CASE REPORT e-ISSN: 2349-0659 p-ISSN; 2350-0964

Hypoglycemic Encephalopathy – A Case Report and Review of the Literature

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Abstract

Glucose is an essential carbohydrate for brain function. Even a short-lasted acute drop in its levels can result in cerebral dysfunction and even death. Early treatment of and decreasing duration of hypoglycemia episodes increases life expectancy and improves the level of consciousness. Furthermore, pharmacological symptoms' management should be continued for at least 2 weeks after hospital admission aiming to preserve the integrity of brain function and the wider well-being of patients.

Keywords: Cerebral dysfunction, Glucose, Hypoglycemia, Mortality

Asian Pac. J. Health Sci., (2023); DOI: 10.21276/apjhs.2023.10.4.02

Introduction

Hypoglycemic episodes are rarely life-threatening or associated with neurological damage. However, frequent and intense episodes of hypoglycemia can cause a variety of symptoms from neurological deficits to coma.[1]

Emergency hypoglycemia (glucose [Glu] value <50 mL/dL) is associated with the induction of hypoglycemic encephalopathy, a syndrome that requires immediate treatment. The clinical outcome and the lesions displayed in magnetic resonance imaging (MRI) vary from patient to patient, from fully reversible neurological deficits to death.[1]

In this article, we present a case report of a 78-year-old woman who developed hypoglycemic encephalopathy and review the relevant literature.

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How to cite this article: Myrou A, Aslanidis T, Kiouli C, Kachtsidis V, Kosmidis G, Chatzintounas A, Theodoridis A. Hypoglycemic Encephalopathy – A Case Report and Review of the Literature. Asian Pac. J. Health Sci., 2023;10(4):7-10.

Source of support: Nil.

Conflicts of interest: None.

Received: 11/09/2023 **Revised:** 12/10/2023 **Accepted:** 17/11/2023

Case Description

A 78-year-old, non-smoking female patient with a history of insulin-dependent diabetes mellitus (DM) type 2, arterial hypertension, and diaphragmatic hernia was presented to the emergency department of the University General Hospital of Thessaloniki AHEPA with focal epileptic seizures mainly at the upper extremity, decline in level of consciousness, and a score at the Glasgow coma scale (GCS) of (E2/V2/M4). The patient was found unconscious (no information on the duration with loss of consciousness) by her relatives and caffeine-like vomiting was reported.

On clinical examination, the patient's vital signs were within normal limits with values: BP 120/75, SpO_2 91%, HR 90/min (with normal electrocardiogram), and temperature 36°C. On lung auscultation, there were rhonchi sounds bilaterally. Abdominal examination revealed slightly decreased enteric sounds. A neurological examination was also performed. However, a glucose value <13 mg/dL was found. A brain computer tomography was performed which did not show any abnormal findings.

The patient was placed on $D_{10}W$ civ. Due to continuous vomiting, a nasogastric tube was set and suctioning was performed. After initial stabilization, the patient was admitted to the department of internal medicine. In the following hours, ceftriaxone 2 g × 1 IV, clindamycin 600 mg × 3 IV, gastric protection (omeprazole 40 mg × 1 IV) enoxaparin 4.000 IU × 1 s, and levetiracetam 1 g × 2 IV were administered. Despite dextrose solution continuous administration, a hypoglycemic episode re-emerged after admission and the patient experienced a tonic-clonic (grand mal) seizure lasting 3 min and a decrease in GCS (E1/V1/M1). The patient was intubated and was admitted to the intensive care unit (ICU), where she was put on sedation and mechanical ventilation.

One day later, MRI of the brain was performed which showed diffusely increased MR signal on T2 and fluid-attenuated inversion recovery sequences of the basal ganglia and gray matter, with limited diffusion on diffusion-weighted imaging (DWI) sequences and no enrichment of these lesions after the administration of a contrast agent which led to the conclusion of hypoglycemic encephalopathy [Figure 1]. Six days later, the patient underwent percutaneous tracheostomy. Seven days later, percutaneous endoscopic gastrostomy was placed, and a chest X-ray showed bilateral lung infiltrates.

