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Subcortical Structure Disruption in Diffusion Tensor Tractography of the Patient With the Syndrome of Irreversible Lithium-Effectuated Neurotoxicity Combined With Neuroleptic Malignant Syndrome: A Case Report

Seung Yeon Rhee, MD and Hyoung Seop Kim, MD

Background: Lithium can cause not only acute neurotoxicity but also chronic and persistent neurotoxicity known as syndrome of irreversible lithium-effectuated neurotoxicity (SILENT). The combined use of lithium and antipsychotics increases the possibility of SILENT. Neuroleptic malignant syndrome (NMS) is a reversible, idiosyncratic, and potentially life-threatening reaction, which is usually caused by antipsychotics and other agents, such as mood stabilizers (eg, lithium and metoclopramide). Neuroleptic malignant syndrome is characterized by hyperpyrexia, muscle rigidity, and altered mental status. We describe a case of SILENT combined with NMS in this case report.

Case Report: A 46-year-old man who had been treated with lithium for bipolar II disorder since 2008 was prescribed lorazepam, lithium, and aripiprazole at his last outpatient visit. The patient experienced financial difficulties (bankruptcy) and suffered severe emotional stress. Subsequently, he overused lorazepam, lithium, and aripiprazole. Two days after the overdose, he experienced a high fever, confused mental status, and rhabdomyolysis and was diagnosed with NMS. However, even after resolution of NMS-related symptoms, quadriplegia, visual field defects, ataxia, and severe dysarthria persisted. A positron emission tomography-computed tomography brain scan showed decreased ^{15}F-fludeoxyglucose uptake in bilateral primary motor cortices and in the thalamus, midbrain, and cerebellum. Brain magnetic resonance imaging diffusion tensor imaging and diffusion tensor tractography of the subcortical tracts revealed structural disruptions, especially in the corticospinal tract, dentatorubrothalamic tract, and optic radiation, which seemed to be correlated with the clinical symptoms of the patient.

Conclusion: This case suggests that the clinical use of diffusion tensor tractography could be helpful to explain the clinical features in the case of SILENT combined with NMS.

Key Words: lithium, neuroleptic malignant syndrome, neurotoxic disorder

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The use of lithium as a treatment for bipolar disorder has increased recently. Because of its narrow therapeutic window, it is important to check the serum dose. Since lithium was first introduced in the field of psychiatry in 1949, a number of cases of lithium neurotoxicity and potentially life-threatening complications have been reported.[1–3] Among neurotoxic complications of lithium, there are reported cases of acute and reversible neurotoxicity.[4,5] Adityanjee[6] reported 55 cases of chronic and persistent neurotoxicity and sequelae associated with the use of lithium. In these cases, the main sequelae of the patients were persistent cerebellar symptoms. Adityanjee[7] was the first to propose the name syndrome of irreversible lithium-effectuated neurotoxicity (SILENT) to represent persistent neurotoxic sequelae of lithium. Lithium intoxication is associated with several neurological symptoms, such as tremor, ataxia, encephalopathy, comatous mental change, and dysarthria.[8] Also, SILENT mostly induces cerebellar and extrapyramidal symptoms.[8]

Neuroleptic malignant syndrome (NMS) is an idiosyncratic and potentially life-threatening reaction, characterized by hyperpyrexia, muscle rigidity, autonomic dysfunction, mental status change, tremors, leukocytosis, and creatinine kinase (CK) elevation.[9–11] Although the reported incidence of NMS is reported to be just 0.01% to 0.02%, it is responsible for a significant portion of morbidity and mortality in patients who use antipsychotics.[11–13] In terms of pathophysiological aspects, NMS is thought to be a subcortical motor syndrome caused by dopaminergic dysregulation.[14] Neuroleptic malignant syndrome is associated with the use of conventional, old-generation antipsychotics. Recently, the development of newer generation antipsychotic agents has decreased the incidence of NMS.

