Case Report

Capsula Eburnea
a multidisciplinary biomedical journal for young doctors

Case report of one case of hyperinsulinism and hyperammonemia syndrome

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Summary

We describe a case of neonatal hyperinsulinism. A boy suffered from seizures due to hypoglicemia on 6 months after birth. Ammonia level, tested when he was one year old was slightly elevated. He is now ten years old and showed mild but persistent hyperammonemia and frequent hypoglicemia, but he never presented seizures since he was 10 months old. He has also been suffering from mild mental retardation.

Keywords: hyperinsulinism, hypoglicemia, hyperammonemia

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Received: November 29th, 2008
Revised: February 12th, 2009
Accepted: March 3rd, 2009

Language of the Article: English.

No conflicts of interest were declared.

ISSN: 1970-5492

DOI: 10.3269/1970-5492.2009.4.4

Introduction

Hyperinsulinism and hyperammonemia syndrome is a rare disease (1:50000 live births) and it has been reported as a cause of moderately severe hyperinsulinism with diffuse involvement of the pancreas. The disorder is caused by gain of function mutations in the GLUD1 gene, resulting in a decreased inhibitory effect of guanosine triphosphate on the glutamate dehydrogenase (GDH) enzyme, that causes excessive activity of glutamate dehydrogenase, which oxidizes glutamate to alpha-ketoglutarate and which is a potential regulator of insulin secretion in pancreatic beta cells and of ureagenesis in the liver. This simultaneously increases the release of insulin by pancreatic beta cells, with increased volume (1), and impair the detoxification of ammonia in the liver

The phenotypes are clinically heterogeneous, with neonatal and infancy-onset hypoglycemia and variable responsiveness to medical (diazoxide) and dietary (leucine-restricted diet) treatment. Hyperammonemia (2-5 times normal) is constant and not influenced by oral protein, by protein- and leucine-restricted diet, or by sodium benzoate or N-carbamylglutamate administration (2-3).

Case report

The case is an Italian boy who was born at 38 weeks from non consanguineous parents, and his mother was a healty woman with no history of hypoglicemia. On 6 months of age he experienzed convulsion and he was referred to pediatric hospital. In the emergency area his blood glucose level was 16 mg/dl and there was not ketone body in urine test.

He had other hypoglicemic episodes during the admission, so glucagon administration test was per-

formed and blood glucose levels showed tipical pattern of hyperinsulinism raisening from 32 mg/dl to 80 mg/dl, was perfomed. Therapy with diazoxide was started, but was not effective to avoid hypoglicemia. Lukely, he didn't experienced seizures anymore. Ammonia level was tested when he was 12 months old and revealed a slight elevation first, and then a moderate and constant increase (average level was 100 μg/dl), not influenced nor by medical therapy with Na benzoate, or by dietary treatment based on low protein rate and leucine-restricted diet. He is now ten years old and showed mild but persistent hyperammonemia and frequent hypoglicemia, but no seizure, despite his electroencephalogram doesn't showed any sporadic spikes He never underwent anticonvulsant therapy. He has also been suffering from mild mental retardation.

Discussion

The hyperinsulinism-hyperammonemia syndrome is a genetic disease due to mutation of the glutamate dehydrogenase gene on chromosome 10 which leads to disorders both in insulin secretion and in urea excretion. It is characterized by hypoglicemia and hyperammonemia. Frequent finding in the disease is mental retardation, first because of severe hypoglicemia dur-