On discharge from the ICU, 10 days after admission to hospital, the patient was placed on Home Ventilator (IPAP = 18, EPAP = 5, FiO_2 55%) and a GCS E1/V1T/M1.

Electroencephalography (EEG) was in accordance with MRI findings: Burst suppression with in a nearly flat EEG, very low amplitude, and reactivity in pain and sound stimuli [Figure 2].

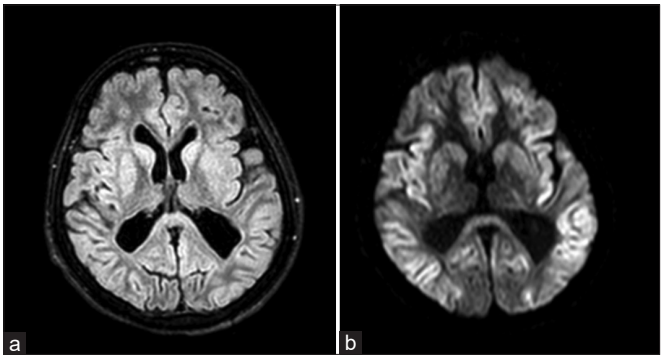

Figure 1: (a) Fluid-attenuated inversion recovery sequence after the intravenous administration of a contrast agent showing increased signal intensity of the basal ganglia and gray matter. (b) Diffusion-weighted magnetic resonance (MR) imaging of the brain showing enhanced MR signal of the basal ganglia and gray matter (Reil island, temporal, frontal, and parietal)

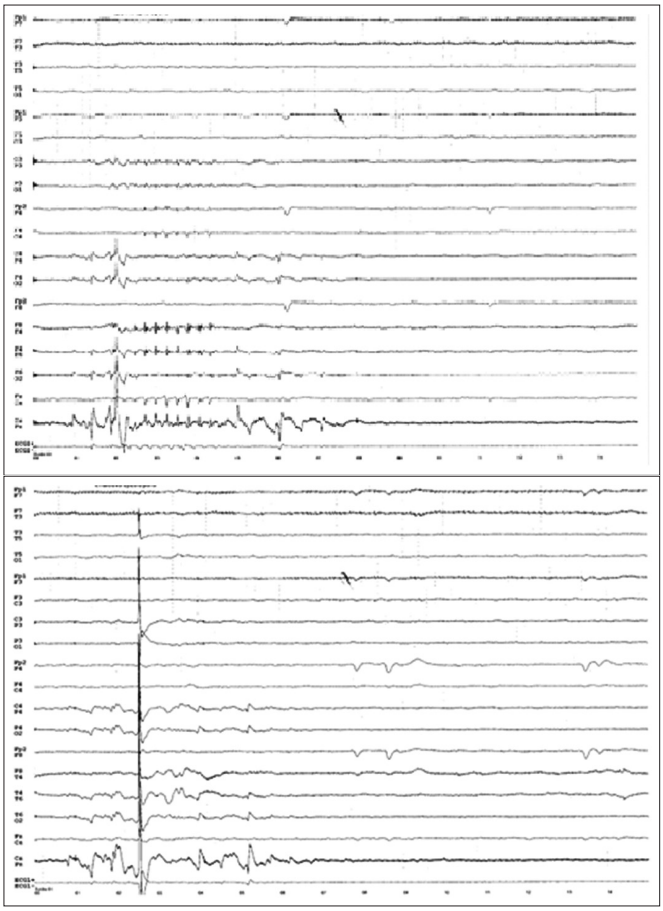

Figure 2: Electroencephalography screenshots of sound (above) and pain (below) stimuli. Finding revealing a severe diffuse encephalopathy

Three days later, the patient referred to a rehabilitation center with a Glasgow outcome coma scale score 2, and a modified Rankin scale (mRS) of 5.

