

## Case Report

# Congenital Transient Neonatal Hyperinsulinism Associated with Severe Hyperlactataemia: Case Report

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### Abstract

Congenital hyperinsulinism is the most common cause of persistent hypoglycemia in infants and it is a major cause of neurological damage with high rates of neurodevelopmental deficits. For this reason, it is very important in front of a newborn with hypoglycemia; perform a rapid and early evaluation to establish the diagnosis, this is key to start appropriate treatment for preventing sequelae.

Here we report a female newborn, low weight birth and small for gestational age that presented a severe hypoglycemia two hours after birth whose cause was a hyperinsulinism associated a severe hyperlactataemia and where both (hyperinsulinism and hyperlactataemia) were transient.

**Keywords:** Hyperinsulinism; Hypoglycemia; Hyperlactataemia; Neonate

### Introduction

Congenital Hyperinsulinism (HI) is the main cause of persistent hypoglycemia in the newborn and infancy. Its incidence ranges from 1/27.000 to 1/50.000 live births. In Uruguay, there are no data except for a few reported cases.

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**Citation:** Keshishian R, Rodriguez M, Carrara D, León DD, Rosselló JD (2020) Congenital Transient Neonatal Hyperinsulinism Associated with Severe Hyperlactataemia: Case Report. J Neonatol Clin Pediatr 7: 047.

**Received:** February 22, 2020; **Accepted:** March 06, 2020; **Published:** March 13, 2020

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HI is a condition leading to recurrent hypoglycemia due to an inappropriate insulin secretion by the pancreatic islet  $\beta$  cells. It is defined by an inadequately elevated insulin level in presence of hypoglycemia. Hyperinsulinemia does not allow the use of endogenous glucose, which is the cause of hypoglycemia. HI is a heterogeneous disorder with respect to clinical presentation, histology, molecular biology and genetics [1].

HI can be permanent or transient. Permanent forms are due to abnormalities in 10 genes encoding proteins that play an important role in the regulation of insulin secretion. Mutations in either of the two components of the  $K^+$  ATP channel: SUR1 and KIR 6.2, of the B cell membrane are the most common cause of permanent HI. The permanent forms lead to a severe illness and when refractory to medical treatment, they may require pancreatectomy [2].

Transient HI is common in infants born to diabetic mothers, usually in macrosomic newborns, but they have also been reported in newborns with normal birth weight or even small for gestational age and in infants with perinatal asphyxia [3]. HI may also occur in neonates where there is no predisposing factor [4] and in preterm newborns [5]. The severity of HI is assessed by the glucose administration rate required to maintain normal glycemia and its response to medical treatment.

From a clinical point of view, two major problems should be addressed. First, the delay in the immediate treatment given the vulnerability to neurological damage that correlates directly with the degree of severity of hypoglycemia and its duration. Second, the possibilities to precise diagnosis of the cause, which determines its treatment and prognosis.

After birth, every day counts as a vulnerable period for developmental disability, which occurs in approximately 25 to 50% of children with congenital hyperinsulinism [6]. Neurodevelopmental delays in hyperinsulinism affects both forms: Permanent and transient hyperinsulinism [7].

Early recognition and treatment is key for preventing sequelae [8,9]. Neonatal onset is the main risk factor for the development of severe retardation or epilepsy [8].

A rare condition associated with congenital hyperinsulinism is hyperlactataemia. We present the clinical and biochemical features of an infant with transient hyperinsulinism associated with severe transient primary hyperlactataemia.

### Case Report

Female newborn infant born by spontaneous vaginal delivery at 37<sup>th</sup> week of gestation. She is the first daughter of healthy non-consanguineous parents. The mother is 27 years Uruguayan and the father is Nigerian, both of African descent origin. Birth parameters were: Weight 2245 g, length 45 cm and head circumference 32.5 cm; Apgar score at 1 and 5 minutes was 7/9.

Arterial umbilical blood gases taken at birth were pH 7.04,  $\text{paCO}_2$  64 mmHg,  $\text{paO}_2$  17.9 mmHg, BE -13.8, lactate 13.9 mmol/L.

She was admitted to the NICU for observation. Severe asymptomatic hypoglycemia was diagnosed and immediately treated with parenteral dextrose and oral feeding increasing to a total of 20 mg/kg/min. Hydrocortisone was also prescribed 10 mg/kg/day in 4 doses every 6 hours.

Hemoglucotest (HGT) ranged between 0.50-0.65 g/lt.

- Expanded neonatal screening for Carnitine profile, amino acid profile, immune reactive trypsin, CoA Acyl. Phenylalanine and 17 OH progesterone. All in normal levels:
- Lactic acid in urine
- Cholesterolemia: 1.46 g/L (0.5-2)
- Triglyceridemia: 1.2 gr/L (0.15-1.5)
- Electroencephalogram: Normal

The glucagon test was positive; measurement of plasma glucose by glucometer was greater than 30 mg/dl. On the 10<sup>th</sup> day, oral diazoxide was initiated at a dose of 9 mg/kg/day (divided every 8 hrs). After three days, we could not decrease parenteral intake of glucose and without cardiac and pulmonary contraindication, we progressively increased the dose to 18 mg/kg/day because of persistent hypoglycemia. To reduce the risk of complications with this dose higher we used aggressive diuretic therapy and dextrose more concentrated to reduce volume. For this reason, we began with Hydrochlorothiazide to prevent fluid retention. An immediate response was obtained and no hypoglycemic levels were detected since then.

