Diazoxide-Associated Pulmonary Hypertension in Patient with Hyperinsulinemic Hypoglycemia

Raed Sadek1*, Shaimaa M. Azab2, Yousef Ghazal3, Badi Alenazi4, Ghada Shiekheldin5

1Consultant Pediatric Intensive Care, King Fahad Medical City and Alyamamah Hospital, Head of PICU-Alyamamah Hospital, Riyadh, KSA
2Pediatric Intensive Care Specialist, MD, Alyamamah Hospital, Riyadh, KSA
3Consultant Pediatric Intensive Care, King Fahad Medical City and Alyamamah Hospital, Riyadh, KSA
4Consultant Pediatric Endocrinologist, Pediatric Department, Alyamamah Hospital, Riyadh, KSA
5Consultant Pediatric Cardiologist, MD, King Fahad Medical City, Riyadh, KSA

DOI: 10.36347/sjmcr.2022.v10i03.027 | Received: 12.01.2022 | Accepted: 17.02.2022 | Published: 30.03.2022

*Corresponding author: Dr. Raed Sadek
Consultant Pediatric Intensive Care, King Fahad Medical City and Alyamamah Hospital, Head of PICU-Alyamamah Hospital, Riyadh, KSA

Abstract

**Background:** Congenital hyperinsulinism (CHI) is the most common of persistent hypoglycemia in infancy characterized by inappropriate insulin secretion in the presence of hypoglycemia. **Objective:** This case report evaluates the effect of Diazoxide treatment in inducing pulmonary hypertension in a patient with hyperinsulinemic hypoglycemia. **Case findings:** A full-term baby male, birth weight 4.3kg, was born at 41 weeks gestation by emergency caesarean section due to fetal distress born in Al-Dawadmi Hospital. He developed convulsions started postnatally loaded with phenobarbitone then shifted to AL-Yamammah hospital as lifesaving case to be admitted in Neonatal ICU. He was found to have hyperinsulinemic hypoglycemia and started on Diazoxide. The patient readmitted in Pediatric ICU at age of 2 month with hypoxic respiratory failure. After evidence of pulmonary hypertension by Echocardiography, Diazoxide was held at 2nd day of admission but he developed recurrent attacks of hypoglycemia required Octreotide with intermittent glucagon. After 14 days, Echocardiographic study repeated and showed findings of non-obstructive hypertrophic cardiomyopathy with good systolic function and no evidences of pulmonary hypertension (PH). **Conclusions:** Pulmonary hypertension may be developed during Diazoxide therapy. Pulmonary hypertension was evaluated by echocardiography at regular intervals. This complication resolved once Diazoxide had been withdrawn.

**Keywords:** Congenital hyperinsulinism, diazoxide, pulmonary hypertension, hypoglycemia.

**INTRODUCTION**

Hyperinsulinemic hypoglycemia (HH) is a clinically, genetically, and morphologically diverse collection of illnesses caused by insulin secretion dysregulation [1]. It's the most prevalent cause of hypoketotic hypoglycemia in newborns and babies, and it's linked to a high risk of lasting brain damage [2]. As a result, it's critical to have a quick diagnosis and start treatment right once to avoid problems like epilepsy, cerebral palsy, and neurodevelopmental abnormalities [3]. Insulin's metabolic effect on glucose and fuel metabolism raises the risk of brain damage. Insulin increases peripheral glucose intake, stimulates glycogen synthesis, and inhibits glycogenolysis and gluconeogenesis, lowering blood glucose levels [4]. Insulin, on the other hand, has an anabolic effect on fat cells. Because the brains of neonates and babies consume more glucose than adult brains, they are more susceptible to hypoglycemia brain injury [5]. HH usually manifests as severe hypoglycemia in newborns, but it can also manifest in infancy, childhood, and even adulthood, with varying severity and origin [5]. In the neonatal era, there are numerous causes of recurrent and chronic hypoglycemia. The most prevalent cause of recurrent and chronic hypoglycemia is hyperinsulinism [6]. Hyperinsulinism can be primary or secondary, resulting from a malfunction in the pancreatic cells [7]. Insulin secretion gene mutations are a rather uncommon occurrence. It is thought to affect one out of every 50,000 live births around the world. Inactivating mutations in the KATP channel genes are known etiologies of chronic congenital hyperinsulinism (CHI).
[8]. There are two types of histopathological abnormalities that are clinically indistinguishable: diffuse and localised. Most severe diazoxide-unresponsive CHI is caused by recessive ABCC8 mutations (encoding SUR1, a potassium channel subunit) and, less frequently, recessive KCNJ11 mutations (encoding Kir6.2, a potassium channel subunit) [9].