Discussion

Hypoglycemic episodes are seen in patients receiving insulin or insulin-secreting drug treatment for the treatment of DM and are the most important and common complication in its treatment.[2] The incidence of hypoglycemia in DM2 is much lower than in DM1.[2] Hypoglycemia is more frequent in patients treated with sulfonylureas, especially long acting or meglitinides. Antidiabetic drugs such as metformin, alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, and sodium glucose cotransporter 2 (SGLT-2) inhibitors do not cause hyperinsulinemia and, therefore, do not cause hypoglycemic episodes. The risk of hypoglycemia is only increased when they are administered with insulin or insulin-secreting drugs.[2]

A sudden drop in the levels of glucose in the bloodstream can occur due to an overabundance of insulin from external or internal sources, as well as the use of drugs that induce hypoglycemia. This results in a reduction in the activity of the ATPase pump in cell membranes and the release of stimulating neurotransmitters like aspartate.[3,4]

Severe hypoglycemia is associated with a risk of hypoglycemic encephalopathy which is defined as an acquired metabolic syndrome with glucose levels <50 mL/dL, a comatose state that persists for ≥24 h despite improvement in blood glucose levels and has excluded any cause from which this state results.[5] In hypoglycemic encephalopathy, the main pathological disorders involve denaturation and neuronal necrosis due to lack of energy.[5] The clinical manifestations of hypoglycemia are determined by the extent, speed, duration, and responsiveness of blood glucose levels.[5] Severe hypoglycemia displays HE as a notable clinical characteristic. HE may manifest as seizures, coma, or focal neurologic deficits, often leading to misdiagnosis as stroke or other neurologic disorders.[1]

As far as, our case is concerned, the initial symptoms that appeared were focal epileptic seizures mainly at the upper extremity, decline in level of consciousness, and a score at the GCS of E3/V2/M4 which, in combination with the finding of hypoglycemia, led us to suspect hypoglycemic encephalopathy.

Witsch *et al*.[1] reported results from studies evaluating the outcome of patients with hypoglycemic encephalopathy. The appropriate diagnostic criteria they recorded were the following:

1. Rankin scale (mRS)
2. Glasgow scale (GOS) and finally
3. Barthel index (BI).

Fifteen patients with a mean age of 60 years (range 29–79) were included in his study. Two patients dropped out. Of the remaining 13 patients, 6 patients died (46%). In the seven survivors, the mean mRS scale score was 0 (range 0–5), the mean GOS scale score was 5 (range 2–5), and the mean BI score was 100 (range 0–100). The results suggest that mortality rates were high, but long-term survival with little or no disability appeared to be possible and can be observed in most survivors.[1]

The anatomical brain structures most affected due to low glucose levels are the cerebral cortex, hippocampus, cerebellum, nucleus accumbent, parts of the corpus callosum, thalamus, hypothalamus, brain stem, and cranial nerve nuclei.[5] In our case, the affected areas coincide with those found in the literature (basal ganglia and gray matter-Reil island, temporal, frontal, and parietal).

For early diagnosis and treatment of patients with cerebral dysfunction, blood glucose monitoring should be performed. Diabetic patients need to take adequate hypoglycemic agent. Furthermore, regular monitoring of blood glucose levels is

necessary to prevent hypoglycemic episodes.[6] Ikeda *et al*.[7] conducted a study to investigate factors that predict poor prognosis in patients with hypoglycemic encephalopathy. According to the study, prognostic factors that predict poor outcome in patients with hypoglycemic encephalopathy are prolonged hypoglycemia, normal or higher body temperature, and low lactic acid level in the presence of a hypoglycemic episode.[7]

Prognostic factors for HF were investigated by Lee *et al*.[8] in 44 patients to determine when treatment of HF is deemed ineffective. The functional outcome of the patients was assessed using the GOS scale. Their results showed that patients with short-term hypoglycemia had an improved level of consciousness and a lower incidence of brain damage, in contrast to patients who did not show an improved level of consciousness. Furthermore, hypoglycemic brain damage detected on initial MRIs predicted a worse prognosis of YE. However, treatment should be provided for at least 14 days after admission.[8]

Sangare *et al*.[9] conducted a cohort study in 20 patients to describe the neurological outcomes in patients with hypoglycemic encephalopathy hospitalized in ICU. Their results showed that the overall prognosis of patients with severe hypoglycemic encephalopathy was negative as after 2 years 75% of patients died. Only a small percentage of patients improved haltingly after discharge from the ICU. Notably, patients who did not improve in the first 6 months did not regain consciousness.[9]

The diagnosis of hypoglycemia is fundamental for the selection of appropriate treatment to prevent its recurrence and to prevent a serious CNS disorder.[10] Blood sampling is required while symptoms are present; if clinically suspected and if possible before glucose is administered to objectively record glucose levels. In diabetic patients, blood tests should include measurements of insulin, C-peptide, sulfonylurea, cortisol, and ethanol levels. In the absence of documented spontaneous hypoglycemia, overnight fasting or food deprivation during outpatient follow-up will sometimes reveal hypoglycemia and allow diagnostic assessment.

