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## CLINICAL REPORT

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# Serum Calcium Concentration Affects Signal Changes on Diffusion-Weighted Imaging in Hypoglycemic Encephalopathy

**BACKGROUND AND PURPOSE:** Abnormal signals in brain DWI may appear in patients with HE. The aim of this study was to compare the clinical condition and various physiologic factors between patients with HE with and without abnormal signal intensity changes on DWI.

**MATERIALS AND METHODS:** We retrospectively enrolled patients with HE who underwent brain DWI studies from January 2002 to November 2010. A diagnosis of HE was defined as low serum glucose levels ( $<50$  mg/dL) with alteration of consciousness. Several clinical conditions and physiologic parameters were compared between patients with and without abnormal signals on DWI, including consciousness levels; outcome; body temperature; blood pressure; and serum levels of glucose, calcium, sodium, blood urea nitrogen, and creatinine.

**RESULTS:** Nine patients with HE were included, and 3 of them (33%) had abnormal signals on brain DWI. There was a trend toward serum calcium concentrations being lower in patients with normal findings on DWI studies compared with patients with abnormal DWI signals ( $7.6 \pm 1.7$  versus  $9.4 \pm 0.7$  mg/dL,  $P = .07$ ). Serum glucose concentration, duration of hypoglycemia, consciousness levels, other physiologic parameters, and clinical outcome did not reveal any differences between the 2 groups.

**CONCLUSIONS:** One-third of patients with HE had abnormal signals on brain DWI, and patients with low serum calcium levels may be less likely to present with abnormal DWI signals.

**ABBREVIATIONS:** EEG = electroencephalogram; GCS = Glasgow Coma Scale; HE = hypoglycemic encephalopathy

Glucose is an essential substrate for brain metabolism and profound hypoglycemia may cause HE with manifestations ranging from focal neurologic symptoms to alteration of consciousness.<sup>1-5</sup> Although emergent glucose supplementation usually reverses neurologic deficits, some patients still enter a persistent vegetative state or even die. Because glucose deprivation leads to energy failure followed by cytotoxic brain edema, several authors have reported that HE may produce abnormal signals on brain DWI, especially at the internal capsules, cerebral cortex, hippocampus, and basal ganglia.<sup>1,5,6</sup> The appearance of cortical DWI abnormalities in  $>2$  lobes is a poor prognostic factor for HE, while patients with HE having DWI signal-intensity changes in 1 lobe or only in the white matter usually recovered completely.<sup>1</sup> These DWI abnormalities can be reversible<sup>3,7-10</sup> but are not consistent in all patients with HE.<sup>11</sup> The aim of this study was to compare the clinical conditions and various physiologic factors between patients with HE with and without abnormal signal-intensity changes on DWI.

## Materials and Methods

We retrospectively enrolled patients who were diagnosed as having HE and also underwent brain DWI studies from January 2002 to

November 2010 from both the Far Eastern Memorial Hospital and the National Taiwan University Hospital. A diagnosis of HE was defined as low serum glucose levels ( $<50$  mg/dL) with alteration of consciousness (GCS score,  $<12$ ). All patients underwent brain DWI studies, in which abnormal consciousness was still apparent. Patients who had the comorbidity of ischemic stroke, seizure, encephalitis, or other neurologic disorders, which may potentially cause signal-intensity changes with regard to DWI, were also excluded.

Patients were classified into 2 groups: 1) HE with abnormal signal intensity changes on DWI, and 2) HE with normal DWI results. DWI was performed with single-shot spin-echo imaging with 2 diffusion-sensitivity values of 0, 1000, and 2000  $\text{s/mm}^2$  along all 3 axes. The results of DWI were analyzed by 2 neurologists, retrospectively. In a recent study, focal DWI hyperintensity with ADC isointensity could be found in the posterior limbs of internal capsule, cortical spinal tracts, cingulate gyrus, insula, medial lemniscus, and cerebellar peduncles without clinical significance.<sup>12</sup> To avoid false recognition of nonspecific signal-intensity changes on DWI, we defined the abnormal DWI in the present study as high signal intensity on DWI and low signal intensity of ADC in the corresponding area.

