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【 CASE REPORT 】

Left Hemiplegia Possibly Due to Glucose Reperfusion Injury after Recovery of Severe Hypoglycemia in a Woman with Type 2 Diabetes Mellitus

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Abstract:
A 79-year-old woman with type 2 diabetes receiving insulin was rushed to our hospital due to severe hypoglycemia. Glucose was administered, and the consciousness disturbance was promptly improved. A few hours later, conjugate deviation of the eyes to the right and left hemiplegia occurred at a normal glucose level. Cerebral magnetic resonance imaging (MRI) showed hyperintensities of the right posterior limb of the internal capsule and the medial thalamus on diffusion-weighted imaging sequences. However, the changes observed using MRI disappeared completely on the third day, and her symptoms subsequently improved. This may have been a case of glucose reperfusion injury.

Key words: hypoglycemic encephalopathy, neuronal damage, glucose reperfusion

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Introduction

Hypoglycemia, particularly severe hypoglycemia, has been associated with vascular events and death (1, 2). In addition, severe hypoglycemia can result in coma, seizure, and cognitive impairment (2). Hypoglycemic encephalopathy is defined as a coma, seizure, or other neurological deficits caused by hypoglycemia (3, 4). On magnetic resonance imaging (MRI), hypoglycemic encephalopathy is a characteristic of the earliest changes in diffusion-weighted imaging (DWI) sequences (5). Hypoglycemic encephalopathy is commonly reversible by glucose administration.

We herein report a Japanese woman who may have experienced glucose reperfusion injury a few hours after improvement in severe hypoglycemia.

Case Report

A 79-year-old Japanese woman was diagnosed with type 2 diabetes mellitus 20 years ago. Her medications included insulin glargine 8 units/day, glimepiride 4 mg/day, sitagliptin 50 mg/day, and miglitol 150 mg/day. Her glycated hemoglobin (HbA1c) level was 7.2%.

The patient was well before her son left at 8:00 a.m. on that day. When her son returned home at 6:30 p.m., she was found lying unresponsive on her bed. She was rushed to the National Center for Global Health and Medicine in Tokyo, Japan, at 7:30 p.m. Her Glasgow Coma Scale (GCS) level was E1V1M1, blood pressure was 186/71 mmHg, and other vital signs were deemed unremarkable. Her blood glucose level was 20 mg/dL, and she was immediately administered glucose. Her GCS level became E4V4M6 at 8:30 p.m. She had no abnormal neurological findings, and emergent cere-

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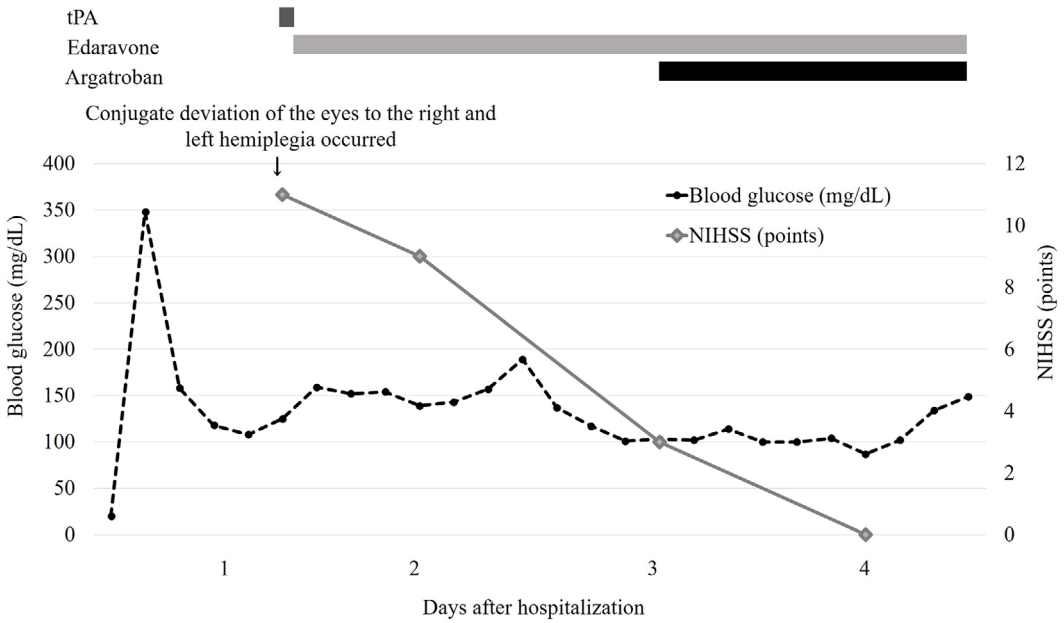

