

## A Neonate with persistent hypoglycemia and seizures .

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### Abstract

A three day old girl presented with repeated episodes of seizures from hypoglycemia hyperinsulinemia a rare disorder was diagnosed and managed with limited success as the episodes hydroglycemic seizures persisted.

### Introduction

Neonatal seizures are a major concern in resource poor countries in terms of investigation and management costs. Some of the common causes of neonatal seizures include neonatal trauma, metabolic disorders and infections. A three day old girl was admitted to the neonatal intensive care unit with repeated tonic-clonic type of seizures following a normal full term delivery. Hypoglycemia of <20mg/dl was confirmed on admission. Full blood count, urine analysis, electrolytes, thyroid and liver function tests were normal. The substrate test for insulin confirmed the presence of hyperinsulinemia as the cause of the hypoglycemic dependent seizures.

### Case Presentation

A three day old girl was admitted to the neonatal intensive care unit because the mother reported a history of convulsion. According to the mother, the baby started to experience a tonic – clonic type of seizure repeatedly.

The infant was born at 39 weeks of gestation to a 26-year-old GII, PII mother after an uneventful pregnancy. The birth weight was 3200gm. The Apgar score was 8-9/10 in one minute. There was no maternal history of gestation or insulin dependent diabetic mellitus.

The blood glucose level measured during admission was 20mg/dl. 50% glucose (2cc/kg) was given followed by 10% glucose (80cc/kg) as maintenance.

The infant has one normal sibling. The temperature was 35 °C. The pulse rate was 123 beats/min and respiratory rate was 60 breaths/min. On examination the infant had normal skin appearance (no cyanosis, rashes or plethora) and was normal for her gestational age. The Moro, grasping and sucking reflexes were all present.

On the second day after admission gentamycin and ampicillin were started and a history of convulsion and RBS <20mg/dl were documented. The following day prednisolone was added on top of the above-mentioned antibiotics and continued for three days and there was slight improvement in the infant's condition with RBS ranging between 54-94mg/dl and as a result the infant was discharged.

One day after discharge the infant was admitted

again with the same complaint of the previous admission having a RBS <20mg/dl, gentamycin and ampicillin were given immediately. The next five days of hospitalization the infant was on glucose maintenance.

On the sixth day of admission prednisolone with 10% glucose were given for five days and prednisolone was replaced with dexamethasone. Hypoglycemia persisted. The infant had several episodes of seizure, each of which lasted for 25 to 40 seconds and was characterized by facial grimaces, twitching of the left eye, and a cat-like scream, followed by tonic-clonic movements of the arms and legs and lethargy of a few minutes' duration.

Nutrition of enriched formula (f-100) of 30cc every 2 hours plus 12% glucose (50cc/24hrs) was given. The infant condition was better and she was discharged with additional formula food. However the infant started to convulse at home ten hours after discharge then she was admitted for further investigation.

On the second admission the C-reactive proteins (CRP), thyroid and hepatic investigations were done and they were within the normal limit. Urine analysis for ketone bodies was negative. USG of the liver and pancreas showed normal size and texture. 300µg/Kg glucagon was administered while the infant's blood glucose was less than 20mg/dl and there was a rise in the blood glucose to 85mg/dl 30 minutes after the administration of glucagon.

Substrate investigation was done for free carnitine concentration 24.7µmol/l (reference range 15-60µmol/l). The acetylcarnitine concentration of 36.5µmol/l (reference range 2.5-30µmol/l) was slightly elevated, but with no indication of fatty acid oxidation disorder.

Finally the insulin level was measured while the newborn was convulsing and having < 20mg/dl blood glucose and it was found to be higher than normal, 94µU/ml (654pmol/l) This strongly suggests hyperinsulinemia.

**Clinical Diagnosis****Neonatal hyperinsulinism.****Discussion**

This newborn had severe hypoglycemia shortly after birth. The glucose level remained low despite vigorous treatment with intravenous glucose and pharmacologic agents. The clinical effect of low blood glucose in children depends on the child's age, the availability of alternative fuels, and the duration of the metabolic derangement. Our initial diagnosis included sepsis, meningitis, and perinatal hypoxia. There were no other signs of infection during the first few hospital days. Although the mother had no history of gestational or insulin-dependent diabetes, we measured her hemoglobin and a random blood sugar, which was within the normal range.

Many factors can contribute to hypoglycemia in infants and young children. Newborns, particularly those born prematurely, may have a developmental immaturity of the enzymes required for gluconeogenesis and ketogenesis.<sup>1</sup> Infants and young children have a higher demand for glucose than do adults, because the brain is proportionately larger and metabolically more active than that of an adult.<sup>1</sup> Finally, familial and congenital hypoglycemic disorders are usually diagnosed early in life.

