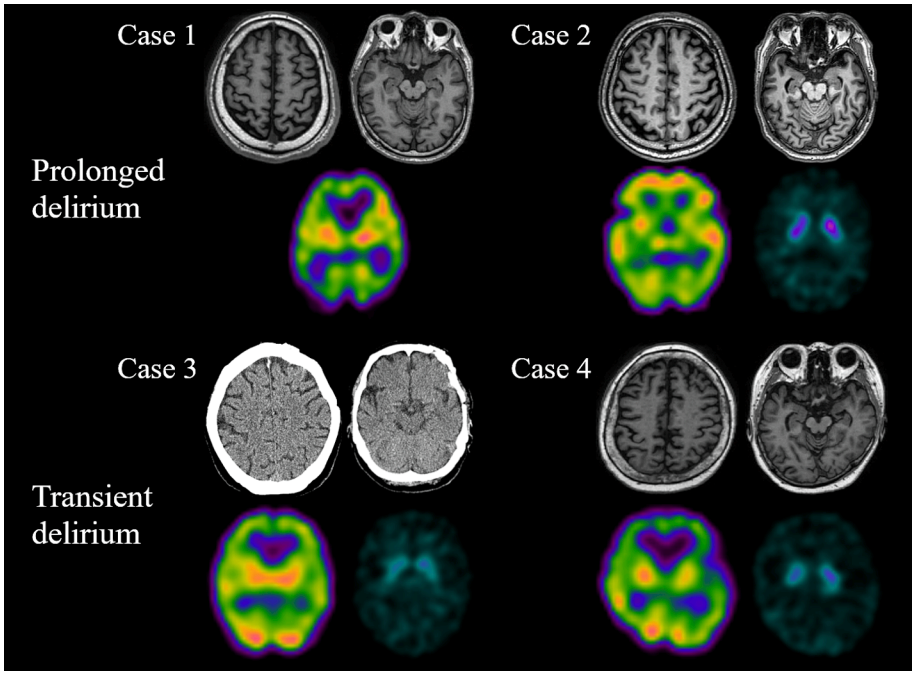

Fig. 1. Neuroimaging findings. Cases with prolonged delirium and those with transient delirium are shown in the top and bottom rows, respectively. The left side of each image corresponds to the right side of the brain.

of delirium, he was treated with lemborexant, ramelteon, and several antipsychotics, but his delirium did not resolve. Thirty-three days after surgery, he was admitted to the psychiatric unit for treat of delirium. His MMSE scores were 23/30 and 27/30 at one and two months after surgery, respectively (Table 1). Neurological examinations revealed no parkinsonism or other sensorimotor abnormities. He had constipation, hypersomnia, and hyposmia. Cardiac MIBG scintigraphy showed decreased myocardial uptake. ^{123}I-N-omega-fluoropropyl-2-betacarbomethoxy-3-beta (4-iodophenyl) nortropane dopamine-transporter single-photon emission computed tomography (DAT-SPECT) showed no abnormalities (Fig. 1). He was treated with quetiapine 50 mg/day and trazodone 100 mg/day, but his delirium was only partially improved. Two months after surgery, he was started on donepezil 5 mg/day. Two weeks later, his delirium completely resolved, and he was discharged to his home. Twenty-six months after surgery, his MMSE score was 30/30.

2.3. Case 3

A woman in her 70 s was admitted for colon cancer surgery. She and her family reported no cognitive problems, and she was actively working just prior to her cancer diagnosis. Her medical history included hypertension, dyslipidemia, and previous surgeries for middle cerebral artery aneurysm and pituitary meningioma. She received hydrocortisone 20 mg/day for hypopituitarism. Her family history was unremarkable. Six months prior to her admission, she began to display intermittent aberrant nocturnal behaviors suggestive of RBD, including nightmares and episodes of falling out of bed. Following the surgery, she developed severe agitation with visual hallucinations. With a diagnosis of delirium, she was treated with haloperidol 2.5 mg IV and asenapine 2.5 mg/day, and was then maintained with quetiapine 25 mg/day. Her delirium was resolved within a week, and she was discharged to her home after fifteen days after the surgery.

The patient was followed up in the psychiatric outpatient clinic. Her cognitive function remained impaired. She was constipated. Her MMSE score was 25/30 at ten months after the surgery. Nineteen months after surgery, she developed fluctuating cognition and visual hallucinations and has progressed to dementia. Her MMSE score at that time was 21/30. Neurological examinations did not reveal parkinsonism or other sensorimotor abnormities. DAT-SPECT showed significant bilateral striatal uptake reductions (Table 1 and Fig. 1). Twenty months after surgery, the patient was started on donepezil 5 mg/day, and her fluctuating cognition and visual hallucinations improved. Two months after starting donepezil, her MMSE score improved to 27/30. Thirty-five months after surgery, she was able to continue living alone.

2.4. Case 4

A woman in her 60 s was admitted for myocardial infarction and pulmonary embolism surgery. Prior to her hospitalization, she was living independently, and her family was unaware of her cognitive impairment. Her medical history included dyslipidemia and surgeries for breast cancer and hip osteoarthritis. Her family history was unremarkable. From one year prior to the admission, she exhibited mild forgetfulness. Following the surgery, she developed severe agitation with visual hallucinations. With a diagnosis of delirium, she was treated with lemborexant 10 mg/day and trazodone 25 mg/day.

