

Hypoglycemic encephalopathy caused by overdose of metformin in an adolescent

Jing-Xue Li^{1,2}, Zhe Li², Wei Jin², Tian-Jun Wang², Qiao-Zhen Guo^{2,3}, Ming-Yue Fan²

¹Graduate School of Hebei Medical University, Shijiazhuang, Hebei 050017, China;

²The Fifth Department of Neurology, Hebei General Hospital, Shijiazhuang, Hebei 050000, China;

³Graduate School of Hebei North University, Zhangjiakou, Hebei 075000, China.

To the Editor: Hypoglycemic encephalopathy is an acute brain dysfunction caused by hypoglycemia. Its clinical manifestations are complex, and sometimes its symptoms are not typical. Therefore, it can be misdiagnosed. This article shares a case of hypoglycemic encephalopathy caused by excessive ingestion of metformin for a suicide attempt in an adolescent.

A 14-year-old girl was discovered unconscious by her family 12 hours prior to presentation on May 4th, 2019. She had hanging eyes, urinary incontinence, and stiff limbs. She was sent to the emergency department of Hebei General Hospital. Cerebral computed tomography showed low density in the right hemisphere, sulci narrowing or disappeared, and an unclear gray matter margin [Figure 1A]. Cerebral diffusion-weighted imaging (DWI) showed that there was a high possibility of acute cerebral infarction in the right frontal, temporal, parietal, and occipital lobes and the splenium of the corpus callosum [Figure 1B]. Cerebral magnetic resonance angiography (MRA) showed that the edge of the blood flow signal in the right middle cerebral artery was not smooth, and endarteritis could not be eliminated [Figure 1B]. The white blood cell count was 22.16×10^9 cells/L, and the neutrophil ratio was 87.30% in a routine blood test. The blood glucose level was 4.01 mmol/L. Medicine for anti-infection and consciousness-promoting drugs were given, but the consciousness of the patient did not improve. On the second day, the patient was admitted to our neurology department. On admission, the patient was comatose, but she showed a response to painful stimulus. Babinski signs were negative bilaterally. The Kernig sign was positive. We were told that she had a respiratory infection 8 days prior. Her family denied any history of birth injury, previous trauma, toxic or drug exposure, and other diseases. Therefore, the primary diagnosis was “causes of unconsciousness to be

identified: central nervous system infection or acute cerebral infarction”?

On admission, blood glucose was 0.03 mmol/L. Therefore, we further inquired about her medical history. The family members complained that the patient was sensitive and introverted. She had quarreled with her mother 2 days ago. Her mother had diabetes. There were metformin, glyburide, and insulin at home. Therefore, we performed a toxicologic analysis. The metformin concentration was 25.4 mg/L (treatment dose <15 mg/L). We considered that the hypoglycemia was caused by excessive ingestion of metformin. We hypothesized that the patient had suffered from long-term hypoglycemia, which caused severe brain dysfunction. Therefore, the final diagnosis was hypoglycemic encephalopathy. She was given treatments to correct hypoglycemia, decrease cranial pressure, and provide nutritional support, but her consciousness was not improved. On May 5th, 2019, a cerebral DWI showed that there were abnormal signals in the bilateral cerebral hemispheres [Figure 1C]. The range of abnormal signals was larger than that observed at the time of admission. On May 8th, 2019, her family decided to transfer her to the higher-level hospital for further treatments. After follow-up, the patient was still in a coma on June 18th, 2019. A cerebral fluid attenuated inversion recovery (FLAIR) showed brain necrosis in the bilateral hemispheres [Figure 1D]. Cerebral MRA showed decreased branches of bilateral anterior, middle, and posterior cerebral arteries [Figure 1D].

Hypoglycemic encephalopathy is often due to the unreasonable use of drugs, excessive endogenous insulin secretion, sepsis, alcoholism, liver and kidney failure, and unexplained endocrine diseases. When a patient's blood glucose level is below 2.3 mmol/L, the patient can fall into a coma. A coma lasting more than 6 hours can cause irreversible damage to nerve cells. The pathophysiologic

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Correspondence to: Dr. Tian-Jun Wang, The Fifth Department of Neurology, Hebei General Hospital, Shijiazhuang, Hebei 050000, China
E-Mail: wangtianj2007@126.com

