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A Case of Hypoglycemic Brain Injuries with Cortical Laminar Necrosis

We report a case of 68-yr-old male who died from brain injuries following an episode of prolonged hypoglycemia. While exploring controversies surrounding magnetic resonance imaging (MRI) findings indicating the bad prognosis in patients with hypoglycemia-induced brain injuries, we here discuss interesting diffusion-MRI of hypoglycemic brain injuries and their prognostic importance focusing on laminar necrosis of the cerebral cortex.

Key Words : *Diabetes; Hypoglycemia; Brain Injuries; Diffusion Magnetic Resonance Imaging; Cerebral Cortical Necrosis; Prognosis*

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INTRODUCTION

The neurological manifestations complicated by profound hypoglycemia range from reversible focal deficits to irreversible coma (1, 2). And the brain-imaging abnormalities and their sequelae changes are also variable in subjects with hypoglycemia-induced brain injuries. Although infarction is the most common cause of a hyper-intense lesion on diffusion magnetic resonance imaging (MRI), hypoglycemia also exhibits similar findings on diffusion-MRI. Previous literature reports that reversibility of hyper-intense lesion in diffusion-MRI indicates the good prognosis. And laminar necrosis of the cerebral cortex, neuropathologically characterized by delayed selective neuronal necrosis, results from hypoglycemic encephalopathy and other brain diseases. Here we report a 68-yr-old male who suffered diffuse brain injuries following an episode suggestive of prolonged hypoglycemia and showed reversible hyper-intense lesions on diffusion-MRI and laminar necrosis of the cerebral cortex.

CASE REPORT

A 68-yr old male with a 10-yr history of type 2 diabetes receiving a biphasic insulin analogue was brought into the emergency room by ambulance after being found in an unresponsive state by his colleague at his home. The patient lived alone, and he was in his usual state of health when he was last seen 3 days ago. On arrival, the patient's physical exam was unremarkable except for his neurological examination. He could not open his eyes spontaneously and his pupils were equal, round, and reactive to light and accommodation, there were no corneal reflexes and Doll's eye reflexes were present. He had no purposeful speech and did not withdraw to nail bed pressure in all extremities. There was decreased tone throughout all four extremities. He had no evidence of focal neurology. Blood pressure was 122/80 mmHg; pulse 75 beats/min, respiratory rate 20 breaths/min; and temperature 36.1℃. The blood glucose was found to be 24 mg/dL, which lead to immediate administration of 10% glucose with a bolus followed by continuous infusion. During oxygen administration, arte-

rial pH was 7.40, $Pa0_2$ 78.6 mmHg, $PaC0_2$ 33.1 mmHg, base excess-3.9 mM/L, and oxygen saturation 91.4%. Electrolytes were normal. Other chemistry results were unremarkable except for LDH (468 IU/L, reference rage: 240-460) and CK (265 IU/L, reference rage: 38-160). Computed tomography scans showed no findings of acute cerebrovascular injury except for non-prominent diffuse brain edema. No prior history could be taken until two days later after admission. His relative denied any medical history except for the diabetes. His A1c level was 11.0%. The glucose blood levels were gradually corrected. This combination of test results suggested that the patient's severe hypoglycemia was most likely caused by exogenous insulin or perhaps insulin receptor antibodies.

Neuroimaging with a 1.5 T MR scanner (Magnetom Vision, Siemens Medical solutions, Erlangen, Germany) on hospital day 2 showed multiple bilateral hyper-intense lesions at the cortex (frontal, temporal, parietal and occipital lobes) with gyral distribution, hippocampus, caudate, globus pallidus and putamen on diffusion-MRI and hypo-intense lesions on apparent diffusion coefficient (ADC) map (Fig. 1). This was prominently seen in the occipital lobe. Low signal intensity at T1-weighted image and high signal intensity at T2 weighted image lesion were seen at the same area (Fig. 1B). These abnormalities were global in appearance and did not conform to vascular distributions; furthermore, they look like a train track. Following MR angiography of the brain and neck showed no abnormalities (Fig. 2A). We performed function neuroimaging single photon emission computed tomography (SPECT) with 99mTc-HMPAO) to look for cerebral perfusion defects on hospital day 8. It showed only focal hypoperfusion areas in the left temporal lobe (Fig. 2B). His electroencephalographic examinations on hospital day 10 showed a moderate diffuse cerebral dysfunction but no definite epileptiform discharge. During the supportive medical management in ICU, there was no event and the patient's mental and neunological changes were not noticed. Follow-up