At the age of 11 days there was a clinical deterioration: Poor appearance, tachypneic, with tremors, tachycardia, cold extremities, poor perfusion; and a sepsis work up showed pH 7.15, EB -15.5 and lactate 17 mmol/L. *Staphylococcal epidermidis* was detected in hemoculture.

Hemoglucotest remained over 0, 90 mg/dl and 6 days after the initiation of diazoxide, the administration of intravenous glucose and corticosteroid therapy was reduced and suspended. The hyperlactataemia progressively decreased as hypoglycemia improved with diazoxide therapy.

Prior to hospital discharge a 6-hour fasting with diazoxide 7 mg/kg/day was performed and finally at 47 days of age she was withdrawn of diazoxide and normoglycemia was maintained since then (Tables 1 & 2).

Other Investigations	Value	Normal Range
Thyroid-stimulating thyroxine hormone (U/ml)	5.69	0.72 to 11
Free thyroxine (ng/dl)	2.92	0.89 to 2.2
Reducing bodies in urine	negative	
Cortisol (µg/dl)	16	1 a 24
Growthhormone (ng/ml)	9	> 7
Urea (g/l)	0.23	0.1-0.45
Uric acid in blood (mg/dl)	2.3	2.4-5.7
Total carnitine nmol/ml	27	28-83
Free Carnitine (FC) nmol/ml	19	22-66
Carnitine Acyl (CA) nmol/ml	8	3-32
Ratio CA/FC	0.4	0.1-0.9
Cholesterolemia g/l	1.46	0.5-2
Triglyceridemia gr/Ll	1.2	0.15-1.5

**Table 2:** Lab tests.

## Discussion

The goal of this case report is to highlight risk population for hyperinsulinism especially to show the association of hyperinsulinism with lactic acidosis both of them were and transient and resolved simultaneously with medical treatment. Pediatricians, neonatologists and pediatric endocrinologists should know this entity and know how to assess and manage hypoglycemia in neonates, infants and children.

The clinical presentation of the transient and permanent forms of HI can be very similar and may even be initially asymptomatic. Symptoms can be mild and unspecific as the following: Irritability, poor sucking and lethargy, or severe, according to glucose levels, such as apnea, seizures and coma. Hyperinsulinism should be considered in cases of persistent hypoglycemia, unresponsive to oral intake; requiring high glucose parenteral administration to maintain a blood glucose level > 50 mg/dl [2,10].

The diagnosis should be completed with plasma concentrations of the hormones and alternative fuels involved in the physiologic response to fasting: Detectable insulin at the point of hypoglycemia with raised C peptide, Inappropriately low blood free fatty acid < 1.7 mmol/l (suppression of lipolysis) and low B-hydroxybutyrate < 1.8 mmol/l (suppression of ketogenesis) body concentrations at the time hypoglycemia, positive response after the administration of glucagon: Increase of plasma glucose by greater than 30 mg/dl and absence of ketonuria. Intravenous glucagon (0.2 mg/kg) implies no risk during hypoglycemia as a diagnostic procedure or treatment [11].

The biochemical profile of hypoketoneic hypo fatty acidemic hypoglycemia arises from the anabolic effects of insulin preventing metabolic counter regulation of hypoglycemia.

Counter-regulatory serum cortisol hormone levels are blunted in HI due to the lack of drive from the hypothalamic-pituitary axis and replacement therapy with glucocorticoids does not seem to affect the severity of the disease [12]. If cortisol and hormone growth levels in the critical sample are not elevated, evaluation for possible hypopituitarism should be carried out [12].

Investigations During Hypoglycemia	value	Normal Range
Maximum glucose requirement (mg/k/min)	24	
Glucose (mg/dl)	33	
Plasma Insulin (mU/l)	14,1	In hypoglycaemia should be undetectable)
Lactate (mmol/l)	22	1,1-2,3
Ammonia (µg/dl)	71	35 a 102
Ketonemia	negative	

**Table 1:** Lab tests during hypoglycemia.

Causes of hyperinsulinism are: Congenital (permanent forms: Focal or diffuse pancreatic affected areas), perinatal stress: Transient forms and genetic syndromes: Beckwith-Wiedemann, Sotos, Costello, Kabuki [2] or associated with inborn errors of metabolism: Defects in the oxidation of fatty acids, ketone body metabolism disorders, fructose-1, 6-biphosphatase deficiency and type 1 glycogen storage disease.

