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Case report

Case report- sulfonylurea poisoning mimicking vertebrobasilar acute ischemic stroke

Kamila Kędra[1], Izabela Michalik[1], Michał Oleszko[1], Marcin Wiącek[1]

Department of Neurology, Institute of Medical Sciences, Medical College of Rzeszow University, 35-301 Rzeszow, Poland

Abstract: *Background*: We report the case of sulfonylurea induced hypoglycemia manifesting as acute encephalopathy with focal neurological signs misdiagnosed as posterior circulation acute ischemic stroke (AIS) and discuss the potential effects of hypoglycemia on central nervous system, as well as its differentiation from AIS. *Case presentation*: A 64-year-old patient with type II diabetes treated with glimepiride was transferred to the Department of Neurology after the procedure of radical prostatectomy. On admission, the patient was unconscious with four limb paresis and bilateral Babinski sign. Non-contrast head CT and CT angiography vessels did not reveal any abnormalities. Due to exceeded therapeutic window the patient was disqualified from intravenous thrombolysis. At the admission hypoglycemia was observed and promptly corrected with the 5% dextrose infusion. For the next 72 hours repeated intravenous glucose infusions were needed to maintain its levels above 70 mg/dl. Based on the absence of ischemic changes on MRI and repeated decreases in glucose level for the next 3 days, glimepiride induced hypoglycemic encephalopathy was diagnosed. Within 24 hours of admission the patient regained consciousness and eventually presented four-limb paresis as a result of prolonged neuroglycopenia. *Conclusions:* Prolonged insufficient brain nutrition can result in permanent or long-lasting brain damage, manifesting as impaired consciousness and focal neurological signs. Perioperative sulfonylureas intake may result in prolonged hypoglycemia.

Keywords: sulfonylurea-poisoning; neuroglycopenia; tetraplegia; hemiparesis

1. Introduction

Hypoglycemia is defined as a plasma glucose level below 70 mg/dL however may manifest itself without any symptoms until the level drops below 55mg/dL. The brain requires a constant supply of glucose, therefore interruptions in its supply may result in neurological complications. [1] Depending on blood glucose levels, hypoglycemia can affect the brain in different ways. Autonomic symptoms such as irritability, sweating, and dizziness were noted at blood glucose levels of 68 mg/dL, while more severe neurological symptoms such

as seizures, confusion, and paresis were observed at levels of 50 mg/dL. Below this measure, hypoglycemic coma has been observed as well as neuronal death causing irreversible changes in the brain at the level of 18 mg/dL of blood glucose [2]. Hypoglycemia may be caused by different factors, such as alcohol intoxication, paraneoplastic syndromes, antibiotics (e.g., fluoroquinolones) or endocrinopathies. However, antidiabetic medication, especially oral sulfonylureas or insulin remain its most common cause [1]. Sulfonylureas were discovered in 1942 as sulfonamide antibiotics with a side effect of inducing hypoglycemia in animals. In the following years, there was an intensive development of this group of drugs and the glycemic-lowering effect became mainly used in medicine. [3] However, their use poses a risk of hypoglycemia, which in some cases can lead to neuroglycopenia that can be manifested as focal neurological signs [4]. Some studies show that oral hypoglycemic agents are the most common exogenous cause of hypoglycemia among elderly [5]. Additionally, among this group acute onset of focal signs due to hypoglycemia can easily be misdiagnosed as cerebrovascular accident, especially in those with cardiovascular diseases [6] According to the studies hypoglycemia may create some diagnostic difficulties in clinical practice as it can manifest itself as a wide spectrum of symptoms ranging from mild dizziness to hemiparesis or hypoglycemic coma. Some studies showed that the diagnosis of neuroglycopenia is particularly problematic in comparison with AIS, as it may also present changes in imaging studies. Some studies reported hypoglycemic hemiparesis (HH) as a distinct diagnostic challenge. HH usually occurs at blood glucose levels of ≤1.8 mmol/L (32.4 mg/dL) and the possible etiology of its formation is asymmetric cerebral blood flow, cerebral vasospasm, and selective neuronal vulnerability. According to studies there are not any methods that could lead to definite diagnosis, especially when the lesion is unilateral, focal and and corresponding to hemiparesis. In radiological studies, common areas of HH changes,that usually resolve after 10 days, are the hippocampus, basal ganglia insular cortex, corona radiata, and splenium. Additionally, cases of neuroglycopenia observed in the therapeutic window, which remain hard to diagnose reversible mimics of stroke, have been described [2,7]. To date, only a few cases of hemiparesis or tetraplegia caused by hypoglycemia associated with sulfonylureas were reported. Only one case with persistent neurological deficits after glucose level normalization and 1 case of tetraplegia after taking sulfonylureas, which disappeared after administration of glucose were described [8]. Hemiplegia induced by hypoglycemia usually disappears immediately with the administration of intravenous glucose, however in our case permanent neurological changes have remained [9].