Catatonia, which refers to cortical psychomotor immobility and abnormal behavior, shares similar features with NMS, but it is the result of GABAergic dysregulation.[14] In some previous cases, the initial presentation of NMS was catatonia.[10,14,15]

We describe the case of a 46-year-old man with bipolar disorder who was diagnosed with SILENT and NMS by the clinical symptoms after drug intoxication, such as persistent catatonia and quadriplegia, tremor, ataxia, and dysarthria. Moreover, imaging analysis by using diffusion tensor tractography (DTT) in this case was also performed.

CASE REPORT

A 46-year-old man had received treatment for bipolar II disorder since 2008. In September 2018, he suffered severe emotional stress due to bankruptcy. In October 2018, he visited the outpatient clinic of a university hospital and was prescribed lorazepam, lithium, and aripiprazole. The same day, he took a massive overdose of the medication. He became delirious 1 day later and exhibited abnormal behaviors, including confusion. He developed a high fever (40°C) 2 days later, with concomitant aggravation of his mental status. A laboratory study showed CK elevation (over 40,000 IU/L; reference value = 44–245 IU/L) and metabolic acidosis. At that time, his serum lithium level was 1.63 mmol/L (reference value = 0.6–1.2 mmol/L). Subsequently, oliguria with azotemia due

Department of Physical Medicine and Rehabilitation, National Health Insurance Service Ilsan Hospital, Ilsan, Republic of Korea.

Address correspondence and reprint requests to Hyoung Seop Kim, MD, Department of Physical Medicine and Rehabilitation, National Health Insurance Service Ilsan Hospital, 100 Ilsan-ro, Ilsandong-gu, Goyang, Gyeonggi Province 10444, Republic of Korea; E-mail: rehappydoc@gmail.com

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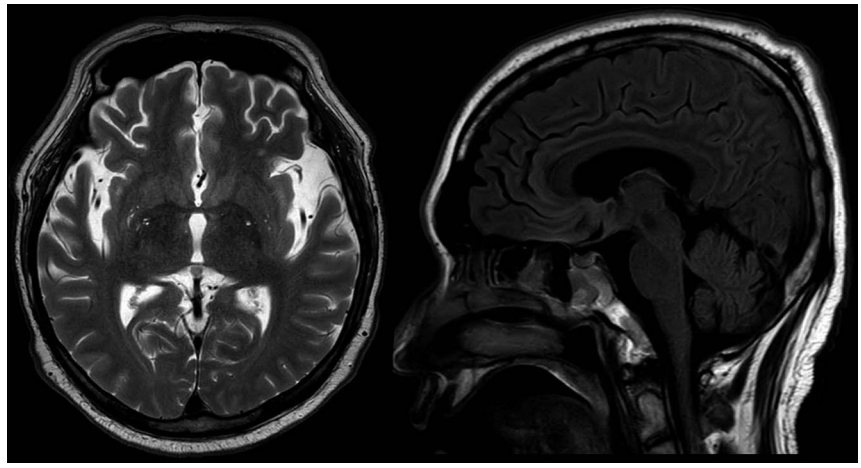

FIGURE 1. Brain MRI T2 Axial and T2 FLAIR Sagittal (2019.1.18). There was no remarkable finding.

to acute kidney injury after rhabdomyolysis and hemodynamic instability developed. Continuous renal replacement therapy was administered, with intensive care unit management for 8 days. Blood, sputum, and urine culture, in addition to abdomen and pelvic computed tomography (CT), cerebrospinal fluid tapping, and brain imaging, including magnetic resonance imaging (MRI) (Fig. 1) and CT, were performed, none of which revealed any significant findings. Due to the suspicion of NMS, the patient was treated with dantrolene via the intravenous route. Seven days after the administration of dantrolene, the patient's CK level began to decrease.

However, even after resolution of rhabdomyolysis and acute kidney injury, catatonia, limb and trunk ataxia, visual field defects, and severe dysarthria remained. To rule out possible organic problems, electroencephalography and brain positron emission tomography (PET) were performed. The electroencephalography showed sharply formed diffuse theta and delta and theta dominant waves, which suggested mild nonspecific diffuse cerebral dysfunction. A PET brain scan taken in May 2019 revealed decreased ^{15}F-fludeoxyglucose (FDG) uptake in bilateral primary motor cortices and the thalamus, midbrain, and cerebellum (Fig. 2).