Although increased serum glucose levels are a well-known side effect of diazoxide, octreotide, and nifedipine, these treatments are the primary pharmaceuticals used in the long-term therapy of CHI [10]. Diazoxide is an antihypertensive antidiuretic benzothiadiazide that inhibits insulin production by opening the KATP channel in pancreatic cells [11].

Diazoxide treatment is still the cornerstone of CHI medical treatment. Although diazoxide has a high level of tolerance, it has been linked to a number of side effects. Diazoxide induces sodium and water retention, thus it should be used with caution in individuals who have congestive heart failure or have a low cardiac reserve. Long-term usage of diazoxide has been linked to hypertrichosis, coarsening of the facies, decreased blood immunoglobulin G levels, and hyperosmolar nonketotic comas [10]. This case study examines the effects of Diazoxide, which has been linked to the development of pulmonary hypertension in patients with hyperinsulinemic hypoglycemia.

**CASE REPORT**

A full-term baby male, birth weight 4.3kg, was born at 41 weeks gestation by emergency caesarean section due to fetal distress with Apgar score at 1, 5 & 10 minutes of 2, 6 & 6 respectively needed initial steps of resuscitation and intubation. He developed convulsions started postnatally loaded with phenobarbitone then shifted to AL-Yamamah Hospital as lifesaving case to be admitted in NICU. No history of consanguinity, No family history of similar condition& No history of recurrent abortion or history of unexplained neonatal or infantile death. Baby admitted in NICU at age of 9 hours postnatal, connected to mechanical ventilator, started total body cooling for completed 3 days, full septic workup done and started on antibiotics. He developed frequent attacks of hypoglycemia. Glucose infusion rate increased gradually to reach high rate up to 12mg/kg/min to maintain normoglycemia. There were recurrent attacks of refractory seizures needed phenobarbitone and phenytoin to be controlled.

Critical sample was taken and the result came with (Insulin 30.47μU/mL and C-peptid 2.85ng/ml with normal levels of lactate, growth hormone and cortisol) which was going with hyperinsulinemia. Extended metabolic screening was normal, ammonia level in plasma was 68.1μmol/l and lactate level in plasma was normal. Initial MRI Brain showed severe form of acute profound Hypoxic Ischemic Insult. His electroencephalography (EEG) showed frequent electrographic seizure arising from bi-occipital areas & severely attenuated background. Abdominal ultrasounds was normal and initial Echocardiography (ECHO) showed: moderate left ventricular hypertrophy without left ventricle outflow obstruction, hypertrophied septum, normal pulmonary venous drainage, normal atra, Patent Foramen ovale (PFO), normal Atrioventricular valves and right ventricle outflow tract with confluent Pulmonary Artery branches and no evidences of pulmonary hypertension).

After a diagnosis of hyperinsulinism was established, treatment with diazoxide (8mg/kg/day) was started at age of 6 days old. Doses of diazoxide increased to 10mg/kg/day then to 12mg/kg/day later during next 2 weeks after discharge.

**At Home**

He was discharged after 1 month and 14 days from admission to NICU of being diagnosed as a case of sever hypoxic ischemic encephalopathy (HIE) with seizure disorder and hyperinsulinaemic hypoglycemia. The patient was discharged on diazoxide as discharge medication with instruction of twice daily check of blood sugar before feeding. He stayed approximately two weeks with recurrent attacks of hypoglycemia required IV glucose infusion twice despite of persistentlytaken of diazoxide. In the 2nd week post discharge, he retransferred to AL-Yammamah hosptal as lifesaving case of severe respiratory distress.

**At time of admission**

The history was reported of fever for one week, difficulty of breathing and respiratory distress for 3 days, vomiting and feeding intolerance for one day and generalized tonic seizure with up rolling eyes for one day. At time of admission, He looked irritable, pale, distress not cyanosed, in a state of exaggerated respiratory distress, febrile with special craniofacial appearance (full check, full lips, wide mouth, prominent epicantal fold, wide nasal bridge, short full nose, short neck& low scalp hair line. Temperature was 38, heart rate was 150, blood pressure was 120/55, respiratory rate was 60/min and SPO2 79% room air (RA).