Hypoglycemia is caused by decreased production or increased use of glucose or possibly both. Normoglycemia is maintained through a complex interaction of substrates, regulatory enzymes, and hormones. A deficiency or excess of any of these can result in a homeostatic imbalance and lead to hypoglycemia. In this case, the onset of hypoglycemia shortly after birth rules out all primary defects in carbohydrate and lipid metabolism as well as growth hormone or cortisol deficiency and sepsis. Because all these disorders result in the depletion or unavailability of liver glycogen, the marked rise in glucose after the administration of glucagon suggests that there is a stored glycogen but not mobilized.

**Hyperinsulinism:**

Hyperinsulinism is a metabolic disorder that affects both glycogenolysis and gluconeogenesis and most common cause of severe hypoglycemia in infants.<sup>1, 2</sup> Hypoglycemia can result from a diminished output of glucose by the liver, as well as inadequate conservation of glucose. A slight increase in insulin suppresses lipolysis and ketogenesis, decreasing the availability of alternative fuels, and results in hypoglycemia.<sup>2</sup> Persistent hyperinsulinemic hypoglycemia is a rare disorder characterized by severe hypoglycemia, inappropriate secretion of insulin, hypoketonemia, seizures, and, if inadequately treated, varying degrees of brain damage.<sup>2,7</sup> An increased level of insulin also inhibits the release of glucose from the liver and enhances the entry of glucose into cells, augmenting hypoglycemia.<sup>1, 3</sup> In this infant, the manifestation of hypoglycemia shortly after birth suggests that hyperinsulinism was probably present before birth. The fetus depends on maternal glucose transported

across the placenta.<sup>4</sup> Fetal islet cells are relatively insensitive to transient changes in glucose levels.<sup>4,5</sup> Chronic hyperglycemia, however, results in increased secretion of insulin.<sup>5</sup> Neonatal hyperinsulinism can be transient, lasting for a few days, or persistent.<sup>1,3</sup> The prolonged duration of hyperinsulinemic hypoglycemia in this infant rules out all forms of transient hyperinsulinism. Persistent hyperinsulinism is caused by an islet-cell adenoma, focal hyperplasia, or diffuse hyperplasia (nesidioblastosis).<sup>1</sup> Adenoma, a common cause of hyperinsulinism in adults, is rare in infants.<sup>1, 2,3</sup> Focal hyperplasia has also been considered unusual in infants.<sup>1</sup> Persistent hyperinsulinemic hypoglycemia is rare in the general population.<sup>8,9</sup> The autosomal recessive form, however, can occur as much as frequently as once per 2675 persons in populations with high rates of consanguinity.<sup>7,8,9</sup> The gene for this disorder is on the short arm of chromosome 11 (11p14–15.1).<sup>8,9</sup> Loss of the maternal allele (11p15), analogous to abnormalities of chromosome 15 in the Prader–Willi syndrome, has been reported in association with the Beckwith–Wiedemann syndrome and focal islet-cell hyperplasia.<sup>1,10</sup> Because hyperinsulinism is relatively mild in patients with the Beckwith–Wiedemann syndrome, its severity in patients with focal hyperplasia suggests that this disorder results from somatic deletion of the maternal allele in the affected islets, in combination with a paternal mutation.<sup>10</sup> Multiple mutations within the gene for sulfonylurea receptor 1 (SUR1) have been identified.<sup>8</sup> Mutations in the Kir6.2 gene also cause persistent hyperinsulinemic hypoglycemia.<sup>8,9</sup> Patients with mutations of either gene have a poor response to treatment with diazoxide.<sup>7</sup>

**Treatment**

Medical treatment of persistent hyperinsulinism is not satisfactory.<sup>7</sup> Large quantities of glucose must be administered intravenously to maintain a relatively normal level. Treatment with diazoxide, which stabilizes potassium–ATP channels in an open state, requires intact SUR1 and Kir6.2 genes.<sup>1,7,9</sup> Therefore, it is not effective in most infants with severe hyperinsulinism.<sup>7</sup> Somatostatin and its synthetic analogue, octreotide, inhibit insulin secretion through hyperpolarization of beta cells, and these agents have been used with some success.<sup>1,7</sup> Because the activation of gated calcium channels, resulting in the influx of calcium into the cell, is a prerequisite for insulin secretion, calcium-channel blockers may also diminish the rate of insulin secretion.<sup>7,9</sup> hyperinsulinemic hypoglycemia in neonates is often caused by focal adenomatous islet-cell hyperplasia.<sup>2</sup> This disorder can be recognized by transhepatic pancreatic catheterization and intraoperative histologic studies and can be treated effectively with partial pancreatectomy, which is effective and carries little risk of causing diabetes mellitus.<sup>2</sup>

Our initial diagnosis included sepsis, meningitis, and perinatal hypoxia. There were no other signs of infection during the first few hospital days. Although the mother had no history of gestational or insulin-

dependent diabetes, we measured her hemoglobin and a random blood sugar, which was normal.

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