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Letter to the Editor

Delayed Post-Hypoxic Leukoencephalopathy Caused by Fentanyl Intoxication in a Healthy Woman

Jeongyeon Kim,[1] **Sung Wook Hyung**,[2] **Junghee Seo**,[1,2] **Heejin Lee**,[2] **Hyun-Jeong Yu**,[2] **Mun Kyung Sunwoo**[2]

[1]Department of Neurology, Sanggye Paik Hospital, Inje University, Seoul, Korea
[2]Department of Neurology, Bundang Jesaeng General Hospital, Seongnam, Korea

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Correspondence to
Mun Kyung Sunwoo
Department of Neurology, Bundang Jesaeng General Hospital, 20 Seohyun-ro 180 beon-gil, Bundang-gu, Seongnam 13589, Korea.
E-mail: jelemy0322@gmail.com

ORCID iDs
Jeongyeon Kim
https://orcid.org/0000-0002-7106-2773
Sung Wook Hyung
https://orcid.org/0000-0001-8846-7956
Junghee Seo
https://orcid.org/0000-0002-9545-6216
Heejin Lee
https://orcid.org/0000-0003-1944-0359
Hyun-Jeong Yu
https://orcid.org/0000-0002-9081-4846
Mun Kyung Sunwoo
https://orcid.org/0000-0002-5973-3888

Conflict of Interest
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Delayed post-hypoxic leukoencephalopathy (DPHL) is a rare disease caused by an anoxic event, such as carbon monoxide (CO) or asphyxial gas poisoning, cardiac arrest, and opiate or benzodiazepine overuse.[1-4] At the time of prolonged cerebral hypo-oxygenation, the first manifestation is altered mental status, which is followed by a dramatic recovery. After a few days to weeks, cognitive impairment, gait disorders, parkinsonism, akinetic mutism, and psychosis can appear. We report a patient with DPHL following fentanyl patch intoxication who recovered fully, as confirmed by neuropsychiatric testing.

A 54-year-old woman who had no medical and surgical history visited the emergency room due to reduced alertness after using fentanyl patches prescribed to her mother to control cancer pain. She used a 16.8 mg fentanyl patch for 7 days. In the emergency room, her vital signs were stable including oxygen saturation, but laboratory tests showed elevated creatine kinase (1,480 U/L), creatine (1.9 mg/dL), and aspartate/alanine transaminase (58/42 IU/L) levels. The neurological examination showed decreased alertness with pupil myosis, a sluggish light reflex, and mild weakness (grade 4/5). Brain magnetic resonance imaging (MRI) showed bilaterally symmetric high signal intensity on diffusion-weighted imaging (DWI), with a reduced apparent diffusion coefficient (ADC) in the globus pallidus and perilesional edema presenting as a high ADC signal (**Fig. 1A**). She was diagnosed with toxic encephalopathy due to the fentanyl patch because there was no evidence of CO poisoning or other toxic exposure. After conservative care for 2 weeks, she recovered consciousness with no neurological deficits and was discharged. Twenty days later, she was readmitted with impaired cognition and gait disturbance. Reduced activities, psychomotor slowing, and apathy with cognitive impairment progressed very quickly over the 3–4 days period. Neurological examination revealed impaired awareness, disorientation, and akinetic mutism, but no motor weakness, sensory change, or ataxia. She had bilaterally symmetric bradykinesia and rigidity in both extremities. Her gait was very slow with a stooped posture, short stride, and disequilibrium. Her vital signs and laboratory tests were normal, including CO-oximetry. Brain MRI with DWI on readmission showed a decrease in the bilateral symmetric DWI high signal intensity changes in the globus pallidus, but bilateral cavitation transformed. New lesions with high signal intensity on DWI and fluid-attenuated inversion recovery images were seen in the periventricular and subcortical white matter bilaterally. These findings suggested DPHL induced by the fentanyl patch (**Fig. 1B**). Her Mini-Mental State Examination (MMSE) score was 7/30, which indicated severe encephalopathy. After 1 month, her responses had become faster, and her verbal output had increased. Her cognition

Author Contributions

Conceptualization: Yu HJ; Investigation: Hyung SW, Seo J, Lee H, Yu HJ; Supervision: Sunwoo MK; Writing - original draft: Hyung SW, Sunwoo MK; Writing - review & editing: Kim J.