**On Examination**

Initial systemic examination was done at admission including: Central Nervous System examination which showed irritable infant with abnormal bizarre movements associated with bilateral spasticity and exaggerated deep tendon reflexes with clonus. Cardiac examination: There was systolic murmur with no thrill and no gallop rhythm. Abdominal examination: No abdominal distension or gardening with palpable lower border of right lobe of liver 3cm below right costal margin. Respiratory examination showed signs of severe respiratory distress including grunting, tachypnea and subcostal retractions, with
initial oxygen saturation was 79% RA and became 90% with 15 L/min oxygen by nonrebreather mask together with marked expiratory wheezing.

We treated him as obstructive lung disease with frequent salbutamol nebulization and magnesium sulfate (MGSO4). We tried Non-Invasive Ventilation (NIV) and patient connected to BIPAP with IPAP (inspiratory airway pressure) 15 and EPAP (expiratory airway pressure) 8 with FIO2 100% and x ray chest as well as ECHO requested, (Fig 1).

**Fig 1: Patient at time of admission**

**Laboratory Investigations**

Initial routine investigation (CBC showed microcytic hypochromic anemia, kidney function test normal results with no evidences of acute kidney injury or electrolyte disturbances, Liver function test showed slightly elevated liver enzymes, Blood and urine cultures with no growth and normal coagulation studies.

**Echocardiography (ECHO)**

Done at admission to PICU showed moderate bilateral ventricular hypertrophy with good systolic function (EF88%), moderate to severe Tricuspid regurgitation (TR) with bidirectional PFO. Estimated Right Ventricle pressure (ESRVP) was suprasystemic. These findings supported the diagnosis of marked pulmonary hypertension without underlying CHD that can lead to PH).

Twelve-leads electrocardiography (ECG) showed sinus rhythm, right-axis deviation, a tall P wave in the II-lead, and positive T waves in leads V1 to V3, (Fig 2).

**In Hospital Course**

The patient admitted in PICU at age of 2 months with primary diagnosis of hypoxic respiratory failure due to pulmonary hypertension and secondary diagnosis of Hyperinsulinemic Hypoglycemia, severe HIE with seizure disorder. He didn’t not respond to NIV trial so he was intubated and connected to mechanical ventilation after development of oxygenation and ventilation failure with respiratory acidosis. We started him on PRVC mode with TV 7ml/kg rate 35 with PEEP 6 and FIO2 90%. Nitric oxide was started with significant rapid improvement regarding to his oxygenation status, (Fig 3).

After evidences of pulmonary hypertension by Echocardiography; Diazoxide was held at 2nd day of admission but patient developed recurrent attacks of hypoglycemia required to increased rate of glucose infusion with order to give glucagon if blood sugar dropped to less than 50mg/dl. From day 4 of admission; recurrent attacks of convulsions needed to be loaded with levetiracetam with gradually increasing the doses of levetiracetam and phenobarbitone until being controlled on phenobarbitone 7mg/kg/day and levetiracetam of 50mg/kg/day.

**Fig 2: X ray at admission**

**Fig 3: X ray after intubation**
During the first week after admission

Despite of glucose infusions, there were recurrent attacks of hypoglycemia required start of Octreotide which gradually increasing in dose until reached 10 microgram/kg/day to maintain normoglycemia. Five days after diazoxide discontinuation; ECHO repeated showed mild TR with hypertrophied RT ventricle; ESRVP 1/2 systemic and mild pulmonary hypertension. Ten days after diazoxide discontinuation; ECHO done showed mild TR with ESRVP 1/3 systemic and evidences of resolved pulmonary hypertension after approximated 10 days from stoppage of diazoxide. After 14 days Echo repeated and showed findings of the primary pathology of non-obstructive hypertrophic cardiomyopathy with good systolic function and no evidences of pulmonary hypertension. The patient was extubated at day 16 after admission to PICU then connected to HFNC after that gradually weaned to nasal cannula then patient shifted to GPW after completed 30 days in PICU.

DISCUSSION

This case report evaluates the effect of Diazoxide associated as inducing pulmonary hypertension in a patient with hyperinsulinemic hypoglycemia. Congenital hyperinsulinism (CHI) is the most prevalent form of persistent hypoglycemia in children, characterized by insufficient insulin secretion in the face of hypoglycemia. Diazoxide, a benzothiadiazine that was originally explored as an antihypertensive but was discovered to produce hyperglycemia in patients, is the backbone of medical treatment for CHI [12].