Our purpose was to emphasize the role of antidiabetic drugs as the probable cause of hypoglycemia, which can manifest itself under the mask of severe neurological conditions such as paresis and leave permanent neurological deficits. We also want to highlight the role of quick diagnosis by differentiating hypoglycemia from ischemic stroke in order to quickly implement proper management in order to reduce a patient's disability.

2. Case Report

A 64-year-old patient with diabetes, type II, treated orally with Glibetic 2x2 mg and Siofor 2x500 mg was transferred from the Department of Urology to the Department of Neurology after the procedure of radical prostatectomy. On admission, the patient was unconscious with the return of the eyeballs on top, four-limb paresis, four-limb reaction in pain test extension, Babinski's symptom was positive on both sides. In CT of the head and angio-CT of the cerebral vessels no abnormalities have been found. Due to the exceeded therapeutic time window (>4,5 h) the patient was disqualified from reperfusion therapy and from thrombolytic treatment because of the lack of the closure of large vessels (basilar artery).

Based on the clinical trials data (neurological examination, emergency) the patient has been diagnosed with a brain stem ischemic stroke. In laboratory tests, the low level of glucose (46%) attracted attention. Despite the continuous infusion of glucose, the 5% level first, followed by the 10% level, blood glucose level was still under 70 mg/dL - therefore 20% and 40% infusions of glucose were used. By continuing the glucose infusion for the next 24 hours, blood glucose level ranging from 90 to 210 mg / dL was achieved. The next day, the measured blood glucose value reached a maximum level of 276 mg / dL. Small doses of insulin were applied, followed by the glucose values ranging between 180-230 mg /d. In a double MRI of the head performed on the second and seventh day after admission no fresh ischemic lesions were found. Therefore ischemic stroke was excluded. Based on the absence of ischemic changes in MRI performed twice and repeated reductions in glucose levels for 3 days, hypoglycemic encephalopathy was diagnosed as a result of glimepiride poisoning.

Within 24 hours, the patient regained consciousness and was agitated. A week later, the patient opened his eyes in response to pain and took a standing position. Four-legged paralysis was more pronounced on the left side and a positive Babinski’s sign on the left side- clinically presented symptoms of prolonged encephalopathy neuroglycopenia. More than a month after the start of hospitalization, the patient was conscious, selectively complied with the instructions, slight tetraparesis persisted, Babinski’s sign was absent. The patient was moving with security and glycemia remained normal.

4. Discussion

We present the first case of sulfonylurea-induced hypoglycemia tetraparesis that has not been resolved despite proper treatment. According to literature, approximately 200 cases of hypoglycemia induced hemiparesis [10], of which 10 occurred with the use of sulfonylureas, have been published. [11- 20]. One case of hemiparesis appeared with tolbutamide [11], four with glibenclamide [12-14], three with glyburide [16-18] and two with gliclazide treatment [19-20]. Only one case of tetraplegia after sulfonylureas was reported, however, in comparison to our case, neurological deficits disappeared after proper glucose level was restored. [11-21]. Only one case study described an incident of hypoglycemia imitating cerebellar AIS in a 55-year-old diabetic woman with sudden onset of unilateral cerebellar symptoms treated with glibenclamide [14]. Most of the neuroglycopenia cases were caused by sulfonylureas in the standard dose and one of them was an attempted suicide with 30 tablets of 75 mg glybenclamide [15]. Out of 10 cases of hemiparesis after hypoglycemia, only one case described a child (a 6-year-old took her grandmother's medications) [16]. It was reported that glibenclamide can cause hypoglycemia that lasts up to 60 hours, especially in elderly, who often suffer from kidney and liver diseases, which can result in prolonged glibenclamide's half-life ranging from 10 to 16 hours [21]