In June 2019, the patient was admitted to our hospital. In a neurological examination at that time, his Mini-Mental Status Examination score was 28 points, with slight time disorientation and attention deficit detected. In the manual muscle test using the Medical Research Council (MRC) scale, the patient was grade III to IV for both the upper and lower extremities. Brain MRI

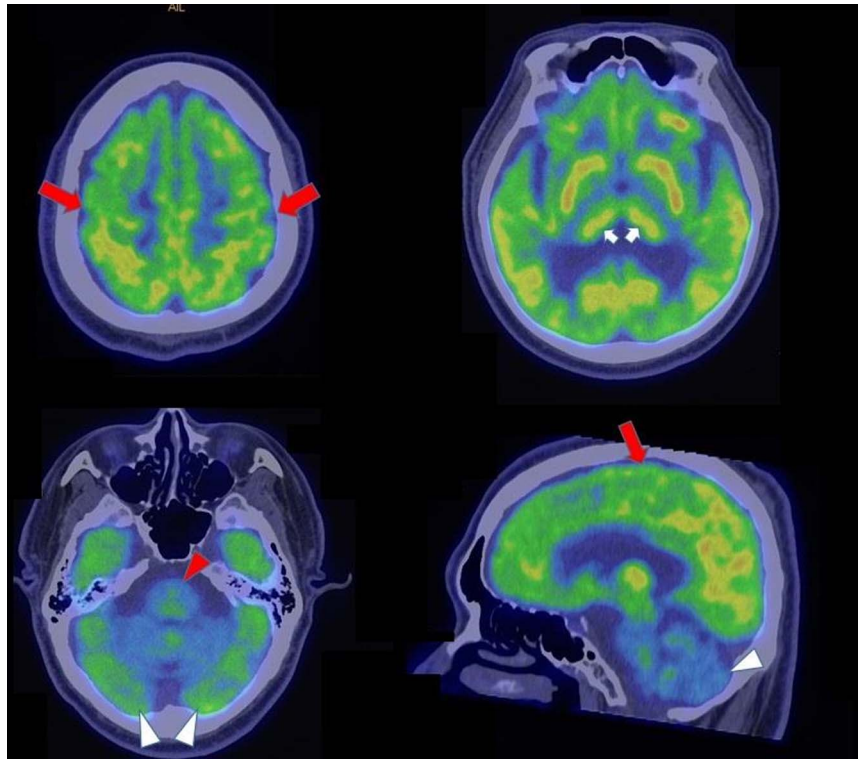

FIGURE 2. PET-CT brain scan (2019.5.15). Decreased FDG uptake in bilateral primary motor cortices (red arrow), thalamus (white arrow), midbrain (red arrowhead), and cerebellum (white arrowhead) was shown.

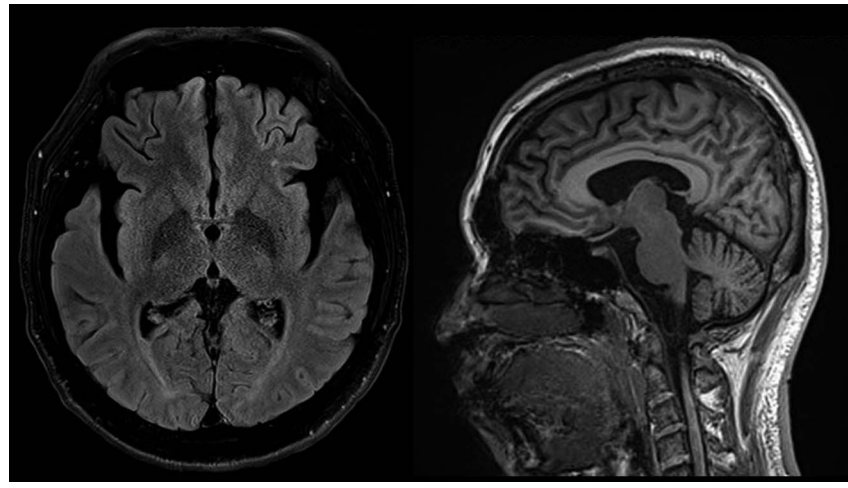

FIGURE 3. Brain MRI T2 FLAIR Axial and T1 Sagittal (2019.6.14). There was no remarkable finding. Compared with a previous study (2019.1.8), no interval change was observed.

