

Development of Pulmonary Hypertension in an Infant Treated With Diazoxide for Hyperinsulinism, a Case Report and Literature Review

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Abstract: Congenital hyperinsulinism (CHI) is heterogeneous disorder in the neonatal period characterized by inappropriate insulin secretion in the presence of hypoglycemia. Known etiologies include inactivating mutations of the KATP channel. Its management can be extremely complicated, and may involve medical therapy and surgery. We describe a full term baby male at one month-old without dysmorphic features or congenital anomalies, the baby was presented with asymptomatic hypoglycemia by routine screening at the age of 1.5 hour of life, he was treated with diazoxide for prolonged neonatal hyperinsulinism. Tolerance of diazoxide is usually excellent, but several adverse effects of this drug have been described. During diazoxide therapy he presented with tachycardia and low oxygen saturation, the baby became dyspnoeic with fluid retention and facial edema. Echocardiography showed moderate pulmonary hypertension. Diazoxide was withdrawn, his clinical status and pulmonary hypertension dramatically improved and returned to baseline.

Keywords: Hyperinsulinism, Diazoxide, Pulmonary Hypertension

1. Introduction

Congenital hyperinsulinism (CHI) is the most common of persistent hypoglycemia in infancy characterized by inappropriate insulin secretion in the presence of hypoglycemia.

CHI usually present in the first month of life with hypotonia, seizures, irregular respiration, apnoea and loss of consciousness. The incidence of persistent CHI is generally estimated as 1 in 50,000 live births (1).

Known etiologies of persistent CHI include inactivating mutations of the KATP channel genes. There are two main clinically indistinguishable histopathological lesions: diffuse and focal. Recessive ABCC8 mutations (encoding SUR1, subunit of a potassium channel) and, more rarely, recessive KCNJ11 (encoding Kir6.2, subunit of the same potassium channel) mutations, are responsible for most severe diazoxide-unresponsive CHI (1,2). Diagnostic criteria of hyperinsulinemic hypoglycemia are perfectly reported by

Yorifuji T (1). Genetics and 18 F-fluoro-L-DOPA positron emission tomography (PET) help to diagnose diffuse or focal forms of CHI. (3). Therapy can be accomplished either surgically or pharmacologically.

Diazoxide, octreotide, and nifedipine are associated with increased serum glucose levels as a well-known adverse effect, these drugs are the primary medications used in long-term treatment of CHI.

Surgical treatment is indicated if medical therapy does not maintain normoglycemia (4).

Diazoxide is an antihypertensive antidiuretic benzothiadiazine, its action on the pancreatic β - cells opens the KATP channel, thereby inhibiting insulin secretion. Diazoxide treatment remains the mainstay of medical therapy of CHI.

Tolerance of diazoxide is usually excellent, but several adverse effects of this drug have been described. Diazoxide causes sodium and water retention and should be used cautiously in patients with congestive heart failure or poor

cardiac reserve. Hypertrichosis, coarsening of the facies, decreased serum immunoglobulin G levels, and hyperosmolar nonketotic comas have been reported with diazoxide, especially with long-term use.

We present a rare case and literature review of diazoxide-induced pulmonary hypertension in newborns with CHI.

2. Case Report

A full term baby male - In vitro fertilisation, birth weight 5 kg, was born at 40 weeks' gestation by Caesarean section for impending fetal hypoxia, asymptomatic hypoglycemia (1.2 mmol/l) by routine screening was detected at the age of 1.5 hour of life, later recurrent hypoglycemia was observed. His serum insulin levels were persistently elevated during hypoglycemic episodes. A blood sample, obtained during hypoglycemia (2.6 mmol/l), showed normal levels of blood lactate, growth hormone and cortisol, while insulin and C-peptide levels were high (102.2, pmol/l and 1.35 nmol/l, respectively). Glucose intravenous infusion was started and the patient required a considerably higher rate of glucose infusion (18 mg/kg/min) to maintain normoglycemia. The baby did not have any dysmorphic features or congenital anomalies. Initial laboratory findings revealed normal electrolytes, and liver enzymes, hepatomegaly was detected by abdominal sonography. Investigations for inherited metabolic disease, hypothyroidism and adrenal insufficiency, cranial sonography and echocardiography were all normal, ABCC8/KCNJ11 and HNF4A mutations were excluded. Our patient was supposed to have a transient form of CHI.

