

# ACUTE PULMONARY EDEMA AND INSULIN-INDUCED HYPOGLYCEMIA IN A NON-DIABETIC SUBJECT

**Catalina Lionte, Laurentiu Sorodoc, Victorita Laba**

## REZUMAT

Asocierea dintre edemul pulmonar acut și hipoglicemie este bine documentată și descrisă în literatură, deși se întâlnește rar în practică. În ultimele decade au fost publicate doar câteva cazuri și de aceea considerăm că descrierea unui nou caz poate fi relevantă, împreună cu discuția mecanismelor implicate. Prezentăm în continuare un caz de hipoglicemie severă indusă de insulină la un subiect tânăr, nediabetic, care a încercat să se sinucidă și care a fost internat în comă, cu convulsii și edem pulmonar acut. Datorită diagnosticului corect și a tratamentului intensiv pacientul și-a revenit complet.

**Cuvinte cheie:** edem pulmonar, hipoglicemie insulinică

## ABSTRACT

The association between acute pulmonary edema and hypoglycemia is well documented and described in literature, although rare in clinical practice. Only few reports of this association have been published over last decades, so we consider that the description of a new case may be relevant, together with the discussion of the mechanisms involved. We hereby present a case of severe insulin-induced hypoglycemia in a young non-diabetic subject in an attempted suicide, who was admitted with coma, seizures and pulmonary edema. Through accurate diagnosis and intensive care, the patient recovered completely.

**Key words:** pulmonary edema, insulin-induced hypoglycemia

## INTRODUCTION

Non-cardiogenic acute pulmonary edema secondary to hypoglycemia was described by Ortega and his colleagues<sup>1</sup> in order to remind the clinicians this well-known association, which has been mentioned in the literature for several decades.<sup>2,3</sup> Few cases were reported over the years with this association, so we considered useful to describe a case of severe insulin-induced hypoglycemia in a non-diabetic subject, who had a favourable outcome after establishing a rapid diagnose and intensive care.

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Department of Internal Medicine, Grigore T. Popa University of Medicine and Pharmacy; Medical Clinic, Emergency Clinic Hospital, Iasi, Romania

Correspondence to:  
Catalina Lionte MD, PhD, Medical Clinic, Emergency Clinic Hospital, Gen Berhtelot Str. 2, 700483 Iasi, Tel: +40-232-226-144  
Email: clionte@yahoo.com

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Received for publication: Nov. 24, 2003. Revised: Jul. 02, 2004.