Figure 1. Clinical course after the patient was transferred to our hospital. On the first day after the patient was transferred to our hospital, we monitored her blood glucose level every 30 minutes using a glucose meter. At first, her blood glucose level was 20 mg/dL, and after administering a glucose injection, her blood glucose level was 100-160 mg/dL on the first day. The doses of tPA, edaravone, and argatroban administered were 24×10^6 units, 60 mg/day, and 60 mg/day, respectively. NIHSS: National Institutes of Health Stroke Scale, tPA: tissue plasminogen activator

bral computed tomography revealed no particular findings. Her thyroid and adrenal functions were determined to be at normal levels. Therefore, we diagnosed the primary cause of the consciousness disturbance as hypoglycemia with antidiabetic medications, including insulin. We administered continuous glucose, which increased her blood glucose level to >100 mg/dL (Fig. 1).

Conjugate deviation of the eyes to the right and left hemiplegia occurred at 10:00 p.m. She was unable to raise her left arm and maintain her left leg in the raised position for 5 seconds. The Babinski sign was negative bilaterally. Her National Institutes of Health Stroke Scale (NIHSS) score was 11. Her blood glucose level was 125 mg/dL, which indicated an absence of hypoglycemia. Cerebral MRI showed hyperintensities of the right posterior limb of the internal capsule and the medial thalamus on DWI sequences (Fig. 2A). Furthermore, slight hypointensity of the right posterior limb of the internal capsule was observed on apparent diffusion coefficient (ADC) maps (Fig. 2C). We suspected acute cerebral infarction; therefore, we administered tissue plasminogen activator (24×10^6 units) and edaravone (60 mg/day). On the third day after the patient was transferred to our hospital, there was an unexpected and complete disappearance of changes on MRI and ADC map (Fig. 2B, D). Her symptoms subsequently improved.

Discussion

Hypoglycemic encephalopathy has been determined to be caused by damage to the brain cells as a result of hypoglycemia prolongation (3). Patients may experience memory impairment, consciousness disturbance, coma, and in the worst case, death (4, 6). Brain disorders are often reversible, and glucose supplementation typically provides rapid recovery, even if the hypoglycemic coma lasts for several hours, provided the patient has no other serious illnesses (1).

Hyperintensity on diffusion-weighted magnetic resonance imaging (DW-MRI) is seen in both stroke and hypoglycemic encephalopathy, as ischemia and glucose deprivation lead to ionic pumping failure in the cell membrane (7, 8). At times, it becomes essential to distinguish hypoglycemic encephalopathy from acute cerebral infarction.

Our patient experienced conjugate deviation of the eyes, and hemiplegia with reversible hyperintensity lesions in the right posterior limb of the internal capsule and the bilateral medial thalamus on DW-MRI. The right posterior limb of the internal capsule and medial thalamus derive their blood supply from different arteries. Therefore, the changes we observed on MRI of the medial thalamus were determined to be bilateral, and simultaneous development of cerebral infarction seemed unlikely. In similar cases, Albayam et al. and Böttcher et al. reported hemiplegia from hypoglycemic encephalopathy with MRI showing bilateral changes (7, 9).

The mechanism underlying the appearance of hemiparesis symptoms despite bilateral hyperintensity on DW-MRI has been discussed but remains unknown. On the third day, our patient was still recovering from the after-effects; however, the changes on MRI disappeared entirely. If our patient had had cerebral infarction, MRI would have displayed the changes fractionally. Previous reports indicate that it is com-

