

## Letter to the Editor

## Ketotic hyperglycemia-related seizure with reversible white matter lesion: Metabolic implication of its reversibility based on magnetic resonance spectroscopy study



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Dear Editors,

## 1. Introduction

Hyperglycemic seizures are an important complication of diabetes mellitus because this is often refractory to the antiepileptic drugs and responds well to blood glucose level normalization. This condition is usually related with non-ketotic hyperglycemia, and ketotic hyperglycemia-related seizure has rarely been described [1,2], which could presumably be due to the neuro-protective effect of ketone bodies [3,4]. Here, we report a case of ketotic hyperglycemia-related seizure with a reversible T2-hypointense lesion in the white matter by magnetic resonance imaging (MRI). Our case indicated that hyperglycemia accompanied by ketosis can also cause seizures, and provided an insight into the mechanism of its reversibility based on MRI and magnetic resonance spectroscopy (MRS) findings.

## 2. Case report

A 59-year-old man with no medical history presented with recurrent hemifacial seizures. A twitching sensation on the left side of his body had appeared a month prior to admission, and a facial jerk had developed 5 days prior. On admission, clonic seizures involving the left jaw and bilateral eyelids were observed every 10–15 min, which continued for 1–2 min and spontaneously resolved with subsequent Todd's palsy. The distribution of the seizure strongly suggested epileptic foci involving the primary motor cortex for facial movement, although the electroencephalogram was unremarkable even during the attack. MRI scans showed T2 hypointense lesion in the white matter of the right frontal operculum corresponding to the sensorimotor area of the left face (Fig. 1A), suggesting that this lesion was responsible for his neurological symptoms. MRS at this area showed decreased *N*-acetyl aspartate (NAA) with a preserved creatine and absence of a lactate peak (Fig. 1B). Arterial spin labeling (ASL) suggested a regional increase of blood flow at the cortex corresponding to the white matter lesion (Fig. 1C). Laboratory examination revealed ketotic hyperglycemia

without acidosis (blood glucose, 371 mg/dL; hemoglobin A1c, 13.4%; 3-hydroxybutyric acid, 373  $\mu$ mol/L (normal 0–74  $\mu$ mol/L)). The blood glucose level normalization resolved his symptoms in four days, and the hypointense lesion on T2-weighted image on day 15 (Fig. 1D). Moreover, the decreased NAA on the MRS and hyperperfusion in ASL were also resolved (Fig. 1E, F).

## 3. Discussion

Hyperglycemia-related seizures are a well-recognized complication of diabetes mellitus. Several studies have reported that reversible T2-hypointense lesions in the white matter develop in association with hyperglycemic seizures [4–7], which can presumably be attributable to the hyperosmolar hyperglycemic state. However, to our best knowledge, no report has described the metabolic aspects of the lesion based on MRS analysis. In our case, a decreased NAA peak in the lesion definitely indicated the presence of neuronal damages, however, the preserved creatine peak suggested that the neuronal damages were not severe so as to cause neuronal death. The absence of a lactate peak indicated that energy production is presumably dependent on aerobic metabolism even in the case of dysfunction of the Krebs cycle due to intracellular dehydration, implying that ketone bodies may have been efficiently employed for energy production. These findings suggested transient dysfunction of neuronal cells in the lesion. A completely reversible clinical course, without any neurological sequelae, supports this assumption.

Hyperglycemia-related seizures are thought to occur due to a compensatory increase in GABA consumption. Hyperglycemia increases serum osmolality, which draws water out of the cell, leading to intracellular dehydration. This condition inhibits energy production by the Krebs cycle, resulting in a compensatory consumption of GABA. Depletion of GABA impedes the activity of the inhibitory neurons leading to hyperexcitability due to excitatory neuron activity [8]. In our patient, the increased blood flow in the ASL study during the facial seizure potentially indicated the neuronal hyperexcitability. In this scenario, the contribution of ketone bodies to energy production in the