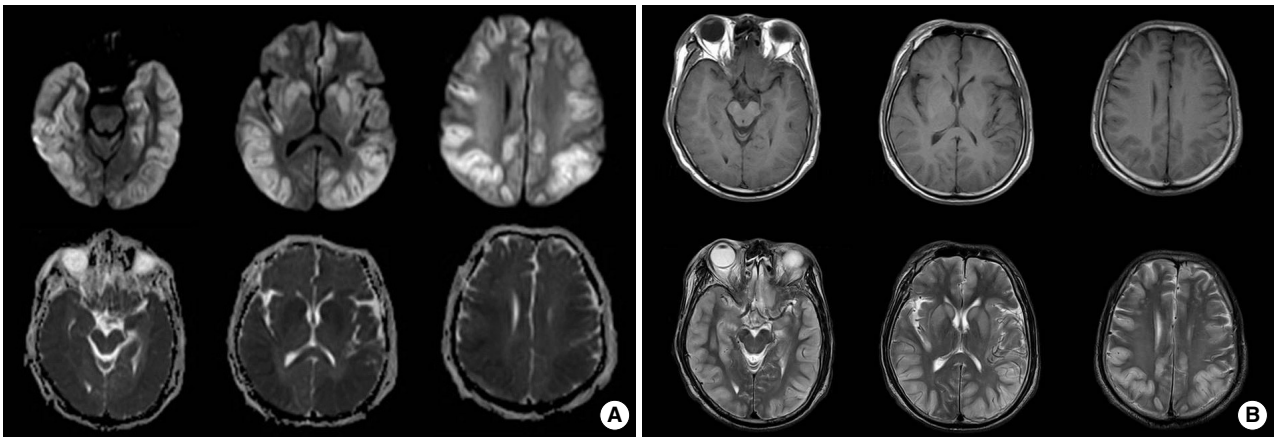

Fig. 1. The initial magnetic resonance imaging. (**A**) Diffusion-Weighted MRI of the brain showed multiple bilateral hyperintense signals along the cortical and subcortical regions (frontal, temporal, parietal, and occipital lobes), hippocampus, caudate, globus pallidus, and putament and ADC (afferent diffusion coefficient) map showed low signal at the same area. (**B**) Low signal intensity lesion at T1-weighted image and High signal intensity lesion at T2 weighted image were seen at same area (Fig. 1B).

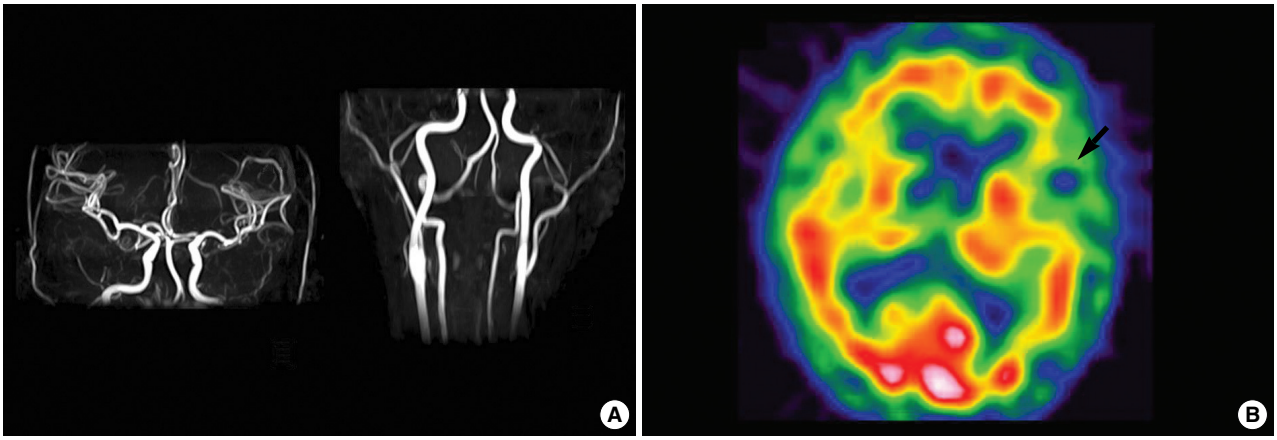

Fig. 2. Angiography and single photon emission computed tomography (SPECT). (**A**) MR angiography of the brain and neck showed no abnormalities. (**B**) The SPECT with 99mTc-HMPAO showed focal hypoperfusion in the left temporal lobe.