was performed twice. Both times, structural brain MRI sequences, including T1WI, T2WI, T2 FLAIR, SWI, MPR, and DWI, showed no abnormalities (lesions) (Fig. 3).

Diffusion tensor imaging (DTI) was performed using a 3.0 T system (Philips Achieva TX, Best, Netherlands). The DTI sequence parameters were as follows: repetition time = 7,958.5 ms and echo time = 71 ms. After this DTI sequence, a DTI diffusion scheme was used, and 32 diffusion sampling directions were acquired. The b-value was 600 s/mm^2. The in-plane resolution was 1.91071 mm. The slice thickness was 2 mm. The b-table was checked using an automatic quality control routine to ensure its accuracy.[16] To obtain the spin distribution function,[17] the diffusion data were reconstructed in the Montreal Neurological Institute space using q-space diffeomorphic reconstruction.[18] A diffusion sampling length ratio of 1.25 was used, with isotropic output resolution of 2 mm. The restricted diffusion was quantified using restricted diffusion imaging.[19]

Then, the DSI Studio software (http://dsi-studio.labsolver.org/) was used to visualize the subcortical tracts. The DSI Studio software has auto-tracking tools for most subcortical tracts, including the corticospinal tract (CST), rubrospinal tract, and spinothalamic tract. However, some tracts, such as the dentatorubrothalamic tract (DRTT), which is associated with motor planning and initiation of movement, motor coordination, verbal fluency, and working memory,[20,21] could not be obtained using the auto-tracking tools. Anatomically, DRTT arises from deep cerebellar nuclei, mainly the dentate nucleus, passing through the superior cerebellar peduncle, and then decussates to the contralateral red nucleus to ascend to the thalamus and brain cortex.[22] In this case, DRTT fiber tracking was conducted using deterministic fiber-tracking algorithm based on Human Connectome Project (Q1–Q3 release, WU-Minn HCP consortium).[20,23]

We obtained DTT of each subcortical tracts, including the CST, arcuate fasciculus, rubrospinal tract, corpus callosum, optic

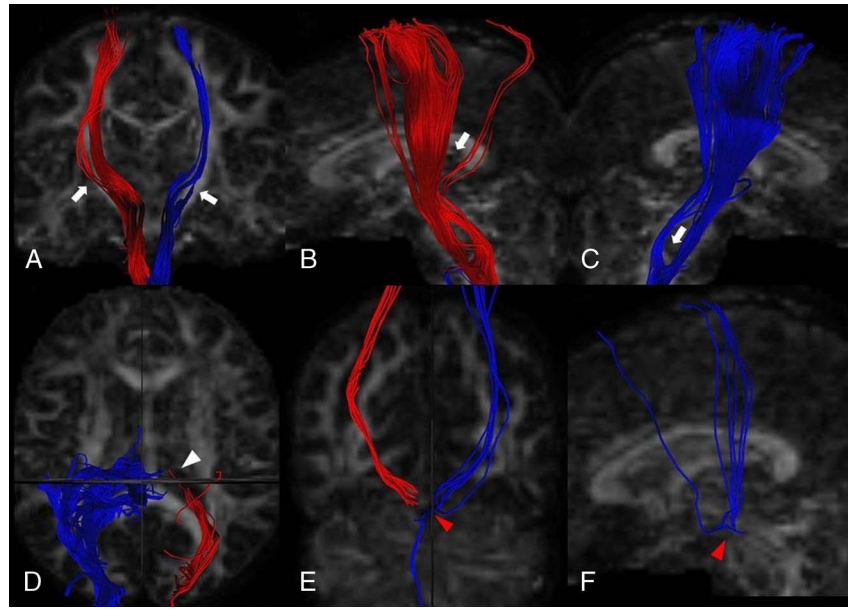

FIGURE 4. DTT of CST (A, B, C), optic radiation (d), and DRTT (E, F) (June 14, 2019). Subcortical disruptions were observed. (Arrows and arrowheads: suspected disruption of each tracts) (red: left, blue: right).