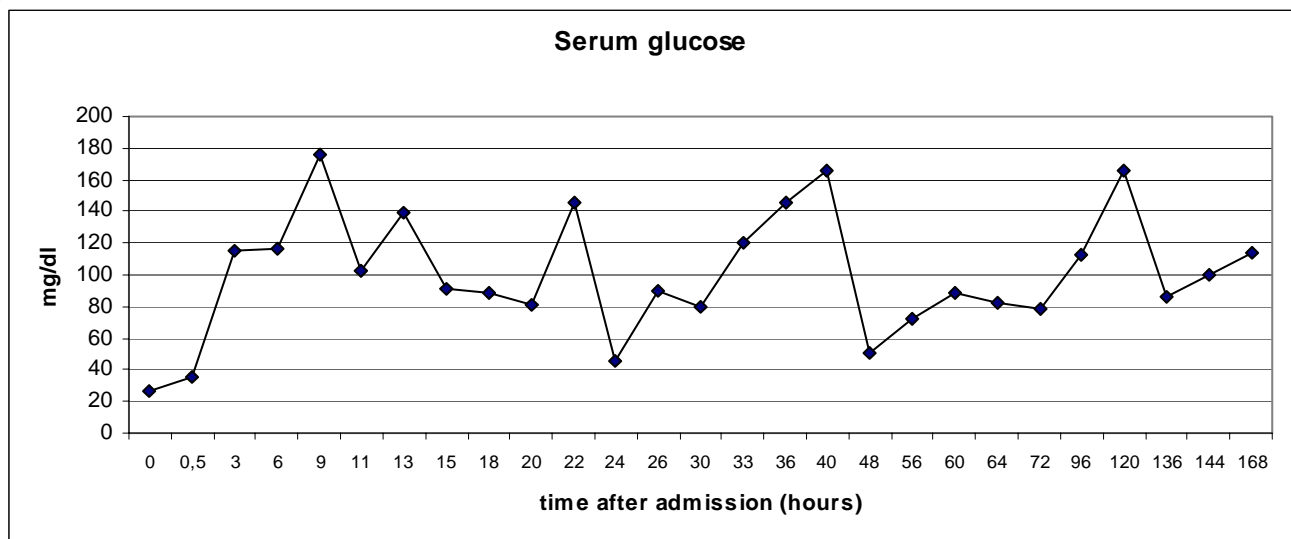
## CASE REPORT

A 34-year-old woman with psychiatric history and previous attempted suicide with antidepressants acute poisoning was brought to emergency room (ER) presenting coma associated with generalized seizures. She was found unresponsive in her office. Her mother had diabetes mellitus treated with insulin. On arrival at ER she was comatose (GCS 6-7), equal pupils that were sluggishly reactive and 6 mm in diameter, hyper-reactive tendon reflexes, Babinski sign bilateral present. Her skin was dry, with puncture signs on her right arm, cyanosis of the extremities, bitten bleeding tongue, and trismus. Vital signs were as follows: blood pressure 150/85 mmHg, heart rate 150/min, dyspnoea, 32 breaths/min, blood-tinged expectoration and rales of various frequency over the lungs. The rest of clinical examination was unremarkable. Laboratory findings were as follows: serum glucose 26 mg/dl, arterial pH 7.26, PaO<sub>2</sub> 48 mmHg, PaCO<sub>2</sub> 33.5 mmHg, HCO<sub>3</sub> 23 mEq/l, with SaO<sub>2</sub> 84% at room temperature, sodium 137 mmol/l, potassium 3.9 mmol/l, with BUN, creatinine, cardiac and liver enzymes within normal

range. Blood and urine toxicological screens showed: blood alcohol 227 mg/dl, salicylates, Isoniazid, cocaine and barbiturates negative, serum cholinesterase normal, and organo-chlorate pesticides also negative. Other tests: ECG – sinus tachycardia, chest X-ray revealed changes characteristic for pulmonary edema and a normal heart shape and dimensions. Fundoscopic examination was normal, cerebrospinal fluid and EEG (in absence of convulsions) showed no abnormalities. Thus we excluded other toxic causes of coma associated with generalized seizures and pulmonary edema (barbiturates, tricyclic antidepressants, Isoniazid, salicylates, propranolol, cocaine, pesticides), or neurological causes (epilepsy, brain tumor, rupture of cerebral aneurysm).

Once the diagnosis of “Acute pulmonary edema secondary to insulin-induced hypoglycemia” in a non-diabetic patient was established, treatment was started (oxygen therapy, Glucagon 1 mg, bolus of 33% glucose and continuous i.v. infusion of 20% - 10% glucose). Thirty minutes after arrival in ER, when serum glucose was 35 mg/dl, she had generalized seizures that remitted with Diazepam, and then she was admitted in intensive care unit (ICU). The patient improved steadily with this treatment, after 3 hours regained consciousness and declared suicidal attempt with self-administration of Insuman® Basal and Insuman® Comb 25/75 after drinking alcohol. She was discharged from ICU 24 hours later with normal chest ray, blood gases and glycemia. During hospitalization she was monitored for serum glucose (Fig. 1) and showed neither clinical nor biological signs of infection. The outcome of our patient was good, without neurological sequelae. After seven days, she fully recovered and was sent for psychiatric evaluation.

**Figure 1.** Evolution of serum glucose with continuous i.v. Glucose and normal food intake.



## DISCUSSION

Acute pulmonary edema (APE) is defined as an abnormal and acute accumulation of fluid in the extravascular compartments of the lung. APE can be divided into four main categories on the basis of pathophysiology: increased hydrostatic pressure edema, permeability edema with diffuse alveolar damage, permeability edema without diffuse alveolar damage, and mixed edema due to simultaneous increased hydrostatic pressure and permeability changes.<sup>4</sup> This classification scheme is helpful because pulmonary edema is often seen especially in the ICU and ER. Among causes responsible for the development of APE, the most frequent are cardiovascular diseases accompanied by left ventricular failure, hypervolemia, acute and chronic renal diseases, and infections with considerable toxemia. Neurogenic pulmonary edema (NPE), first described in 1908 by Shanahan, is seen in up to 50% of patients who have suffered a severe brain insult such as trauma, subarachnoid hemorrhage, stroke, or status epilepticus.<sup>5,6</sup> Less frequent causes associated with NPE are chemical, physical and biological injuries of the lungs associated with barbiturates, morphine, alcohol intoxications, the inhalation of toxic gases or the ingestion of volatile hydrocarbons with subsequent aspiration. The term NPE is reserved for situations when brain injury causes central disorders within vegetative system, excessive release of catecholamines and consequently, overburdening of pulmonary circulation.<sup>7,8</sup>

