



Case Series

Perioperative management of congenital hyperinsulinism (CHI)

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ABSTRACT

Congenital hyperinsulinism (CHI) is one of the common causes of recurrent or persistent hypoglycemia. It is marked by islet cell dysfunction leading to insufficient suppression of insulin secretion in the presence of serious hypoglycemia. CHI is genetic in origin, where children present with symptoms of hypoglycemia like irritability, listlessness, nausea, vomiting, tachypnoea, seizure or with long-term sequelae such as developmental delay and focal neurologic deficits, thus making it a medical emergency. Surgical management becomes essential in most of the cases with challenging perioperative management. We successfully managed three such cases with favorable postoperative outcome.

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1. Introduction

Congenital hyperinsulinism (CHI) is a common cause of persistent or recurrent hypoglycemia in infancy.^{1,2} Hypoglycemia in pediatric patients is a medical emergency and can have long-term sequelae such as neurologic deficits and developmental delay. It is associated with islet cell dysfunction characterized by insufficient suppression of insulin secretion in the presence of serious hypoglycemia.^{1,3} Partial/Total pancreatectomy is definite treatment in most of the cases with potentially challenging and pivotal perioperative management.

After obtaining a written informed consent from parents we followed up 3 such cases in our hospital

2. Case 1

A 9-month-old, 11 kg male child presented with convulsions. Blood Glucose (B.G.) was 31mg/dl for which 5ml/kg of 10% dextrose intravenously (I/v) was

given and continued at 6mg/kg/min. Only significant history was birth weight of 4.5kg born to a non-diabetic mother. Later sugar fortified feeds were added. Tab diazoxide 20mg/kg/day, tab hydrochlorothiazide 250mg BD and tab nifedipine 0.8mg/kg/day were added to maintain normoglycemia (Figure 1). Glucose infusion rate (GIR) was increased to 8mg/kg/min in view episodes of hypoglycemia. ABCC8 mutation was detected on genetic testing; the child was planned for near total pancreatectomy for islet cell hyperplasia, 4 hours fasting with continuation of GIR was advised. Inhalational induction was done (anticipated difficult airway) and anesthesia was maintained with Sevoflurane with intermittent Inj Rocuronium (0.1mg/kg). Caudal epidural (Bupivacaine 10ml 0.25%) was administered. Routine monitoring including ECG, Spo2, NIBP, temperature along with central venous pressure (CVP) monitoring was instituted. Dextrose infusion and Ringer's lactate for replacement of losses and blood were administered. Intraoperative blood sugar monitoring was done half hourly and maintained within 100-160mg/dl. With the dissection of pancreatic tissue blood sugar increased to 370-450mg/dl after which GIR was decreased

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to 4mg/kg/min and subsequently to 2mg/kg/min. Near total pancreatectomy was done, duration 4hrs. Intraoperative hemodynamic parameters were stable (blood loss 70ml) and procedure was uneventful. Post extubation patient shifted to Neonatal ICU with GIR 2mg/kg/min. Oral feeds were started on postoperative day three and GIR stopped on seventh day.

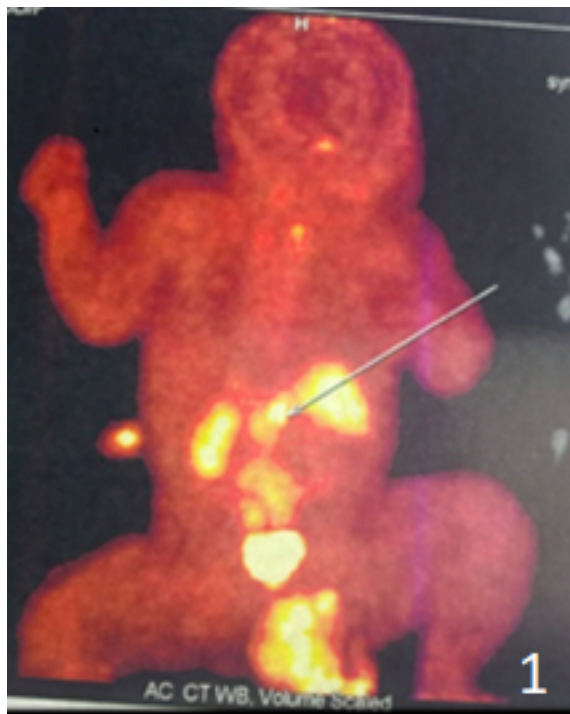


Fig. 1: Coronal PET image showing increased focal radiotracer uptake

3. Case 2

A 15-day, 5kg female baby presented with complaints of decreased oral intake and lethargy. Blood Glucose was 39mg/dl for which glucose infusion was started at a rate of 6mg/kg/min. GIR was gradually increased to 16mg/kg/min for sustaining euglycemia.

She was born to a non-diabetic mother with a birth wt. of 4.54kg. Resuscitation was done as baby did not cry at birth and had episode of bradycardia. On third day the B.G. dropped to 21mg/dl for which Glucose infusion rate (10 mg/kg/min) was initiated. Gradually breast feeds were increased, GIR tapered and baby was discharged at 8th day.

