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

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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 15F-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, dentatourbiculothalamic 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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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...
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 $^{18}$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
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/mm². 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 spinthalamic 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
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 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       |              | 8 times/5 s | 13 times/5 s |
| AMR       | “/ipa/”      | 6 times/5 s | 13.7 times/5 s |
| AMR       | “/ital/”     |          |           |
| 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, alternate motion rate; SMR, sequencing motion rate.

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. 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. Furthermore, we propose the possibility that SILENT might be a chronic subtype of NMS.

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 “anisotropic diffusion.” Therefore, DTI is helpful to analyze the white matter structure and injury of this structure. 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 DTI. In contrast to DTI analysis and diffusion tensor parameter, DTT provides visual information of each tracts. Diffusion
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 DTT 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 DTT sequence and DTT appear to be useful in evaluating and correlating neurological symptoms of patients with SILENT combined with NMS.

**REFERENCES**

1. Corcoran AC, Taylor RD, Page IH. Lithium poisoning from the use of salt substitutes. *J Am Med Assoc* 1949;139(11):685–688.
2. Hanlon LW, Romaine M 3rd, et al. Lithium chloride as a substitute for sodium chloride in the diet; observations on its toxicity. *JAMA* 1949; 139(11):688–692.
3. Stern RL. Severe lithium chloride poisoning with complete recovery; report of case. *JAMA* 1949;139(11):710.
4. Glesinger B. Evaluation of lithium in treatment of psychotinic excitement. *Med J Aust* 1954;41(1):277–283.
5. Noack CH, Trautner EM. The lithium treatment of maniacal psychosis. *Med J Aust* 1951;2(7):219–222.
6. Adityanjee. The syndrome of irreversible lithium-affected neurotoxicity (SILENT). *Pharmacopsychiatry* 1989;22(2):81–83.
7. Adityanjee. The syndrome of irreversible lithium-affected neurotoxicity. *J Neurol Neurosurg Psychiatry* 1987;50(9):1246–1247.
8. Adityanjee, Munshi KR, Thamby A. The syndrome of irreversible lithium-affected neurotoxicity. *Clin Neuropharmacol* 2005;28(1):38–49.
9. Agrawal A, Bajaj D, Bajaj S, et al. Aripiprazole induced late neuroleptic malignant syndrome. *Am J Ther* 2019;26(e772–e773.
10. Reilly TJ, Cross S, Taylor DM, et al. Neuroleptic malignant syndrome following catatonia: vigilance is the price of antipsychotic prescription. *SAGE Open Med Case Rep* 2017;5:2050313X17695999.
11. Chung YJ, Lee SJ. Case report of neuroleptic malignant syndrome with prolonged mental changes and severe dyskinesia. *Asia Pac Psychiatry* 2010;1(1).
12. Stühner S, Rustenbeck E, Grohmann R, et al. Severe and uncommon involuntary movement disorders due to psychotrophic drugs. *Pharmacopsychiatry* 2004;37(Supp 1):S54–S64.
13. Pileggi DJ, Cook AM. Neuroleptic malignant syndrome. *Am Pharmacother* 2016;50(11):973–981.
14. Northoff G. Catatonia and neuroleptic malignant syndrome: psychopathology and pathophysiology. *J Neurol Transm (Vienna)* 2002;109(12):1453–1467.
15. Ihara M, Kohara N, Urano F, et al. Neuroleptic malignant syndrome with prolonged catatonia in a dopa-responsive dystonia patient. *Neurology* 2002;59(7):1102–1104.
16. Nath V, Schilling KG, Parvathaneni P, et al. Deep learning reveals unapped information for local white-matter fiber reconstruction in diffusion-weighted MRI. *Magn Reson Imaging* 2019;62:220–227.
17. Yeh FC, Wedeen VJ, Tseng WY. Generalized q-sampling imaging. *IEEE Trans Med Imaging* 2010;29(9):1626–1635.
18. Yeh FC, Tseng WY. NTU-90: a high angular resolution brain atlas constructed by q-space diffeomorphic reconstruction. *NeuroImage* 2011;58(1):91–99.
19. Yeh FC, Liu L, Hitchens TK, et al. Mapping immune cell infiltration using restricted diffusion MRI. *Magn Reson Med* 2017;77(2):603–612.
20. Moola A, Comert A, Yeh FC, et al. The nondecusating pathway of the dentatorubrothalamic tract in humans: human connectome-based tractographic study and microdissection validation. *J Neurosurg* 2016;124(5):1406–1412.
21. Javalkar V, Khan M, Davis DE. Clinical manifestations of cerebellar disease. *Neuro Clin* 2014;32(4):871–879.
22. Kwon HG, Hong JH, Hong CP, et al. Dentatorubrothalamic tract in human brain: diffusion tensor tractography study. *Neuroradiology* 2011;53(10):787–791.
23. Yeh FC, Verstynen TD, Wang Y, et al. Deterministic diffusion fiber tracking improved by quantitative anisotropy. *PLoS One* 2013;8(11):e80713.
24. Berman BD. Neuroleptic malignant syndrome: a review for neurohospitalists. *Neurohospitalist* 2011;11(1):41–47.
25. Groleau G. Lithium toxicity. *Emerg Med Clin North Am* 1994; 12(2):511–531.
26. Edokpolo O, Fyzyz M. Lithium toxicity and neurologic effects: probable neuroleptic malignant syndrome resulting from lithium toxicity. *Case Rep Psychiatry* 2012;2012:271858.
27. Schou M. Long-lasting neurological sequelae after lithium intoxication. *Acta Psychiatr Scand* 1984;70(6):594–602.