The patient was followed up in the psychiatric outpatient clinic. She reported forgetfulness and orthostatic dizziness. Her MMSE scores were 22/30 and 25/30 at two and three months after the surgery. Neurological examinations revealed no parkinsonism or other sensorimotor abnormalities. DAT-SPECT showed bilateral striatal uptake reduction (Fig. 1). Twenty months following surgery, there was no apparent deterioration in her cognition, and none of the core clinical features of DLB were observed.

2.5. Case 5

A man in his 70 s was admitted to our hospital with a diagnosis of coronavirus infection. Prior to his hospitalization, he was living independently, and his family was unaware of his cognitive impairment. His medical history included hypertension and dyslipidemia. His family history was unremarkable. One year prior to the admission, he began to exhibit abnormal nocturnal behavior indicative of RBD, including clear speech and limb movement during sleep. From 6 months prior to the admission, he exhibited a recurrent phenomenon of light passing over the edge of his vision, which is suggestive of passage hallucinations. At

that time, his cognition fluctuated from day to day. After the admission, he was confused, wandered, and made statements that did not fit the situation. Following the administration of risperidone 0.5 mg/day and haloperidol 5 mg IV, his delirium improved within a few days. Eight days after hospitalization, he was discharged to his home with no medication.

The patient was followed up in the outpatient psychiatric clinic. His MMSE scores were 22/30 and 26/30 at eighteen days and three months after hospitalization. The family reported that his cognitive function continued to fluctuate. Neurological examinations did not revealed parkinsonism or other sensorimotor abnormalities. Cardiac MIBG scintigraphy showed decreased myocardial uptake. Fourteen months after the onset of delirium, he has not progressed to dementia.

3. Discussion

The concept of delirium-onset prodromal LBD is based on epidemiological evidence indicating that the incidence of delirium before the diagnosis of dementia is a 3–5 times higher in patients with DLB than those with AD [4,5]. As outlined in the DLB consortium report, there are phenomenological similarities between delirium and fluctuating cognition in DLB, both of which are characterized by spontaneous alterations in cognition, attention, and arousal [3]. It is possible to consider delirium-onset prodromal LBD to be a prodromal condition in which additional precipitating factors transform subthreshold cognitive fluctuations into clinically detectable states. The present case series documented various precipitating factors for delirium-onset prodromal LBD, including surgery, radiation, chemotherapy, and infection. These factors are similar to those that precipitate delirium in general. All of the patients exhibited at least one of the core or supportive clinical features of DLB, including RBD, minor hallucinations, hyposmia, or autonomic dysfunction, prior to the onset of delirium. Delirium persisted for several months in 2 of the 5 cases (Cases 1 and 2), and prolonged cognitive impairment was observed in most cases. One of the 5 cases progressed to dementia within a few years (Case 3). These findings are consistent with the results of a previous retrospective study, which reported that the median time duration between the last delirium episode and the diagnosis of dementia in DLB was less than one year [4]. In addition, perfusion SPECT showed more severe occipital hypoperfusion in cases with prolonged delirium compared to those with transient delirium (Fig. 1), suggesting that extensive neocortical dysfunction, rather than dopaminergic dysfunction, may be a critical factor in the development of delirium in the prodromal LBD. Collectively, these observations suggest that delirium-onset prodromal LBD may represent the later stages of the prodromal LBD rather than its initial stages. It is of the utmost importance to conduct a comprehensive history taking for symptoms suggestive of LBD, such as RBD, minor hallucinations, hyposmia, or autonomic dysfunctions in order to accurately diagnose delirium associated with prodromal LBD.

Despite the absence of scientific evidence supporting the efficacy of pharmacological interventions for delirium, clinical guidelines recommend antipsychotics as the primary pharmacologic treatment option [8]. However, a more specific approach to management is necessary for those with delirium-onset prodromal LBD due to the severe sensitivity to antipsychotics [9]. Previous studies have not demonstrated the efficacy of cholinesterase inhibitors for delirium in general [8]. The present case series clearly demonstrated that donepezil improved both prolonged delirium (Cases 1 and 2) and residual cognitive impairment in patients with delirium-onset prodromal LBD. This observation is consistent with the established efficacy of cholinesterase for fluctuating cognition and visual hallucinations in patients with DLB [10]. Again, it is crucial to consider the possibility of delirium associated with prodromal LBD through comprehensive history taking and to pursue diagnostic procedures such as DAT-SPECT or MIBG scintigraphy. These will facilitate the implementation of early and appropriate pharmacological intervention.

The primary limitation of this study is that the diagnosis of prodromal LBD relies on cardiac MIBG scintigraphy or DAT-SPECT. These neuroimaging biomarkers have high specificity but low sensitivity for prodromal LBD, with less than 50 % [11,12]. It must be acknowledged that we may fail to diagnose delirium-onset prodromal LBD with negative neuroimaging biomarkers, which are presumably present in large numbers. Future studies employing neuropathological diagnosis, cerebrospinal fluid or plasma alpha-synuclein assays, and long-term follow-up assessments are required to definitively address this issue [13].

CRediT authorship contribution statement

Daiki Taomoto: Writing – review & editing, Writing – original draft, Data curation. **Yoshiyuki Nishio:** Writing – review & editing, Writing – original draft, Supervision. **Yousuke Hidaka:** Data curation. **Hideki Kanemoto:** Data curation. **Shun Takahashi:** Data curation. **Manabu Ikeda:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics Statement

Written informed consent was obtained from the patient and his family for the publication of any potentially identifiable images or data included in this study.

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