All patients also underwent T1- and T2-weighted imaging and fluid-attenuated inversion recovery MR imaging to rule out other kinds of brain pathologic lesions, such as infarct, infection, inflammation, or neoplasm. The topographic distribution of the DWI lesions was also recorded. We also reviewed all the medical records to obtain the clinical conditions and various physiologic parameters evaluated during the period of hypoglycemia, including GCS; clinical outcome; EEG; body temperature; blood pressure; and serum levels of glucose, calcium, sodium, urea nitrogen, and creatinine. Data were presented in mean  $\pm$  SD. We compared the clinical conditions and physiologic parameters between these 2 groups with the Mann-Whitney  $U$  test and the Fisher exact test by using the Statistical Pack-

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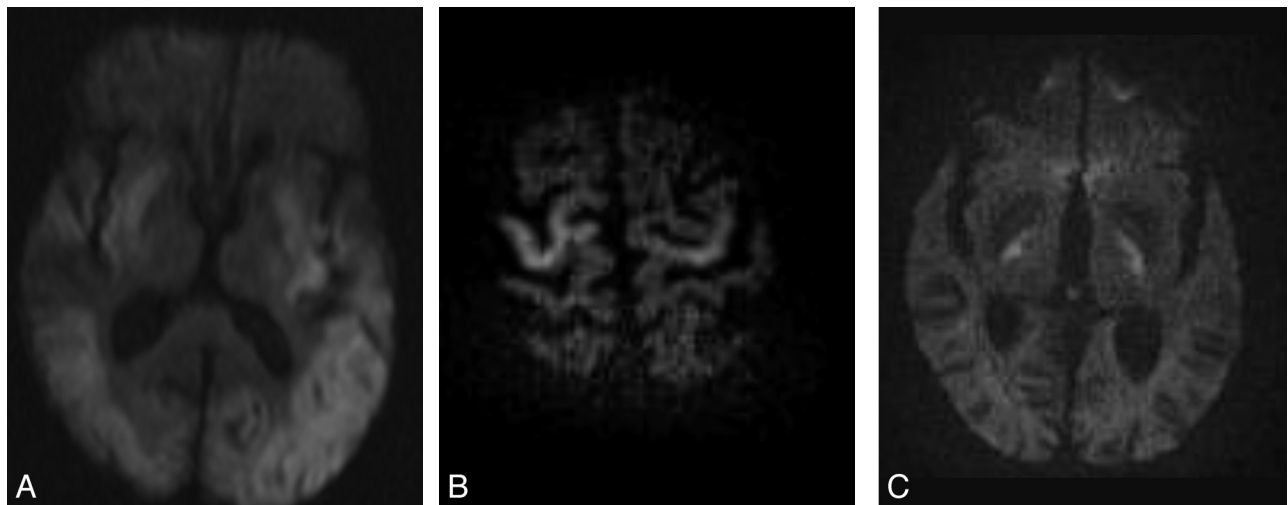
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**Summary of clinical features and lesion distributions on DWI in patients with hypoglycemic encephalopathy**

No.	Age (yr)	Sex	SBP (mm Hg)	Body Temp (°C)	GCS	Glucose (mg/dL)	Ca (mg/dL)	Na (mg/dL)	Cr (mg/dL)	EEG	Hypoglycemia-DWI Interval (hr)	DWI Lesions	Outcome
1	76	F	155	39.4	5	36	10	137	0.7	Diffuse slow waves, 2–7 Hz	48	Bilateral internal capsules, centrum semiovale, precentral gyrus, and temporo-parieto-occipital regions	Coma
2	73	F	141	37.5	9	24	9.6	134	1.28	Diffuse slow waves, 2–5 Hz	36	Bilateral precentral gyrus	Recovered
3	76	M	116	36.2	5	37	8.7	135	0.93	ND	6	Bilateral internal capsules, precentral gyrus	Recovered
4	47	F	129	35.9	7	41	9.7	136	0.7	Normal	48	—	Recovered
5	83	M	186	37.0	8	49	6	141	0.99	Diffuse slow waves, 3–6 Hz	55	—	Recovered
6	78	F	147	36.8	7	25	5	132	4.1	ND	24	—	Coma
7	64	F	161	34.3	6	37	7.8	138	2.22	Diffuse slow waves, 2–5 Hz	8	—	Recovered
8	57	M	81	36.2	9	39	5.2	142	3.59	Diffuse slow waves, 3–4 Hz	120	—	Recovered
9	78	M	127	36.9	10	35	8.6	137	0.65	Diffuse slow waves, 4–7 Hz	9	—	Recovered

**Note:**—Ca indicates calcium; Cr, creatinine; Na, sodium; ND, not performed; Temp, temperature; SBP, systolic blood pressure; —, no DWI lesion.