28. Silva AL, Ourique C, Martins F, et al. Syndrome of irreversible lithium-effectuated neurotoxicity. *Acta Medica Port* 2017;30(2):151–153.

29. Neil J, Miller J, Mukherjee P, et al. Diffusion tensor imaging of normal and injured developing human brain—a technical review. *NMR Biomed* 2002; 15(7–8):543–552.

30. Paerpaoli C, Basser PJ. Toward a quantitative assessment of diffusion anisotropy. *Magn Reson Med* 1996;36(6):893–906.

31. Brandstack N, Kurki T, Tenovuo O. Quantitative diffusion-tensor tractography of long association tracts in patients with traumatic brain injury without associated findings at routine MR imaging. *Radiology* 2013; 267(1):231–239.

32. Kim N, Branch CA, Kim M, et al. Whole brain approaches for identification of microstructural abnormalities in individual patients: comparison of techniques applied to mild traumatic brain injury. *PLoS One* 2013;8(3):e59382.

33. Shenton ME, Hamoda HM, Schneiderman JS, et al. A review of magnetic resonance imaging and diffusion tensor imaging findings in mild traumatic brain injury. *Brain Imaging Behav* 2012;6(2):137–192.

34. Brandstack N, Kurki T, Laalo J, et al. Reproducibility of tract-based and region-of-interest DTI analysis of long association tracts. *Clin Neuroradiol* 2016;26(2):199–208.

35. Danielian LE, Iwata NK, Thomasson DM, et al. Reliability of fiber tracking measurements in diffusion tensor imaging for longitudinal study. *NeuroImage* 2010;49(2):1572–1580.

36. Hasan KM, Kamali A, Abid H, et al. Quantification of the spatiotemporal microstructural organization of the human brain association, projection and commissural pathways across the lifespan using diffusion tensor tractography. *Brain Struct Funct* 2010;214(4):361–373.

37. Lee HD, Jang SH. Injury of the corticoreticular pathway in patients with mild traumatic brain injury: a diffusion tensor tractography study. *Brain Inf* 2015;29(10):1219–1222.

38. Malykhin N, Concha L, Seres P, et al. Diffusion tensor imaging tractography and reliability analysis for limbic and paralimbic white matter tracts. *Psychiatry Res* 2008;164(2):132–142.

39. Wang JY, Abdi H, Bakhadirov K, et al. A comprehensive reliability assessment of quantitative diffusion tensor tractography. *NeuroImage* 2012; 60(2):1127–1138.