radiation, and DRTT. Diffusion tensor tractography of the subcortical tracts revealed subtle impairment of the bilateral CST (Figs. 4A, B, C) and substantial structural impairment of left optic radiation compared with the right side (Fig. 4D). In addition, DRTT showed severe subcortical disruption (Figs. 4E, F) that seemed to be correlated with the quadriplegic, ataxic, catatonic symptoms, and dysarthria of the patient.

The patient received intensive rehabilitation, including physiotherapy (30 min/session, 2 sessions/d, 5 times/wk), occupational therapy (30 min/session, 2 sessions/d, 5 times/wk), and speech therapy (40 min/session, 2–3 three times/wk) until July 2019. In the manual muscle test, his muscle power increased from MRC grade I in November 2018 to MRC grade III to IV in July 2019. In terms of hand function, pinch and grasp power of both hands improved, but fine motor function of his left hand showed no improvement (Table 1). The patient's Functional Independence Measure score improved from 38 in January 2019 to 71 in July 2019. Correspondingly, his modified Barthel Index score improved from 0 in January 2019 to 49 in July 2019. In a speech evaluation, articulation and pronunciation improved slightly, but his speech remained very slow (Table 2). Ataxia-related features also improved, with the CARS score declining from 72 in June 2019 to 60 in July 2019 (Table 3).

TABLE 2. Speech Test (Paradise K-WAB)

	January 2019	May 2019	June 2019
AQ	92.4	94.5	96.2
LQ	—	92.5	94.6
MPT	2.45 s	20.83 s	10.44 s
DDK			
AMR "/pa/"		8 times/5 s	13 times/5 s
AMR "/ta/"		6 times/5 s	13.7times/5 s
AMR "/ka/"		5 times/5 s	12 times/5 s
SMR "/pataka/"		2 times/5 s	4 times/5 s

K-WAB indicates Korean version—the Western Aphasia Battery; AQ, aphasia quotient; LQ, language quotient; MPT, maximum phonation time; DDK, diadochokinetic rate; AMR, alterate motion rate; SMR, sequencing motion rate.

DISCUSSION

Neuroleptic malignant syndrome is a rare but potentially life-threatening complication associated with the use of antipsychotics.[12] The characteristic symptom triad of NMS includes hyperpyrexia, rigidity, and altered mental status.[24] Other clinical features include tremor, urinary incontinence, dysphagia, elevated CK, and leukocytosis.[24]

Over 75% of patients with long-term use of lithium experience some kind of toxicity because of its narrow therapeutic dose.[25] Lithium toxicity is associated with confusion, lethargy, slurred speech, tremor, and gait difficulties.[26] Before 1987, the majority of reported lithium toxicity cases involved acute neurotoxicity, which was reversible.[4,5] In 1987, the first case report of SILENT, which represents persistent and irreversible neurotoxic sequelae of lithium, was described.[6–8] In a literature review, SILENT was mostly associated with extrapyramidal features and cerebellar symptoms.[8,27]

TABLE 1. Hand Function Test

	January 2019	July 2019
Pinch power (kg)		
Tip pinch		
Rt.	1.6	5.5
Lt.	NT	NT
Lateral pinch		
Rt.	3.8	9
Lt.	1	3.5
Palmar pinch		
Rt.	2.5	8.5
Lt.	NT	NT
Box and block (/min)		
Rt.	14	13
Lt.	NT	6
Grip power (kg)		
Rt.	4	26
Lt.	NT	9

NT indicates not testable; Rt., right; Lt., left.