Diazoxide (Proglycem, FDA authorized in 1976) is a pill that is used to treat symptomatic hypoglycemia [13]. Hypoglycemia should be treated as quickly as possible to avoid complications of brain injury, according to a previous study by Chisti et al., [14]. Breast milk or formula should be fed to the newborn as soon as possible. A nasogastric tube can be used for patients who are unable to drink. The mainstay of therapy for children that is alert with intact airway protection. For those who cannot protect their airway or are unable to drink, nasogastric, intramuscular, intraosseous, or intravenous (IV) routes can be used for the following drugs used to raise glucose levels: Dextrose, Glucagon, Diazoxide and Octreotide [15, 16].

In this report, the patient admitted in PICU at age of 2 months with primary diagnosis of non-obstructive hypertrophic cardiomyopathy with pulmonary hypertension and respiratory insufficiency to rule out sepsis and secondary diagnosis of Hyperinsulinemic Hypoglycemia, sever HIE with seizure disorder. Hambly et al., [17] defined Pulmonary hypertension (PH) is a dangerous and progressive lung illness that is characterized by an increase in pulmonary arterial pressure. Dyspnea, tiredness, syncope, and chest discomfort are common symptoms in affected patients, and they are at high risk of right ventricular failure and premature mortality. Transthoracic echocardiography should be performed on all individuals suspected of having PH [18]. This method calculates right ventricular systolic pressure and evaluates the right ventricle for PH-related functional abnormalities (e.g., systolic dysfunction) and morphological changes (e.g., right ventricular dilatation), as well as identifying cardiac causes of PH. Nonspecific symptoms of dyspnea and pedal edema, modest physical indicators like a loud pulmonic component of the second heart sound (P 2), and distinctive abnormalities on frequent noninvasive tests are all clinical characteristics of PH.

Additionally, in 2017, Hansmann et al., demonstrated that, combining commonly-used and more novel echocardiographic variables (e.g., right atrial [RA] size [20, 21]; tricuspid annular peak systolic excursion; right ventricular outflow tract velocity time integral [RVOTVTI]; tricuspid regurgitation velocity/RVTO VTI ratio [22]; RV size [21], LV size, and RV/LV ratio [23]; RV stroke work [24]; LV strain/strain rate [25] and pulmonary artery acceleration time [26] to assess RV/LV function and size, as well as pulmonary blood flow in pediatric PH, may help the clinician to avoid some of the pitfalls of echocardiography, especially the over-reliance on the Doppler pressure estimation in the assessment of children with PH [27]. Also, Beghetti et al., [28] revealed that, the results of diagnostic evaluations performed on patients in the TOPP registry (monitoring outcomes and practice in pediatric pulmonary hypertension) reveal that ECGs, chest radiographs, and echocardiograms are all good screening tests for PH in children. Second, insufficient testing is carried out to determine the causes of PH. Finally, incomplete functional capacity testing is used to determine the severity of the condition. Finally, heart catheterization (HC) problems are more common in children than in adults.

The recent scientific statement of the American Heart Association, on the indications for HC in pediatric cardiac disease, still consider that HC is recommended to assess pulmonary vascular resistance and reversibility of PH in patients with CHD or IPAH when accurate assessment of pulmonary vascular resistance is needed to make a surgical or medical decision with a level or evidence B [29]. This is also supported by Mullen et al., [30], who propose HC in the acute assessment of pediatric PH to confirm the diagnosis and determine severity, assigning a class 1 (condition for which there is evidence and/or agreement that a certain technique is good, useful, and effective) and a level of evidence C to HC (only consensus opinion of experts case studies or standard of care). It was also mentioned that HC along with vasodilator testing is indicated as a starting point for treatment (class 1 level of evidence B).
Infants with Persistent Pulmonary Hypertension (PPHN) require supportive care tailored to the degree of hypoxia and physiologic instability, according to Konduri and Kim [31]. The overall strategy should be to restore cardio-pulmonary adaptation while minimizing lung damage and systemic perfusion consequences. Long-term 100% oxygen exposure and harsh breathing can be avoided with the use of modern therapies including iNO, surfactant replacement, and inotropic support.

Our patient developed pulmonary hypertension while taking diazoxide for CHI and there was resolution of PH after withdrawal of diazoxide. After evidences of pulmonary hypertension by Echo, diazoxide was held 2nd day of admission but patient developed recurrent attacks of hypoglycemia required to increase rate of glucose infusion with order to give glucocheck less than 50mg/dl. Also, 5 days after diazoxide discontinuation, Echo repeated showed mild TR with ESRVP ½ systemic and mild pulmonary hypertension. As well, 10 days after diazoxide discontinuation, Echo done showed mild TR with ESRVP 1/3 systemic and evidences of resolved pulmonary hypertension after approximated 10 days from stoppage of diazoxide.