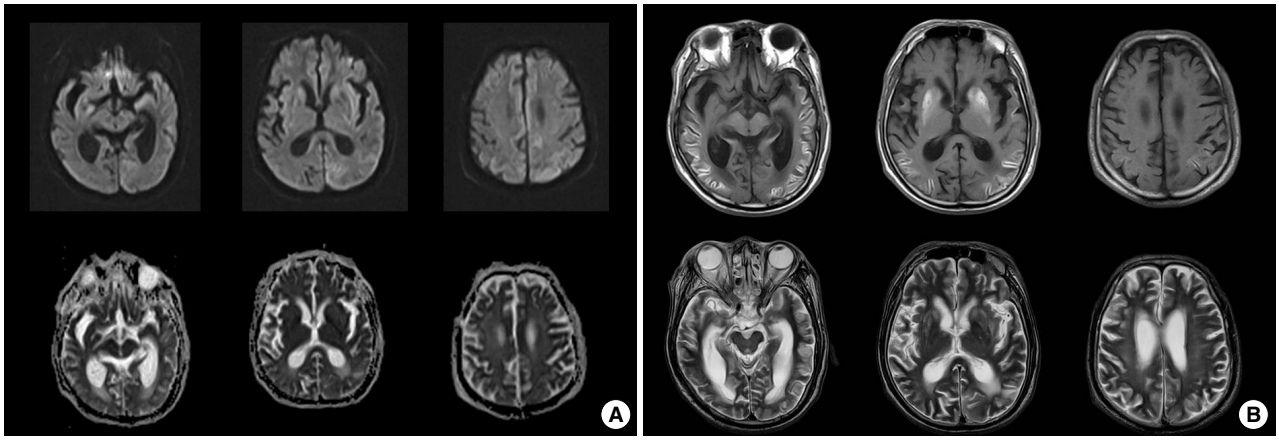

Fig. 3. The follow-up magnetic resonance imaging. (A) Follow-up images on the 20th day show revisal of the hyperintensity lesions on diffusion-MRI and hypointensity lesion on ADC map curvilinear. (B) The T1 and T2-weighted image showed linear high signal intensity selectively along the cortical regions of bilateral hemisphere and basal ganglia.

MRI on hospital day 22 showed a reversal of the hyperintensity lesions on diffusion-MRI and the hypointensity lesions on ADC map (Fig. 3A). The T1 and T2-weighted images showed linear high signal intensity selectively along the cerebral cortex in the cortical regions of bilateral hemisphere and the basal ganglia with severe parenchymal loss, characteristic of cerebral cortical laminar necrosis (Fig. 3B). Despite intensive medical treatment in ICU, the patient's neurologic condition failed to improve. The patient died of systemic infection and respiratory failure on day 98. Postmortem examination was not followed.

DISCUSSION

The neurologic deficits and radiologic images are variable in subjects with hypoglycemia-induced brain injuries. Of the MRI image, diffusion-MRI is a neuroimaging technique that evaluates the movement of water molecule along random pathways, detecting the tissue injury as in acute cerebral damages. Although infarction is the most common cause of such a hyper-intense lesion on diffusion-MRI, hypoglycemia also exhibits similar findings on diffusion-MRI. Despite similar findings on diffusion-MRI in both infarction and hypoglycemia, their mechanisms are distinct (3). In most reported cases with focal brain lesions associated with hypoglycaemia, the brain lesions were transient and the reversibility of both hypoglycemic coma and hyper-intense lesions on diffusion-MRI was also reported (2, 4). However, in some cases with extensively involved brain lesion such as cerebral cortex or basal ganglia, permanent brain damage following hypoglycemia was reported (5-7). In spite of reversibility of hyper-intense lesion of diffusion MRI, our case also showed extensive involvement of cerebral cortex and there was no improvement of patient's neurologic condition.