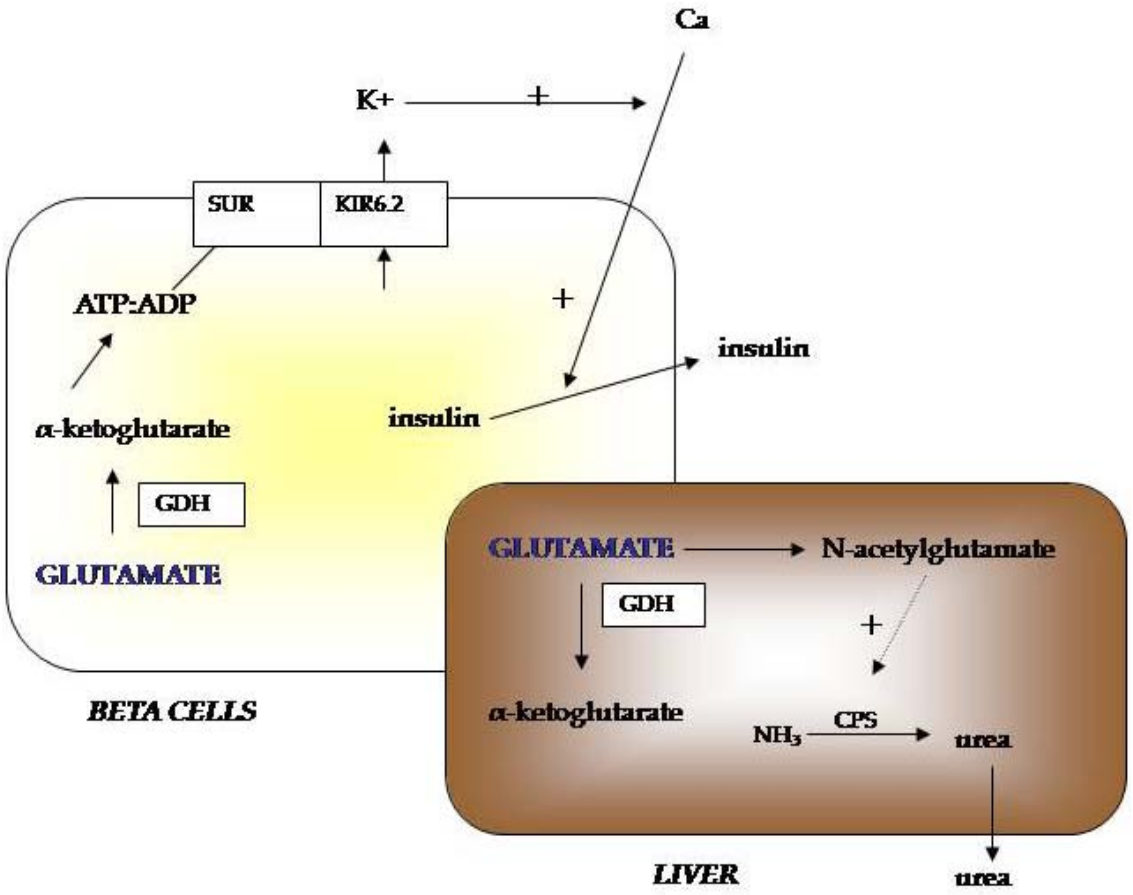

Fig. 1: Glutamate Dehydrogenase (GDH) and the Regulation of Insulin Secretion (Beta cells) and Hepatic Ureagenesis (Liver). Increases in the rate of glucose or glutamate stimulate the secretion of insulin by increasing the ratio of ATP to adenosine 5'-diphosphate (ADP), which causes closure of potassium channels and ultimately leads to the depolarization of beta cells, calcium influx, and the release of stored insulin granules. Leucine stimulates insulin secretion indirectly by allosterically activating glutamate dehydrogenase (GDH) and increasing the oxidation of glutamate by means of the tricarboxylic acid cycle.(6) In the liver, glutamate governs the synthesis of *N* -acetylglutamate, a required allosteric effector of carbamoyl-phosphate synthetase (CPS) the oxidation of glutamate by glutamate dehydrogenase also provides free ammonia derived from the -amino nitrogen of amino acids (7).

ing the neonatal period and because of costant hyperammonemia. Glutamate dehydrogenase plays an important role in the regulation of insulin secretion and in regulating hepatic ureagenesis (4).
Abnormal insulin secretion could be due to increased glutamate oxidation and α-ketoglutarate production that leads to increased production of ATP and closure of K-ATP channel on plasma membrane (5-6). However, further studies of glutamate dehydrogenase in beta cells are necessary to explain other mechanism of hyperinsulinism caused by GLUD 1 mutation.

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UN CASO DI SINDROME DA IPERINSULINISMO-IPERAMMONIEMIA

Descriviamo un caso di iperinsulinismo neonatale di un ragazzo che al sesto mese di vita presentò convulsioni dovute a ipoglicemia. L'ammoniemia, misurata quando aveva già un anno di vita, mostrò un lieve aumento. Il ragazzo, che adesso ha dieci anni, ha sempre presentato iperammoniemia moderata e ha mostrato frequenti crisi ipoglicemiche, sebbene dall'età di 10 mesi non abbia più manifestato convulsioni. In atto soffre di un lieve ritardo mentale.

Keywords: iperinsulinismo, ipoglicemia, iperammoniemia.

CAPSULA EBURNEA, 4(4):1-3, 2009