In the present case, the persistent catatonic features of the patient raised the suspicion of NMS. However, other than in the acute phase of his illness, the patient did not exhibit abrupt onset of mutism, negativism, immobility, or rigidity, all of which are part of the clinical presentation of catatonia. A number of studies have reported chronic neurological sequelae (SILENT) resulting from lithium intoxication.[6–8] In the present case, we assumed that the chronic neurological sequelae were attributed to SILENT rather than persistent catatonia after NMS.

Our patient made some recovery, although extrapyramidal features, cerebellar ataxia, severe dysarthria, and autonomic instability remained. Thus, in this case of lithium toxicity, the patient appeared to exhibit not only NMS-related features in the acute stage but also SILENT-type features in the chronic stage. This case emphasizes the need to consider the possibility of SILENT, especially in cases of combined use of lithium and antipsychotics.[8,28] Furthermore, we propose the possibility that SILENT might be a chronic subtype of NMS.[10,15]

In this case, after the diagnosis of SILENT combined with NMS, we performed imaging studies in an effort to identify possible causes of the patient's symptoms. Among the imaging studies performed, a PET brain scan showed decreased FDG uptake in bilateral primary motor cortices and in the thalamus, midbrain, and cerebellum. Routine brain structural MRI revealed no lesions that could explain the patient's symptoms. As a PET CT brain scan provides only biochemical evidence, we performed DTI to assess the subcortical structure.

To acquire DTI, in addition to the three-dimensional gradient magnetic field, which is already used in the diffusion-weighted image sequence, an extra magnetic field is used to measure the motion of water molecules. If the water molecules in a specific space take same probability of diffusion in any direction, this is called Brownian motion, and it is defined as "isotropic diffusion." On the other hand, if the diffusion of water molecules shows a specific direction, such as in a white matter tract, this is called as "anisotropic diffusion." Therefore, DTI is helpful to analyze the white matter structure and injury of this structure.[29,30] Practically, there are 2 methods to detect injury of white matter tracts. One is to analyze the diffusion tensor parameters of the region of interest, and the other is to reconstruct the region of interest of each tract using DTT.[31–33] In contrast to DTI analysis and diffusion tensor parameter, DTT provides visual information of each tracts. Diffusion

TABLE 3. International Cooperative Ataxia Rating Scale (ICARS)

	June 2019	July 2019
Posture and gait disturbances		
Walking capacities	8	8
Gait speed	4	4
Standing capacities, eyes open	5	5
Spread of feet in natural position/s support, eyes open	4	2
Body sway with feet together, eyes open	4	3
Body sway with feet together, eyes closed	4	4
Quality of sitting position	1	0
Kinetic functions		
Knee-tibia test (decomposition of movement and intention tremor)	3/4	3/3
Action tremor in the heel to knee test	3/3	2/2
Finger to nose test: decomposition and dysmetria	2/3	2/3
Finger to nose test: intention tremor of finger	2/3	2/2
Finger-finger test (action tremor and/or instability)	2/3	2/2
Pronation supination alternating movements	2/3	1/2
Drawing of Archimedes' spiral on a predrawn pattern	2	1
Speech disorders		
Dysarthria: fluency of speech	3	3
Dysarthria: clarity of speech	2	2
Oculomotor disorders		
Gaze-evoked nystagmus	1	1
Abnormalities of ocular pursuit	1	1
Dysmetria of saccade	0	0
Total	72/100	60/100

tensor tractography can be considered an objective, reproducible, and reliable method to ascertain the structural integrity of white matter tracts.[34–39]

The DTT analysis revealed structural disruptions of the CST and optic radiation, which were, respectively, correlated with quadriplegia and visual field defects. In particular, DTT showed severe structural disruption of the DRTT, which is associated with motor planning and initiation of movement. This disruption was not visible on routine brain MRI.

CONCLUSIONS

In the present case, although brain MRI sequences revealed no specific abnormal findings, DTT derived from the DTI sequence revealed severe subcortical disruption of the CST, optic radiation and DRTT, all of which seemed to be correlated with the patient's clinical symptoms. Therefore, the DTI sequence and DTT appear to be useful in evaluating and correlating neurological symptoms of patients with SILENT combined with NMS.

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