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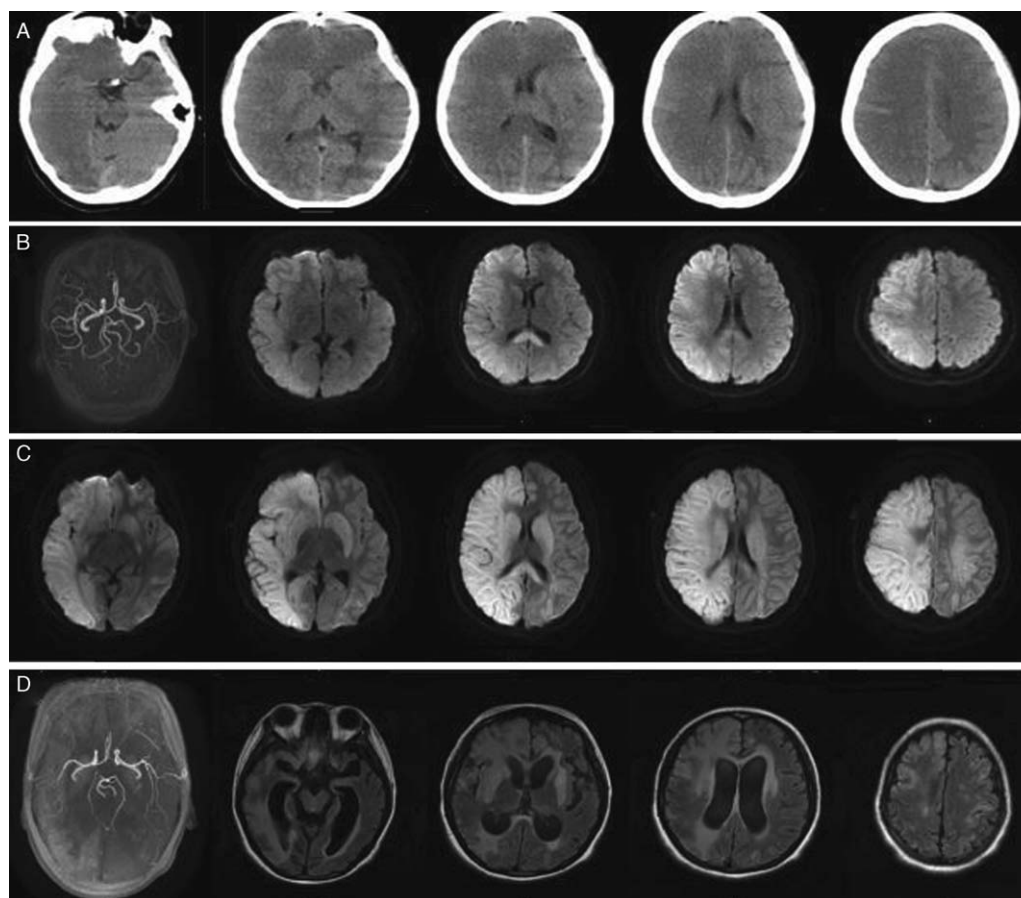


Figure 1: (A) Cerebral computed tomography showing low density in the right hemisphere. (B) Cerebral diffusion-weighted imaging showing abnormal signals in the right hemisphere and the splenium of the corpus callosum. Cerebral magnetic resonance angiography showing the edge of the blood flow signal in the right middle cerebral artery was not smooth, and endarteritis could not be eliminated. (C) Cerebral diffusion-weighted imaging showing abnormal signals in the bilateral cerebral hemispheres. (D) Cerebral fluid attenuated inversion recovery showing brain necrosis in the bilateral hemispheres. Cerebral magnetic resonance angiography showing decreased branches of bilateral anterior, middle, and posterior cerebral arteries.

mechanism of hypoglycemic brain injury is that decreased serum glucose levels promote cellular energy depletion in neurons, leading to the failure of membrane ionic pumps and the loss of membrane ion homeostasis, leading to a shift in water from the extracellular space into the intracellular space. The cerebral magnetic resonance imaging (MRI) features of hypoglycemic encephalopathy are as follows: (1) The cerebral cortex, hippocampus, basal ganglia, and corpus callosum are commonly affected, while the cerebellum, brainstem, and thalamus are spared. This is because of the higher activity of glucose transporters that occurs in the latter and higher levels of adenosine triphosphate in the thalamus.^[1] (2) Cortical lesions do not conform to a specific cerebral arterial distribution.^[2] (3) The features of MRI include hyperintensity on DWI and FLAIR, slight hyperintensity on T2-weighted imaging, and slight hypointensity on T1-weighted imaging. DWI plays an important role in the early diagnosis of hypoglycemic encephalopathy.^[3] (4) Brain imaging of hypoglycemic encephalopathy is not always diffuse or bilateral. The possible mechanism is the presence of metabolic asymmetry between the left and right hemispheres: glucose metabolism in the left hemisphere is lower than in the right.^[4] Therefore, the right hemisphere is more susceptible. (5) Hypoglycemia can also cause

cerebrovascular disease, with swelling of capillary endothelial cells and capillary cavity narrowing, causing circulatory disturbance. This case conformed to the above imaging features. At present, for patients with hypoglycemic encephalopathy, intravenous glucose should be given immediately to quickly and effectively correct hypoglycemia. Then, we should repeatedly monitor blood glucose to keep blood glucose within the normal range. Some studies have suggested that hypoglycemic brain neuronal death is not the result of fuel deprivation but is in fact induced by neuronal nicotinamide adenine dinucleotide phosphate oxidase activation during glucose reperfusion. Therefore, therapeutic hyperglycemia should be avoided.^[5]

The blood glucose level of this patient at presentation was 4.01 mmol/L, which is within the physiological range. However, the blood glucose level found in our neurology department was 0.03 mmol/L. Stress reactions can lead to increased epinephrine, adrenaline, and glucagon, promoting liver glycogen decomposition. Then, the blood glucose levels are elevated reactively. Therefore, for patients in a coma, blood glucose should be measured repeatedly to avoid delaying the diagnosis and treatment of hypoglycemic encephalopathy. Hypoglycemic encephalopathy often involves the cerebral cortex, basal ganglia, and corpus

callosum. In clinical practice, if lesions occur in the above areas and do not conform to a specific cerebral arterial distribution, the possibility of hypoglycemic encephalopathy should be considered. In elderly patients, hypoglycemic encephalopathy is often caused by the overuse of glucose-lowering medications. However, in adolescents, the possibility that the patient took drugs or poisons for suicide should be considered.

Declaration of patient consent

The authors certify that they have obtained the patient consent forms. In the form the patient's parents have given their consent for the patient's images and other clinical information to be reported in the journal. They understand that the patient's name and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflicts of interest

None.

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