The most vulnerable areas of hypoglycemia-related brain injuries are the involvement of hippocampus, basal ganglia, and cortical and subcortical areas in adults (2, 4, 5, 7-11). Of the limited reported cases, neurologic recoveries and good prognosis were found those who were affected on the cortex sparing the basal ganglia (2, 4, 8). The well-documented characteristics of severe brain damage following hypoglycemia are the affected areas of the parietal and occipital lobes (3, 12, 13), and progressive parenchymal loss of predominant occipital lobe (14) in the newborn. Our case showed multiple bilateral hyper-intense lesions at the cortex, hippocampus, caudate, globus pallidus, and putamen. This was prominently seen in the occipital lobe, and severe parenchymal loss in bilateral hemisphere and the basal ganglia was seen on a follow-up MRI. The importance of duration of hypoglycemia was demonstrated in non-human primates: permanent neurological damage after profound hypoglycemia lasting 6 hr was seen in 73% of cases, with a mortality rate of 14% (15). We have no good information on precisely how long the hypoglycemia was present in this patient, so the length of hypoglycemia remains pure speculation.

Aoki et al. (2) suggested that diffusion-MRI is a useful tool for early diagnosis of severe hypoglycemia (16) and predicting prognosis (17). If the hyper-intense lesions regress in the second image, the patient will likely recover. However, if the hyper-intense lesions do not regress in the second image, the outcome will be poor. They noted that they had no information on the time necessary for hyper-intense lesions on diffusion-MRI to disappear in humans after glucose infusion, and signal intensity reversibility in their patient occurred within 10 days. Our case showed similar findings and reversible changes of signal intensity on diffusion-MRI at 22 days after admission. However, the patient showed no recovery from any neurologic deficit, and the reversibility of signal intensity on diffusion-MRI did not correlate with a good prognosis.

Cerebral cortical laminar necrosis, neuropathologically characterized by delayed selective neuronal necrosis of the cerebral

cortex, is a well-known consequence of encephalopathies such as hypoglycemic encephalopathy, cerebrovascular disease, or status epilepticus (18, 19). MRI studies have reported that cortical laminar necrosis is visualized as high-intensity areas on T1-weighted imaging during the subacute period in hypoglycemic encephalopathy (4), brain infarction (18, 19). and others, and the T2-weighted image shows low or high intensity. Necrosis, with the appearance of marked cytolysis and interstitial edema, occurs within a few days. This is followed by resorption, with the subsidence of edema and the phagocytosis of necrotic material, and results in fat-laden macrophages depositions from the 7th to the 42nd day. In histologic studies, hemorrhagic foci have also occasionally been documented in patients with watershed cortical involvement (20). In our subject, a follow up MRI illustrated the cortical laminar necrosis meaning the severe parenchymal loss and linear high-signal intensity selectively along the cerebral cortex in the cortical regions of bilateral hemisphere and the basal ganglia on T1-weighted image.

One might also argue that there may have been other components such as infarction or hypoxia causing the brain injuries in this patient. However, there was no objective evidence or documented episode of hypotension, acidosis, other drug intoxication, and infection before admission, or status epilepticus in this subject. And abnormal MR images were global in appearance and did not conform to vascular distributions; furthermore they looked like a train track. In addition, MR angiography and conventional angiography of the brain and neck showed no abnormalities. Though our subject showed reversible hyper-intense lesions in diffusion-MRI, the subsequent MR images showed laminar necrosis of the cerebral cortex, and patient's neurologic condition failed to improve.

In conclusion, we have described a patient who suffered brain injuries following an episode suggestive of prolonged hypoglycemia. It was previously reported that reversibility of hyper-intense lesions in diffusion-MRI indicates the good prognosis. The subject, however, showed reversible hyperintense lesions but had a poor prognosis. And this one case showed laminar necrosis of the cerebral cortex. Further studies are needed to validate the clinical correlation of the lamina necrosis in subject with hypoglycemic brain injury. We tentatively suggest that cerebral cortical laminar necrosis might be another clue for predicting the poor prognosis in a subject with hypoglycemic injuries.