After a diagnosis of hyperinsulinism was established, treatment with diazoxide (12 mg/kg/day) was started at age 6 days, after 4 days, he tolerated enteral feeding with normal levels of glycemia, after 3 weeks decreasing dose of diazoxide leads to asymptomatic hypoglycemia, at 30 days of age, the diazoxide dose was increased to (15 mg/kg/day), 4 days later, he presented with tachycardia and low oxygen saturation, the baby became dyspnoeic with fluid retention and facial edema. Chest X-ray showed a cardiomegaly with 63% of cardiothoracic (C-T) ratio.

A transthoracic echocardiography revealed atrial septal defect (5*8 mm) - pG 6 torr), pulmonary hypertension (Transpulmonary pressure gradient 41- 44 torr, tricuspid insufficiency (TI) grade 1 and end-systolic flattening of Interventricular septum IVS), other findings were: enlargement left-side of cardiac chambers (left ventricular diastolic dimension (LVDD) 124 %, left atrial dimension (LAD) 134 %, Right atrial area 96 %, right ventricular posterior wall (RVPW) 125 %, tricuspid annular plane systolic excursion (TAPSE) 16 mm , left ventricular ejection fraction Z score (LVEFz): 34.5).

He was treated with O₂, fluid restriction, furosemide. Diazoxide toxicity was suspected, hydrochlorothiazide was added to treatment and diazoxide was withdrawn during 25 days (at 10 weeks of age). After drug suspension, his respiratory and haemodynamic status dramatically improved. Echocardiography was repeated, showing a reduction of pulmonary arterial pressure to 20 mmHg and resolution of left side cardiac enlargement. Later he developed hirsutism.

3. Discussion

Hyperinsulinism is a rare cause of persistent hypoglycemia in the neonatal period. Diazoxide is a specific K⁺ ATP channel agonist, it modulates insulin hypersecretion in responsive patients, and it remains the mainstay of medical therapy (1).

Tolerance of diazoxide is usually excellent, but several side effects of this drug have been described. These side effects are hirsutism, seizures, extrapyramidal syndrome, heart failure and hypertrophic cardiomyopathy (5), immunological neutropenia have also been reported (6). The clinical picture of our patient was mainly characterised by pulmonary hypertension, heart failure and hirsutism, pulmonary hypertension may be caused by some drugs (fenfluramine, dexfenfluramine, diethylpropion, amphetamines, methamphetamines, cocaine, and chemotherapeutic drugs) (7, 8). Diazoxide-related pulmonary hypertension has been previously reported in 5 cases, see Table 1. (9-13).

Table 1. Summary of reported patients with pulmonary hypertension due to Diazoxide toxicity.

Age at starting Diazoxide treatment(days)	Time to toxicity after starting diazoxide(days)	Diazoxide dose(mg/kg/min)	Authors
Neonate	6	15	Demirel F (9)
120	10	15	Yildizdas D (10)
34	31	13	Nebesio TD (11)
41	6	14	Senguttuvan R (12)
43	3-5	17	Silvani P (13)
6	38 *	15	Our patient

* (4 days after dose increasing)

The sings of pulmonary hypertension were observed 3-31 days after starting treatment with Diazoxide. In all reported cases, diazoxide was stopped and patients haemodynamic status and pulmonary hypertension dramatically improved. In our patient, pulmonary hypertension was demonstrated by echocardiography on day 34, he developed the symptoms of pulmonary hypertension 4 days after increasing the dose from

12 to 15mg/kg/min, the diazoxide administration was discontinued on day 42. During the next 21 days, the patient haemodynamic status and pulmonary hypertension dramatically improved.

Chlorothiazide is sometimes used in conjunction with diazoxide for a synergistic effect. Chlorothiazide activates a different potassium channel, and its diuretic action helps

counteract the salt and water retention associated with diazoxide therapy.

Our patient presented a singes of pulmonary hypertension without right chambers enlargement, and with enlargement left-side of cardiac chambers, hypertrophic cardiomyopathy (HCM) is a well-recognised complication in infants of diabetic mothers and is attributed to a compensatory increase in fetal insulin secretion. Infants with congenital hyperinsulinism have excessive prenatal and postnatal insulin secretion due to defects in pathways of insulin secretion (most commonly the KATP channel). HCM has been reported in a few neonates with hyperinsulinism, but its extent and risk factors for its development have not been evaluated.

The mechanism of the diazoxide-induced pulmonary hypertension is unclear, but was probably due to direct toxic vascular drug reactions (11).

In conclusion, pulmonary hypertension may be developed during diazoxide therapy. These complications should resolve once diazoxide has been withdrawn.

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