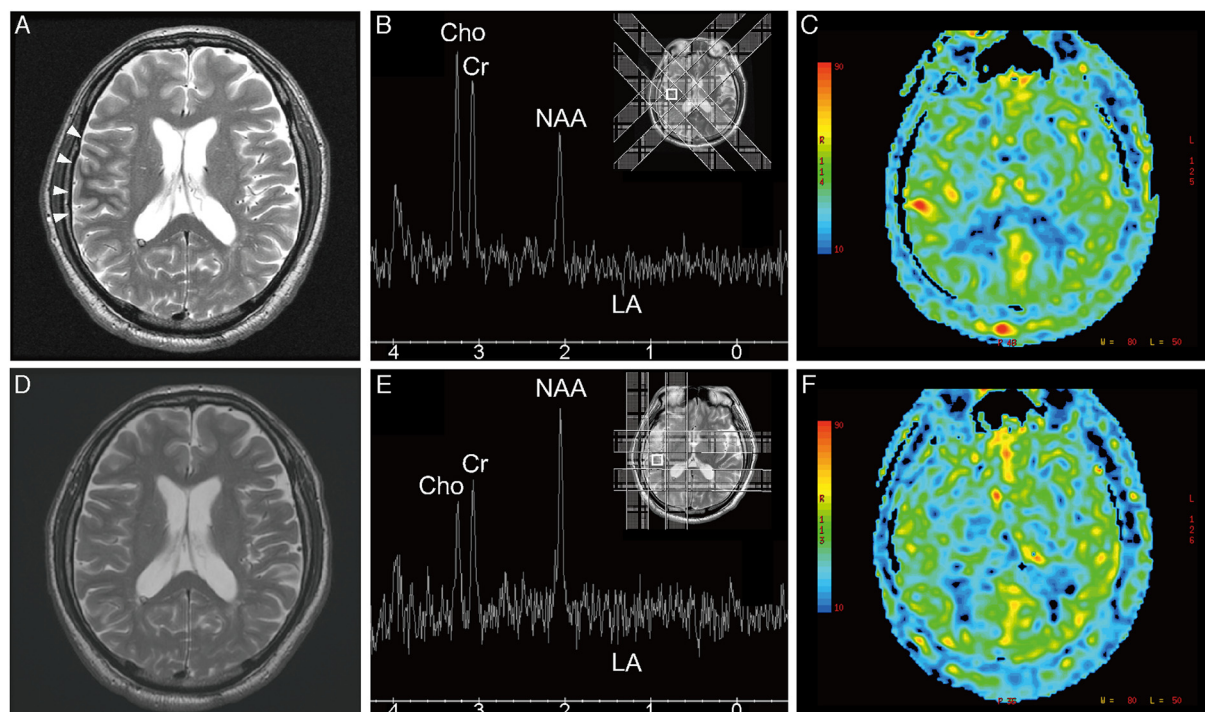
Abbreviations: MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; ASL, arterial spin labeling

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**Fig. 1.** (A) Magnetic resonance imaging on admission showing a T2-hypointense lesion in the white matter of the right operculum. (B) Magnetic resonance spectroscopy showing decreased *N*-acetyl aspartate (NAA) and a preserved creatine (Cr) without lactate peak (NAA/Cr = 0.73, Cho/Cr = 1.12). (C) Arterial spin labeling (ASL) demonstrating regional blood flow increase in the area corresponding to the cortex, adjacent to the T2-hypointense lesion. (D–F) Follow-up T2-weighted image, MRS and ASL on day 15. T2-hypointense lesion resolved after the normalization of blood glucose levels and MRS showed NAA peak recovery (NAA/Cr = 1.43, Cho/Cr = 0.85).

brain is supposed to attenuate neuronal hyperexcitability and suppress epileptic seizure, providing protective effects to the brain. There has been only one report of ketotic hyperglycemia-related seizure [1]. Our case clearly demonstrated that the epileptogenic effects of hyperglycemia can surmount the neuro-protection by ketone bodies and result in seizures.

Our case demonstrated that hyperglycemic seizures could occur even with the neuro-protective effect of ketone bodies. The metabolic and hemodynamic features of the lesion suggested its reversibility; indeed, blood glucose level normalization resolved these conditions rapidly.

#### Consent for publication

Yes

#### Conflicts of interest

None

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#### References

- [1] F. Placidi, R. Floris, A. Bozzao, A. Romigi, M.E. Baviera, M. Tombini, F. Izzi, F. Sperli,

- M.G. Marciani, Ketotic hyperglycemia and epilepsia partialis continua, *Neurology* 57 (3) (2001) 534–537.  
 [2] F. Sasaki, S. Kawajiri, S. Nakajima, A. Yamaguchi, Y. Tomizawa, K. Noda, N. Hattori, Y. Okuma, Occipital lobe seizures and subcortical T2 and T2\* hypointensity associated with nonketotic hyperglycemia: a case report, *J. Med. Case Rep.* 10 (1) (2016) 228.  
 [3] M. Gasiot, M.A. Rogawski, A.L. Hartman, Neuroprotective and disease-modifying effects of the ketogenic diet, *Behav. Pharmacol.* 17 (5–6) (2006) 431–439.  
 [4] M. Maalouf, J.M. Rho, M.P. Mattson, The neuroprotective properties of calorie restriction, the ketogenic diet, and ketone bodies, *Brain Res. Rev.* 59 (2) (2009) 293–315.  
 [5] S. Raghavendra, R. Ashalatha, S.V. Thomas, C. Kesavadas, Focal neuronal loss, reversible subcortical focal T2 hypointensity in seizures with a nonketotic hyperglycemic hyperosmolar state, *Neuroradiology* 49 (4) (2007) 299–305.  
 [6] C.P. Wang, P.F. Hsieh, C.C. Chen, W.Y. Lin, W.H. Hu, D.Y. Yang, M.H. Chang, Hyperglycemia with occipital seizures: images and visual evoked potentials, *Epilepsia* 46 (7) (2005) 1140–1144.  
 [7] A. Hennis, D. Corbin, H. Fraser, Focal seizures, non-ketotic hyperglycaemia, *J. Neurol. Neurosurg. Psychiatry* 55 (3) (1992) 195–197.  
 [8] B.M. Singh, R.J. Strobus, Epilepsia partialis continua associated with nonketotic hyperglycemia: clinical and biochemical profile of 21 patients, *Ann. Neurol.* 8 (2) (1980) 155–160.

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