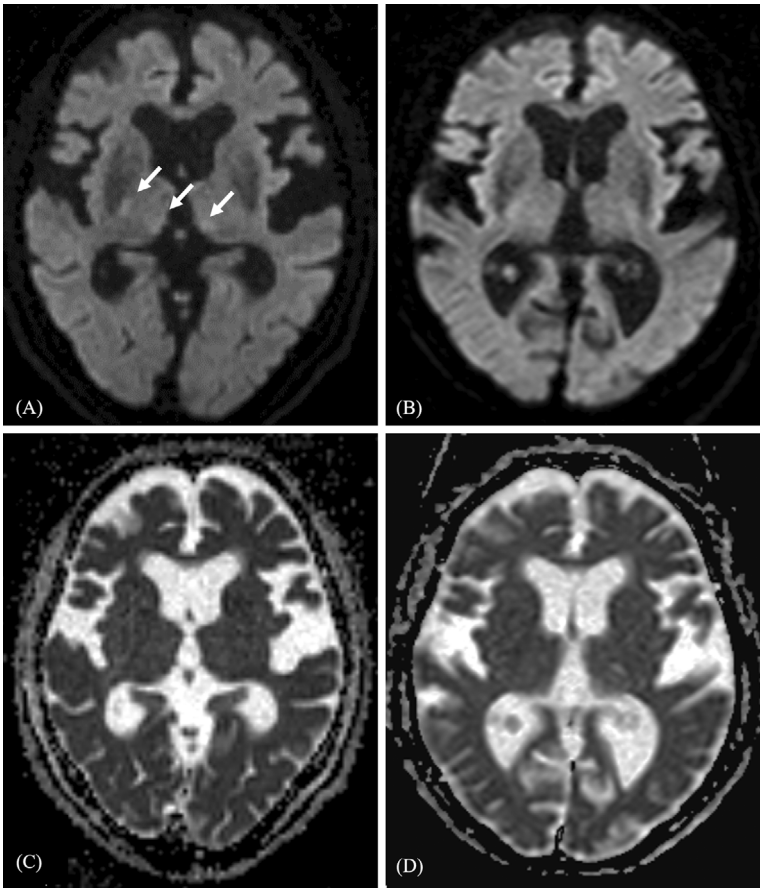

Figure 2. **Magnetic resonance imaging (MRI) of cerebral diffusion-weighted imaging (DWI) sequences (A, B) and apparent diffusion coefficient (ADC) maps (C, D). MRI was conducted immediately after the appearance of conjugate deviation of the eyes to the right and left hemiplegia. The hyperintensities of the right posterior limb of the internal capsule and the medial thalamus on DWI (white arrows in A) and hypointensities on ADC map (C) are shown. Changes disappeared entirely on the third day after transfer (B, D).**

mon for hyperintensities on DW-MRI to reverse over several hours in hypoglycemic encephalopathy (10). Sontineni et al. reported a patient who underwent hypoglycemia-induced pontine infarction (11). In that case, right hemiplegia occurred during hypoglycemia and improved slightly after glucose administration. Cerebral computed tomography revealed no acute abnormalities on the first day. MRI on the third day after the hemiparesis onset showed restricted diffusion in the left half of the pons and lower mid-brain, consistent with acute infarct. In this case, the hyperintensity lesions corresponded with the symptoms; furthermore, the hyperintensities on DW-MRI were demonstrable. These observations support the view that our patient's symptoms resulted not from cerebral infarction but from "glucose reperfusion injury."

Several mechanisms are thought to be involved in hypoglycemia (12-15). During hypoglycemia, reduced glycolysis can lead to an increase in excitatory amino acids, such as glutamate and aspartate, in the extracellular space, and these amino acids further damage postsynaptic cells (12, 13). During hypoglycemia, nitric oxide is produced, which triggers vesicular zinc release. Postsynaptic zinc accumulation leads to neuronal death (12, 13).

Furthermore, recent studies have demonstrated that hypoglycemic superoxide production and neuronal death are increased during glucose reperfusion rather than by the hypoglycemia itself (12-14). Glucose reperfusion leads to activation of NADPH oxidase and superoxide production and a subsequent increase in several factors, such as 4-hydroxy-2-nonenal (4-HNE), a cytotoxic aldehyde that causes neuronal death (14, 15). It has also been reported that administration of Alda-1: *N*-(1,3-benzodioxole-5-ylmethyl)-2,6-dichbrobenzamide inhibits both the production of 4-HNE and neuronal death associated with glucose reperfusion injury (15).

In our case, severe hypoglycemia resolved promptly after glucose administration; however, symptoms associated with hypoglycemia developed a few hours later. We found no obvious cause of these symptoms other than hypoglycemia. As a result, this case was diagnosed as a possible case of "glucose reperfusion injury."

The thalamus is commonly spared in hypoglycemia; however, hyperintensity of the thalamus was seen on DW-MRI in our case. Glucose reperfusion injury after the improvement of hypoglycemia probably occurred; this suggests that

the mechanism underlying glucose reperfusion injury may differ from that of hypoglycemic encephalopathy.

Hyperglycemia can exacerbate cell injury through multiple mechanisms in the setting of reperfusion in acute stroke (16), although hyperglycemia after treatment of hypoglycemia is reportedly not associated with a poor prognosis (3). Despite the pathophysiological mechanism being unclear in our case, a mechanism whereby hyperglycemia damages brain cells in the setting of reperfusion in acute stroke may have been associated with our case in the form of glucose reperfusion injury. To our knowledge, this is the first article to report the relationship between hypoglycemia and glucose reperfusion injury. Further studies are required to clarify the association between severe hypoglycemia and glucose reperfusion injury. In addition, in cases of severe hypoglycemia, careful follow-up is needed to monitor the appearance of symptoms caused by neuronal damage, even after the improvement of hypoglycemia.

The authors state that they have no Conflict of Interest (COI).

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