**Fig 1.** DWI studies in patients with HE show abnormal signals at the bilateral temporo-occipital lobes, patient 1 (A); bilateral precentral gyrus, patient 2 (B); and bilateral internal capsules, patient 3 (C).

age for the Social Sciences, Version 15.0 (SPSS, Chicago, Illinois). Two-tailed *P* values < .05 were statistically significant.

## Results

Nine patients (4 men; mean age,  $70 \pm 12$  years) were enrolled and are presented in the Table. Five of these patients had pre-existing diabetic mellitus. Serum glucose levels were  $35.9 \pm 7.7$  mg/dL, ranging from 24 to 49 mg/dL, and the GCS score was  $7.3 \pm 1.8$ , ranging from 5 to 10. The intervals between the onset of hypoglycemia-related symptoms and brain DWI studies were  $45 \pm 38$  hours, ranging from 6 to 120 hours. Three of 9 patients with HE (33%) showed DWI abnormalities (Fig 1). Patient 1 had extensive DWI abnormalities in the bilateral hemispheres, including white matter (internal capsule, centrum semiovale, and subcortical temporoparietal-occipital

regions) and gray matter (precentral gyrus and temporo-occipital cortex). The DWI of patients 2 and 3 showed symmetric abnormalities in the bilateral internal capsules or precentral gyrus. Seven patients (77%) recovered to their baselines within a few days after receiving glucose supplementation, while 2 patients remained vegetative at discharge.

The age, sex, and consciousness levels by the GCS were not significantly different between patients with ( $n = 3$ ) and without ( $n = 6$ ) abnormal signals on DWI. There were also no significant differences between patients with and without abnormal DWI signals in initial serum glucose concentrations ( $32.3 \pm 7.2$  versus  $37.7 \pm 7.9$  mg/dL) and intervals between the onset of hypoglycemia-related symptoms and brain DWI studies ( $30 \pm 21$  versus  $44 \pm 42$  hours). We further compared various physiologic factors between the 2 groups. There was a

trend toward serum calcium concentration being lower in patients with normal findings on DWI studies compared with patients with abnormal DWI signals ( $7.6 \pm 1.7$  versus  $9.4 \pm 0.7$  mg/dL,  $P = .07$ ). The serum calcium concentration was highest (10 mg/dL) in patient 1, who presented with extensive bilateral cortical DWI abnormalities. Four of 6 patients (67%) with normal DWI results had mild hypocalcemia ( $<8.5$  mg/dL). Other physiologic parameters did not show any differences between the 2 groups, including body temperature; systolic blood pressure; and serum levels of sodium, urea nitrogen, and creatinine. Seven of 9 patients had undergone an EEG study, and all except 1 in the group with normal findings on DWI had diffuse  $\theta$  to  $\delta$  waves. The outcome was also similar between patients with and without abnormal DWI signals so that 1 in 3 patients and 1 in 6 patients became permanently vegetative (33% versus 17%), respectively.

## Discussion

HE is not an uncommon disorder, occurring especially in patients with diabetic mellitus and the elderly. Although emergent glucose supplementation usually reverses neurologic deficits, some patients still enter a permanent vegetative state or even die. Therefore, extensive studies are necessary to investigate the pathophysiology and develop a new therapy for HE. Here, we showed that one-third of patients with HE had brain abnormalities on DWI and that the topographic distributions of DWI abnormalities in HE were similar to those in previous reports, including the bilateral internal capsules, cerebral cortex, and subcortical white matter.<sup>1,5-7,13</sup> In addition, serum calcium concentration showed a trend toward being lower in patients with normal findings on DWI compared with patients with abnormal DWI signals. To the best of our knowledge, this is the first study that has compared patients with HE with and without abnormal DWI results.