In addition, radiological examinations also become important for the diagnosis of HC. Computed tomography may demonstrate enhancing hypodensities in the basal ganglia, cerebral cortex, hippocampus, and medulla oblongata.[4]

MRI is a highly sensitive imaging technique that reveals T2 hyperintensities and limited diffusion in specific brain regions, including the posterior limb of the internal capsules, hippocampi, basal ganglia, cortical areas, and splenium of the corpus callosum. These observed changes likely indicate the presence of cytotoxic edema. Extensive DWI alterations in the basal ganglia and deep white matter are closely linked to unfavorable clinical outcomes.[4] In contrast to stroke, these lesions typically do not follow the pattern of arterial distribution and can be reversed by restoring the blood glucose levels to normal.[11]

Finally, in patients with diseases affecting the hippocampus such as YE, DWI appears to be useful in differentiating between underlying pathologies and may facilitate a definitive diagnosis conducive to optimal treatment.

To prevent hypoglycemia, treatments that do not lead to hyperinsulinemia and predispose to hypoglycemia should be selected The antidiabetic drugs chosen should be those that sensitize the beta-cell to insulin secretion while not preventing glucagon secretion during hypoglycemia (DPP-4 inhibitors and GLP analogs) or those that sensitize the action of insulin (metformin and SGLT2 inhibitors). Furthermore, insulin secretagogues tablets (sulfonylureas and meglitinides) should be avoided.[2]

Furthermore, important is the contribution of long-acting insulin analogs in reducing the incidence of severe hypoglycemia, during the night. On the other hand, the use of rapid-acting insulin analogs offers a modest effect on the incidence of severe hypoglycemia, but contributes significantly to the reduction of nocturnal hypoglycemic episodes.[2]

The role of continuous glucose monitoring systems is becoming yet another method for patients and clinicians in managing type 2 diabetes. In the treatment of insulin-dependent diabetes, as the frequency of 24-h glucose determinations increases, metabolic control improves and the frequency of hypoglycemia decreases. In a clinical setting, the utilization of Continuous Glucose Monitoring (CGM) as a model for loaner distribution facilitates intermittent usage. Alternatively, patients can own a CGM system for home use, providing real-time glucose readings (Real-time CGM). This empowers individuals to promptly assess glucose levels and take timely measures to prevent impending hypoglycemia.[2]

In patients with loss of consciousness or severe dizziness, the use of glucagon to increase blood glucose levels is preferred.[2]

Severe hypoglycemia is treated by administering 1 mg of glucose subcutaneously. As soon as the patient regains consciousness, oral glucose should be given. In a prolonged hypoglycemia where hepatic glycogen stores have been depleted, administration of glucagon is ineffective. For this reason, an initial dose of 0.5 mg is often preferred. The dose may be repeated for 1–2 more times at 20-min intervals.[2]

In prolonged hypoglycemia, 10–30 g of glucose, in $D_{35}W$ solution, is administered intravenously iv in combination with continuous intravenous infusion of glucose solution.[2]

In cases of coma due to possible cerebral edema, oxygen is administered, and glucocorticoids and osmotic diuretics of the mannitol type may be required. Conditions arising from the use of sulfonylureas require special attention as hypoglycemic episodes may be prolonged and recurrent. In these dangerous cases, continuous intravenous infusion of D_5W for at least 12–72 h is required.[2]

Conclusion

Hypoglycemic encephalopathy is a potentially life-threatening condition that may have devastating neurological effects. Proper, early management of hypoglycemia is critical for the prevention of such conditions.

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