In 2013, 3950 sulfonylurea exposures were reported to the US National Poison Data System (NPDS), of which 1590 (40.2%) were single substance exposures and adults accounted for 45.2% of sulfonylurea exposures [22,23]. Sulfonylurea agents were also described as medicines able to rarely cause dermatologic side effects, for example erythroderma and photosensitivity. Furthermore chlorpropamide is able to lower serum sodium concentration and its combination with Moduretic (amiloride plus hydrochlorothiazide) can lead to even greater risk of hyponatremia [24]. There have also been reports of possible hepatotoxicity of glimepiride including hepatitis with cholestasis [25-28]. Occasional hematological disorders, such as leukopenia, haemolytic anemia and thrombocytopenic purpura were described to occur within the use of sulfonylureas. However, according to published studies, the most common adverse event associated with sulfonylureas remains hypoglycemia [29].

Reduced glucose level may clinically manifest itself in two mechanisms: neurogenic or neuroglycopenic. Symptoms of the neurogenic form may result from both the activation of the adrenergic system (including anxiety, tremors, palpitations) and the cholinergic system (including paresthesias, hunger, diaphoresis). In turn, the signs and symptoms of neuroglycopenia result directly from glucose deprivation of the central nervous system. These symptoms and signs arise in response to a release of norepinephrine or acetylcholine in reaction to perceived hypoglycemia. In turn, neuroglycopenia signs and symptoms result directly from reduced levels of glucose accessible to the central nervous system. According to the literature, the manifestations of neuroglycopenia include symptoms such as: headache, confusion, drowsiness, seizures, asthenia and coma [1]. Sympathetic nervous symptoms and impaired consciousness are the most common manifestations of hypoglycemic attack, while hemiparesis is rare (7 of 168 cases- 4,2%) and it is frequently overlooked [9]. In one study Renee Malouf has described a study of 125 visits in Harlem Hospital for symptomatic hypoglycemia, where 3 of admitted patients have presented sudden hemiparesis and stroke manifestation was suspected at first [14].

The diagnosis of acute symptomatic hypoglycemic encephalopathy based on clinical and imaging features can be problematic. In approximately 20% of acute hypoglycemia cases, the imaging features on DWI sequence were similar to those of ischemic stroke and this can cause diagnostic difficulties [30-32]. It was suggested that in hypoglycemic encephalopathy right-sided hemiparesis predominates [33] and the abnormalities can be found in the internal capsule or the splenium of the corpus callosum on imaging. Within 22 cases report published, in 13 (65%) CT, SPECT, DWI or MRI revealed abnormal findings of the contralateral side or both sides of the internal capsule and in 6 (30%) in the splenium of the corpus callosum [34,35]. However, in our case head CT performed on the admission day and two days later have not revealed any ischemic lesions.

Moreover, hypoglycemia may not only mimic an ischemic stroke, but also increase its risk. According to studies hypoglycaemia accelerates vascular complications in diabetic patients by increasing platelet aggregation, fibrinogen formation and inhibiting fibrinolysis. Recurrent, transient hypoglycemia may additive to the inflammatory process, including atherosclerosis through increased secretion of IL-6, IL-8, Il1B, lipid peroxidation, increased levels of the tumor necrosis factor and other proinflammatory mediators [36-38]. Particularly increased activation and aggregation of platelets may contribute to ischemic stroke of the large vessel type [39]. One cohort study reported an association in patients treated with sulfonylureas between

hypoglycaemia and stroke. The increasing incidence of hypoglycaemia was associated with an increased risk of stroke, with the strongest association with 3 or more hypoglycaemic events (RR = 1.57). Major hypoglycemia was strongly combined with stroke, while the association was weakened or not associated with mild hypoglycemia [40].

5. Conclusion

Hypoglycemia may manifest with autonomic symptoms, seizures, headache, confusion, asthenia and more rarely with focal neurological signs such as hemiparesis or dysarthria that may suggest AIS. According to literature, it seems that cerebral vasospasm, asymmetric cerebral blood flow, and selective neuronal vulnerability are the cause of hypoglycemic hemiparesis [1] and it may be impossible to distinguish transitional hemiparesis from hemiparesis as a stroke manifestation by MRI imaging in some cases. It is therefore crucial to measure glucose level, while stroke-like symptoms occur. Neuroglycopenia induced focal signs are potentially reversible with prompt glycemia correction. In our case despite restoration of normal glucose levels, permanent neurological signs have remained.

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