DWI is a specialized technique, which measures the degree of water diffusion within the extracellular space.<sup>14</sup> The DWI signal intensity is high when diffusion is restricted, as seen in cytotoxic damage in cerebral infarct.<sup>14</sup> Hypoglycemia causes cerebral energy failure and leads to reduction of cell membrane ionic pump activity, followed by a shift of cerebral water from the extracellular space to the intracellular space.<sup>15</sup> Subsequently, severe and prolonged hypoglycemia may show abnormally high signals on DWI, and extensive cortical DWI abnormalities were associated with poor prognosis of patients with HE.<sup>1</sup> In this study, 1 patient with diffuse cortical lesions became persistently vegetative, and 2 other patients with only white matter lesions recovered totally. However, the existence of DWI abnormal signals was not associated with lower serum glucose concentrations or longer periods of hypoglycemia.

A previous study also demonstrated that the initial blood glucose level did not predict the clinical outcome.<sup>5</sup> Experimental evidence in animals suggests that excitatory amino acids released into the extracellular space, but not glucose starvation, may be important in the pathogenesis of hypoglycemic neuronal damage.<sup>16</sup> Therefore, the major determinants of severity in HE may not just simply be the degree and duration of hypoglycemia, but there are also other important physiologic factors, which need further investigation. In addition, 1 of our patients with HE with normal DWI results became permanently vegetative, which indicated that the absence of ab-

normal signals on DWI in HE did not guarantee a good clinical outcome. Some pathomechanisms other than cytotoxic edema—related neuronal damage should contribute to severe encephalopathy in extensive hypoglycemia.

Our patients with HE with low serum calcium levels were less likely to present with abnormal findings on DWI. In hypoglycemic status, neuronal energy failure resulted in release of excitatory neurotransmitters (glutamate and aspartate), leading to calcium entry into the intracellular space and finally inducing neuronal apoptosis.<sup>17</sup> Therefore, low extracellular calcium concentrations might reduce the abnormal calcium influx and prevent neuronal death, and low serum calcium levels might thus have a protective role in HE. Notably, calcium signaling pathways play a crucial role in the survival of neurons.<sup>18</sup> In the elderly and patients with dementia, disarrangement of calcium homeostasis in brain tissues leads to cognitive and functional decline.<sup>19</sup> Blockers for calcium channels such as nimodipine have been shown to prevent apoptotic and necrotic cell death after transient focal ischemia,<sup>20</sup> reduce damage resulting from brain edema,<sup>21</sup> and improve clinical outcome for patients with traumatic brain injury and subarachnoid hemorrhage.<sup>22,23</sup> Because standard treatment with emergent glucose supplementation could not rescue all patients with HE, combination therapy might be necessary to improve the outcome in patients with severe HE—for example, applications of calcium channel blockers or calcium-lowering therapy.

This study has some limitations. First, it was a retrospective study, and the possibility of selection bias may exist. Second, the time intervals between the onset of hypoglycemia-related symptoms and brain DWI studies varied in patients with HE. Because all of our patients underwent brain DWI studies when abnormal consciousness was still apparent, the possibility that pre-existing brain abnormalities had been normalized at the time of DWI studies could be lessened. Third, DWI is not a standard diagnostic tool for patients with HE. Most of the time, the symptoms of these patients resolve shortly after glucose supplementation. Therefore, although HE is not uncommon, only a few patients with HE have undergone DWI studies within 5 days after the onset of symptoms.

The small case number thus impaired the power of statistics and made it difficult to achieve a significant difference. Notably, we also detected a 31-year-old patient who had relatively low serum glucose levels (67 mg/dL) with impaired consciousness, who recovered after glucose supplementation. The DWI showed abnormal signal-intensity changes in the bilateral internal capsules. His serum calcium concentration was 12 mg/dL. We did not enroll this patient in the present study because the serum glucose level was not  $<50$  mg/dL. However, if we had included this patient in the present case series, the difference in serum calcium levels between patients with and without DWI signal intensity changes would have become significant ( $10.0 \pm 1.3$  versus  $7.6 \pm 1.7$  mg/dL,  $P = .038$ ).

## Conclusions

One-third of patients with HE had abnormalities on DWI, and the appearance of these abnormalities tended to be associated with the serum calcium concentrations. These preliminary findings imply that calcium-lowering or -blocking therapy might benefit patients with severe HE. However, future large

prospective studies are required to further investigate this issue and confirm these findings.

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