In the study by Ziad et al. [10], a full-term baby boy, IVF, birth weight 5 kg, was born by cesarean section at 40 weeks’ gestation for impending foetal hypoxia, asymptomatic hypoglycemia (1.2 mmol/l) was found by regular screening at the age of 1.5 hour of life, and thereafter recurrent hypoglycemia was reported. During hypoglycemic episodes, his serum insulin levels were consistently high. They discovered that while diazoxide tolerance is usually excellent, the medicine does have a number of adverse effects. Hirsutism, convulsions, extrapyramidal syndrome, heart failure, and hypertrophic cardiomyopathy were among the side effects. Immune-allergic neutropenia was also described [33]. Pulmonary hypertension, heart failure, and hirsutism characterized the patient's clinical picture. Pulmonary hypertension can be produced by some medications (fenfluramine, dexfenfluramine, diethylpropion, amphetamines, methamphetamine, cocaine) [34, 35].

The first signs of pulmonary hypertension appeared three to thirty days after starting Diazoxide medication. The use of diazoxide was discontinued in all of the cases reported, and the patients' hemodynamic state and pulmonary hypertension significantly improved. Echocardiography revealed pulmonary hypertension in their patient on day 34, when he experienced pulmonary hypertension symptoms. On day 42, four days after increasing the dose from 12 to 15 mg/kg/min, the diazoxide was stopped. The patient's hemodynamic state and pulmonary hypertension significantly improved during the next 21 days [36].

Hypertrophic cardiomyopathy (HCM) is a well-known condition in diabetic newborns and is ascribed to a compensatory increase in fetal insulin secretion. Their patient had pulmonary hypertension without right chamber enlargement and left-side cardiac chamber enlargement. Due to abnormalities in insulin secretion mechanisms, infants with congenital hyperinsulinism have increased prenatal and postnatal insulin secretion (most commonly the KATP channel). HCM has been reported in a few infants with hyperinsulinism, although its severity and risk factors have yet to be determined. The exact cause of diazoxide-induced pulmonary hypertension is unknown; however, it was most likely caused by direct hazardous vascular drug responses [36].

**CONCLUSIONS**

In conclusion, pulmonary hypertension may be developed during diazoxide therapy. Pulmonary hypertension was evaluated by echocardiography at regular intervals. We first introduced nitric oxide to treat PH. After that, the estimated pulmonary/systemic pressure ratio dropped slightly until normalized. PH was primarily due to a diazoxide adverse effect since it developed after started diazoxide, and disappeared after diazoxide withdrawal after exclusion of other causes of pulmonary hypertension. These complications should resolve once diazoxide has been withdrawn. Also, parents should be counseled about this serious side effect.

**ABBREVIATIONS**

- Bi-level Positive Airway Pressure (BIPAP)
- Complete Blood Count (CBC)
- Congenital Heart Disease (CHD)
- Congenital Hyperinsulinism (CHI)
- Electrocardiography (ECG)
- Expiratory Airway Pressure (EPAP)
- Heart Catheterization (HC)
- Hyperinsulinemic (HIE)
- Hypersulinaemic Hypoglycemia (HH)
- Hypertrophic Cardiomyopathy (HCM)
- Kidney Function Test (KFT)
- Liver Function Test (LFT)
- Magnetic resonance imaging (MRI)
- Neonatal Intensive Care Unit (NICU)
- Patent Foramen Oval (PFO)
- Persistent Pulmonary Hypertension (PPHN)
- Pressure-Regulated Volume Control (PRVC)
- Pulmonary Hypertension (PH)
- Tidal Volume (TV)
- Estimated RV Systolic Pressure (ESRVP)
- Tracking Outcomes and Practice in Pediatric (TOPP)
- Tricuspid Regurgitation (TR)
- Ultrasound (U/S)

**Funding:** No sources of funding were used to assist in the preparation of this article.

**Informed Consent Statement:** Written informed consent was obtained from the patient’s parents to publish this paper.

**Data Availability Statement:** The data presented in this case report are available on request from the...
corresponding author. The data are not publicly available due to confidentiality policies.

Acknowledgments: The authors would like to thank the patient and their parents to agree to participate in this work.

Conflicts of Interest: The authors declare no conflict of interest.

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