REFERENCES

1. Cho SJ, Minn YK, Kwon KH. *Severe hypoglycemia and vulnerability of the brain. Arch Neurol 2006; 63: 138.*
2. Aoki T, Sato T, Hasegawa K, Ishizaki R, Saiki M. *Reversible hyperintensity lesion on diffusion-weighted MRI in hypoglycemic coma. Neurology 2004; 63: 392-3.*
3. Anderson JM, Milner RD, Strich SJ. *Pathological changes in the nervous system in severe neonatal hypoglycaemia. Lancet 1966; 2: 372-5.*
4. Yoneda Y, Yamamoto S. *Cerebral cortical laminar necrosis on diffusion-weighted MRI in hypoglycaemic encephalopathy. Diabet Med 2005; 22: 1098-100.*
5. Chan R, Erbay S, Oljeski S, Thaler D, Bhadelia R. *Case report: hypoglycemia and diffusion-weighted imaging. J Comput Assist Tomogr 2003; 27: 420-3.*
6. de Courten-Myers GM, Xi G, Hwang JH, Dunn RS, Mills AS, Holland SK, Wagner KR, Myers RE. *Hypoglycemic brain injury: potentiation from respiratory depression and injury aggravation from hyperglycemic treatment overshoots. J Cereb Blood Flow Metab 2000; 20: 82-92.*
7. Christiaens FJ, Mewasingh LD, Christophe C, Goldman S, Dan B. *Unilateral cortical necrosis following status epilepticus with hypoglycemia. Brain Dev 2003; 25: 107-12.*
8. Boeve BF, Bell DG, Noseworthy JH. *Bilateral temporal lobe MRI changes in uncomplicated hypoglycemic coma. Can J Neurol Sci 1995; 22: 56-8.*
9. Fujioka M, Okuchi K, Hiramatsu KI, Sakaki T, Sakaguchi S, Ishii Y. *Specific changes in human brain after hypoglycemic injury. Stroke 1997; 28: 584-7.*
10. Bakshi R, Morcos MF, Gabryel TF, Dandona P. *Is fluid-attenuated inversion recovery MRI more sensitive than conventional MRI for hypoglycemic brain injury? Neurology 2000; 55: 1064-5.*
11. Finelli PF. *Diffusion-weighted MR in hypoglycemic coma. Neurology 2001; 57: 933.*
12. Spar JA, Lewine JD, Orrison WW Jr. *Neonatal hypoglycemia: CT and MR findings. AJNR Am J Neuroradiol 1994; 15: 1477-8.*
13. Barkovich AJ, Ali FA, Rowley HA, Bass N. *Imaging patterns of neonatal hypoglycemia. AJNR Am J Neuroradiol 1998; 19: 523-8.*
14. Cakmakci H, Usal C, Karabay N, Kovanlikaya A. *Transient neonatal hypoglycemia: cranial US and MRI findings. Eur Radiol 2001; 11: 2585-8.*
15. Myers RE, Khan KJ. *Insulin-induced hypoglycemia in the nonhuman primate. II: Long-term neuropathological consequences. In: Bradley JB, Meldrum BS, eds. Brain hypoxia (chapter 20). Reprinted in Clin Devel Med 1971; 39/40: 195-206.*
16. Liwnicz BH, Mouradian MD, Ball JB Jr. *Intense brain cortical enhancement on CT in laminar necrosis verified by biopsy. AJNR Am J Neuroradiol 1987; 8: 157-9.*
17. Tippin J, Adams HP Jr, Smoker WR. *Early computed tomographic abnormalities following profound cerebral hypoxia. Arch Neurol 1984; 41: 1098-100.*
18. Arbelaez A, Castillo M, Mukherji SK. *Diffusion-weighted MR imaging of global cerebral anoxia. AJNR Am J Neuroradiol 1999; 20: 999-1007.*
19. Siskas N, Lefkopoulos A, Ioannidis I, Charitandi A, Dimitriadis A. *Cortical laminar necrosis in brain infarcts: serial MRI. Neuroradiology 2003; 45: 283-8.*
20. Lovblad KO, Wetzel SG, Somon T, Wilhelm K, Mehdizade A, Kelekis A, El-Koussy M, El-Tatawy S, Bishof M, Schroth G, Perrig S, Lazeyras F, Sztajzel R, Terrier F, Rufenacht D, Delavelle J. *Diffusion-weighted MRI in cortical ischaemia. Neuroradiology 2004; 46: 175-82.*

21. Iizuka T, Sakai F, Suzuki N, Hata T, Tsukahara S, Fukuda M, Takiyama Y. *Neuronal hyperexcitability in stroke-like episodes of MELAS syndrome*. *Neurology 2002; 59: 816-24*.

22. Adams JH, Brierley JB, Connor RC, Treip CS. *The effect of systemic hypotension upon the human brain*. *Clinical and neuropathological observation in 11 cases*. *Brain 1966; 89: 235-68*.