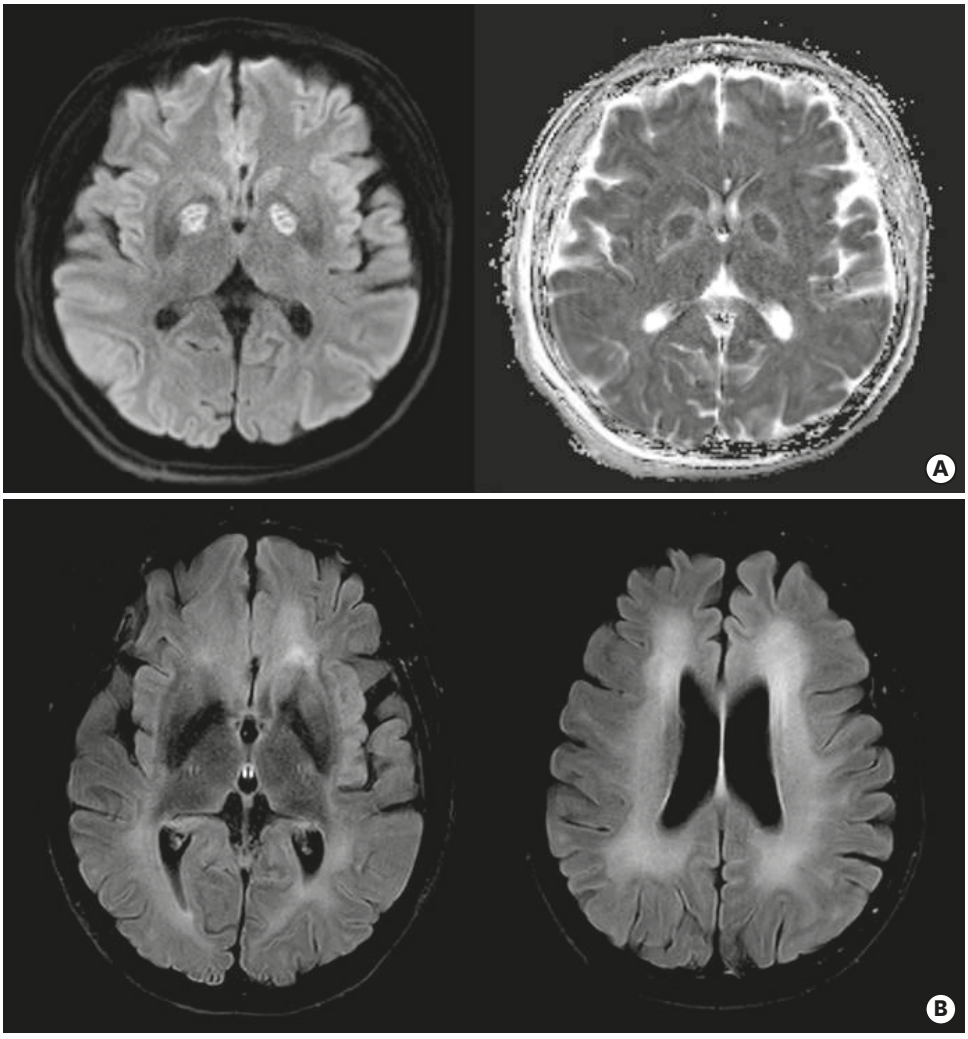

Fig. 1. Bilateral globus pallidi in diffusion weighted image with apparent diffusion coefficient alterations on initial magnetic resonance imaging (A) and bilateral both periventricular and subcortical white matter changes on follow-up fluid-attenuated inversion recovery image (B).

improved slightly, as shown by a follow-up MMSE score of 12/30. After 6 months, she was essentially normal, except for mild left tilting posture while walking. Her MMSE score was 29/30, and neuropsychological tests placed her within the normal range, except frontal and executive dysfunction in Stroop Color and Word and trail-making tests.

DPHL is a rare form of hypoxic brain damage caused by a preceding period of prolonged cerebral anoxia.[1] DPHL is diagnosed based on a combination of clinical manifestations and typical imaging findings.[1] The symptoms characteristically show a biphasic course.[5-7] After an initial hypoxic event with altered consciousness, the patient typically improves within 24–72 hours and, in many cases, returns to normal life. After a lucid interval of 2–40 days additional neurological deterioration such as akinetic mutism or parkinsonism were appeared. The MRI findings of DPHL are nearly pathognomonic and indicate diffuse white matter injury.[8] These are distinct from acute hypoxic–ischemic damage, which predominantly involves the grey matter structures, including the basal ganglia, thalamus, and cerebral cortex.[8] The typical imaging pattern of DPHL is homogenous T2-hyperintense changes in white matter.[1,4,8] These

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are commonly symmetric in both hemispheres, especially in the dorsal frontal region and parietal centrum semiovale. The cortex, U-fibers, brainstem, and cerebellum are mostly spared. These MRI findings reflect the hypothesized pathomechanism of DPHL, although it is not fully understood. Myelin-sheath damage is suspected, which might be caused by prolonged severe hypo-oxygenation. Myelinotoxicity due to hypoxic exposure is mediated in part by the impaired secretion of ATP-dependent enzymes responsible for myelin turnover.[9] The enzyme secretion occurs in 19 to 22 days, which coincides with the 3-week delay in symptoms.[10] An important point of this case is that the patient's cognitive function recovered fully. The reported prognosis of DPHL is relatively good, although some cases have a biphasic course with severe decompensation and death.[1,4-6] Our patient performed serial cognitive tests, and we could trace the recovery of cognitive function, which started after 1 month. Two subsequent tests showed serially enhanced cognitive function. The last detailed neuropsychological tests showed full recovery, except for frontal lobe dysfunction. This is a case of DPHL induced by fentanyl patch intoxication with confirmed nearly full recovery of cognitive function, except frontal lobe dysfunction. In conclusion, this case showed that the cognitive dysfunction of fentanyl intoxication might be reversible if the patient receives proper conservative management. We suggest symptomatic treatment for patients with DPHL as soon as fentanyl intoxication is suspected.

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