Insulin-induced hypoglycemia is frequent in clinical practice, because approximately a quarter of diabetics are treated with insulin and hypoglycemia is the most frequent complication of insulin-therapy. People with type 1 diabetes suffer at least one episode of severe hypoglycemia once a year and 2-4% of deaths in this

population have been attributed to hypoglycemia.<sup>9</sup> A ten-year retrospective study of hypoglycemia, performed on 15497 non-diabetic patients with acute poisoning showed 11 cases of insulin-induced hypoglycemia in suicidal attempts. The severity and duration of hypoglycemia is influenced by the type of insulin, its pharmacokinetics, the dose, and route of administration. Alcohol intake influence also the severity of insulin-induced hypoglycemia, being responsible for the most severe cases of hypoglycemia.<sup>10</sup>

Association in our case of severe hypoglycemia and APE in a young non-diabetic patient without significant medical history and favourable evolution of pulmonary edema once the euglycemia is obtained suggest a causal relationship between this two conditions. Reviewing the literature on this subject showed that this association was mentioned in less than 10 articles, 5 of whom published more than 25 years ago. In 1975 Matz describes 2 cases with recurrent postictal noncardiac pulmonary edema in patients with hypoglycemia and epileptic seizures.<sup>11,12</sup> Association between grand mal convulsions and NPE is also mentioned in literature, in more than 40 cases.<sup>13-16</sup> Pulmonary edema is a well described complication of insulin shock therapy for different psychiatric conditions, with a presentation rate of 12% and a mortality of 16%.<sup>2,3</sup> It is of interest to mention that in some patients, episodes of APE were unilateral and later became bilateral, recurrent, sometimes associated with fever and leucocytosis, situation when confusion with pneumonia and aspiration is frequent. Many of cases reported presented, like our patient, uni- or bilateral APE preceded by generalized seizures.<sup>17-21</sup>

Based on literature reviewed, Matz<sup>11</sup> suggested that, in majority of patients, the common pathway to APE in presence of hypoglycemia is having one or more seizures, hypothesis that strongly supports the neurogenic mechanism in development of hypoglycemia-associated pulmonary edema. Thus, sympathetic hyperstimulation as a consequence of disturbances in subthalamic nucleus and hypothalamus induces lymphatic vasoconstriction and platelet aggregation, which causes microemboli. The hydrostatic pressure increases in pulmonary capillaries and in addition, disruption of alveolocapillary membrane damaged by long-lasting hypoglycemias (its integrity depends on glucose metabolism) could explain the development of APE.<sup>1,7,19,22</sup>

Our patient presented a severe insulin-induced hypoglycemia, with convulsivant coma associated with clinical and radiologic signs of APE, which imposed a quick etiologic differential diagnose and intensive care.

Thus, we had to exclude toxic, neurologic and metabolic causes (other than hypoglycemia) of coma associated with seizures. We consider that association of alcohol intake aggravated insulin-induced hypoglycemia. Episode of hypoglycemia documented 24 and 48 hours after admission is probably a consequence of delayed absorption of subcutaneous insulin and it was easy to control, despite the administration of large amounts of insulin. The study of insulin pharmacokinetics in insulin intoxication could be useful to know the necessary duration of exogenous glucose administration required to manage this medical emergency.<sup>23</sup> Clinical symptoms of NPE could be observed a few seconds or minutes after the seizure and withdraw quickly, therefore some patients do not display all the expected symptoms after being transported to hospital, if the seizures are not repetitive.<sup>7,24,25</sup>

The practitioner must be aware of this association and evaluate a comatose patient with generalized seizures both for etiology and pulmonary complications. APE secondary to severe hypoglycemia could be misdiagnosed as aspiration pneumonia, complication that occurs in a comatose patient. In differential diagnosis of this association must be considered acute poisonings, metabolic conditions (diabetes mellitus), infections and neurological diseases.

## CONCLUSION

Association between severe insulin-induced hypoglycemia and APE is rare in clinical practice, but clinician must be aware of this well known complication of hypoglycemic convulsive coma.

APE in severe hypoglycemia occurs as a consequence of neurogenic mechanisms and is preceded by generalized seizures.

Patients do not display all the expected symptoms because of rapid withdraw of clinical findings after the seizure.

Differential diagnose of a comatose patient with generalized tonic clonic seizures and APE must consider toxic, neurologic, metabolic or infectious etiology of this association.

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