The patient did not present the typical phenotype of a genetic syndrome: Beckwith-Wiedemann, Sotos, Costello and Kabuki, neither elevated transaminases nor abnormal carnitine profile as in the defects of the oxidation of fatty acids or aciduria, hyperammonemia as in disorders of ketone body metabolism. Disorders of gluconeogenesis were also discarded because our patient did not develop hyperuricemia and had a positive glucagon test.

Our patient presented hepatomegaly that disappeared with the medical treatment: Diazoxide and diuretic: Hydrochlorothiazide and we considered that it was caused by glycogen storage due to high glucose, high fluids and hydrosaline retention due to diazoxide [10].

Our patient was a term newborn small for gestational age with transient form of hyperinsulinism induced by perinatal stress with metabolic acidosis and high lactate [13]. Maturation of B cells after birth may be influenced by perinatal factors, resulting in perinatal stress-induced hyperinsulinism. Maternal nutrition can have protective effects on neonatal transient HI. Louvigne M et al., in a control study case they found that mothers with significantly higher gestational weight gain and high fat products consumption are associated to neonatal HI [14]. The weight gain of the patient's mother was normal.

If hyperinsulinism is not diagnosed early, even the transient form can produce neurological damage depending on how severe and manageable is the hypoglycemia. Adverse neonatal outcome can be a cause of neonatal HI [15]. Every newborn infant requiring parenteral glucose to maintain normal glycaemia for more than 48 hours after birth should be studied and strictly monitored and treated to avoid hypoglycemia [13,16].

When our patient at 2 days of life required 15 mg/k/min of glucose (between oral and parenteral) we were concerned: Is this a case of hyperinsulinism or hypopituitarism?

Our patient had a cortisol level greater than 10 ug/dl, and growth hormone greater than 7 ng/ml, but other hormones of the pituitary gland were normal; thus, it hypopituitarism was ruled out. However, as we observed severe hyperlactacidemia initially as high as 20 mmol/l and even higher later; we searched for congenital metabolopathies.

Hyperlactataemia can be primary or secondary. The most frequent and commonly seen in clinical care is the one secondary to hypoxia, hypotension, infection and hypovolemia. These situations determine hypoperfusion and hypoxic cells and anaerobic respiration, with production of lactic acid. We can also see hyperlactataemia secondary to hypoglycemia, due to congenital errors of metabolism such as glycogen storage diseases type 1, disorders of gluconeogenesis (fructose 1,6 diphosphatase deficiency), fatty acids oxidation defects, mitochondrial respiratory chain disorders and pyruvate dehydrogenase complex deficiency. In all these conditions the serum insulin should be appropriate for the level of blood glucose (low or undetectable

glucose level during the critical sample of hypoglycemia) and the child will have a normal glucose requirement [17].

Our patient had very high glucose requirements from the first days of life with high level of insulin and meets all the diagnostic criteria for hyperinsulinism.

The mechanism that may explain the association of congenital hyperinsulinism and hyperlactataemia-is not yet clear, but it may be related to the immaturity of the pyruvate dehydrogenase complex system, or an abnormal accumulation of intermediary metabolites in the mitochondria.

The repeated levels of hyperlactataemia could be secondary to fetal distress suggested by umbilical cord blood gases or the infection episode during hospitalization but the severity of lactate values outweighs these two conditions and we consider that it was a primary hyperlactataemia.

The primary goal of treatment is to maintain glucose greater than 70 mg/dl to prevent long term neurologic damage and may require glucose intake up to 20 mg/k/minute or more. This goal should be achieved with the administration minimal volume of fluids with high concentration dextrose minimizing fluid overload.

Neonates should be allowed to feed on demand. Food modifications alone are not sufficient to treat IH, and forced feedings or continuous feeds may lead to oral aversion and poor feeding skills [2].

Treatment includes as first choice, Diazoxide (5 to 15 mg/k/day orally), that locks the SUR1 component of the K+ATP channel maintaining this channel in an open state, preventing insulin release.

Side effects of diazoxide include fluid retention, hypertrichosis, hyperuricemia, hypotension, rarely leucopenia and thrombocytopenia. Neonates on diazoxide therapy require concomitant therapy with a diuretic, such as chlorothiazide for its hyperglycemic action and to counteract the fluid retention [2,10,18].

If there is no response to initial treatment, it is suggested to treat with somatostatin analogs such as Octreotide (5 to 35 mcg/k/day in bolus or continuous subcutaneous infusion). Other drugs used with less frequency are Nifedipine.

Steroids administration is not an effective therapy for CH and has side effects: Hypertension, bone demineralization and iatrogenic adrenal insufficiency.

In summary, we have seen a term newborn, low birth weight and small for gestational age with transient hyperinsulinism associated with a severe hyperlactataemia. The feasible cause could be immaturity of the pyruvate dehydrogenase complex system or an abnormal accumulation of intermediary metabolites in the mitochondrion.

The patient was discharged free of hypoglycemia and received treatment until 47 days of life. Until her first birthday, she has not experienced repeated hypoglycemia and has developed adequately.

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