With addition of feeds and Tab. Diazoxide, GIR was tapered to 6mg/kg/min. F¹⁸ DOPA PET scan showed diffuse uptake in pancreas more in the tail region and near total pancreatectomy was planned. After initiation of fasting preoperatively, the B.G. decreased to 54mg/dl for which GIR was increased to 10mg/kg/min. Anesthesia was induced with Inj Fentanyl 10mcg followed

by Inj Thiopentone 25mg, sevoflurane and maintained with oxygen, N₂O and Isoflurane. Analgesia provided with caudal epidural (5ml 0.25% Bupivacaine). Routine monitoring along with CVP monitoring was done. Ringer's lactate was used as replacement fluid and dextrose infusion as maintenance. Intraoperative monitoring and fluid management was similar as in case 1. Intraoperative blood sugar monitoring was done half hourly, haemodynamic parameters were stable and procedure was uneventful. Immediate postoperatively, B.G. was found to be 140mg/dl for which GIR was continued at 9mg/kg/min. An awake child with stable vitals was shifted to NICU. With increasing oral feeds from POD2 GIR tapered with blood sugar monitoring and gradually stopped.

4. Case 3

A 2.8 kg, female baby presented at 36 hours of age with decreased oral acceptance, lethargy and abnormal body movements. Examination revealed poor cry, vacant stare with facial twitching. The blood glucose at admission was 16 mg/dl for which bolus of 2 ml/kg 10% dextrose was given followed by GIR 16mg/kg/min. Tab. Hydrocortisone and tab. diazoxide were added on day 8 of life in view of persistent hypoglycemia and glucagon boluses were also tried. PET scan showed focal area of increased radiotracer uptake (Figure 2). Partial pancreatectomy was planned on day 30 of life. Despite maintaining normoglycemia at a very high GIR, the child was lethargic, had poor cry and depressed reflexes. Inhalational induction was done and anesthesia was maintained with intermittent muscle relaxant doses. Intraoperative monitoring and fluid management was similar as in case 1. Glucose infusion was increased to 18mg/Kg/min in view of persistent hypoglycemia. In view of poor respiratory efforts at the end of surgery, the child was mechanically ventilated for 24hrs. Post extubation on day 5 she had multiple episodes of focal myoclonic seizures, which were treated with phenobarbitone loading dose 15mg/kg followed by infusion of 3mg/kg/day. EEG was normal and MRI brain showed diffuse paucity of cerebral white matter with focal areas of encephalomalacia in bilateral parietal lobes with moderately dilated lateral and third ventricle. Baby was discharged on day 57 of life. At the time of discharge baby was alert, exclusively breastfed, gaining weight. Histopathological examination in all the cases confirmed diagnosis of islet cell hyperplasia.

5. Discussion

Congenital hyperinsulinism is primary defect of pancreatic beta cells leading to unopposed insulin secretion even in presence of hypoglycemia.^{1,3} Incidence is 1 in 25000-50,000 live births with male preponderance. CHI is an inherited single gene disorder. ABCC8 and KCNJ11 are most common genetic mutation described.⁴ It encodes

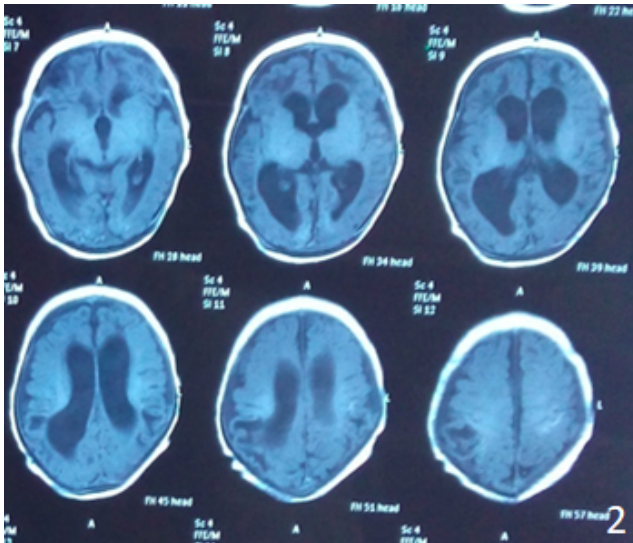


Fig. 2: Postoperative brain MRI

for beta cell ATP sensitive potassium channel (KATP) hence even in absence of glucose availability there is continuous release of insulin from the cells. This alters protective mechanism thereby inhibiting glycogenolysis, gluconeogenesis, cortisol, glucagon, ketone and FFA synthesis, which are alternative substrate to the brain in event of hypoglycemia.⁵ In one of our cases ABCC8 mutation was noted.

In neonates autonomic responses to hypoglycemia are absent. Presence of neuroglucopenic symptoms (irritability, listlessness, tachypnea, seizure etc), glycemia < 3 mmol/L (55 mg/dl), resolution of all symptoms after the normalization of the glycemia constitutes the WHIPPLE's triad.⁵

Criteria for diagnosing Hyperinsulinemia:^{1,6}

1. Insulin: glucose (I: G) ratio is 0.4 or greater
2. Hypoketonaemia, low fatty acid levels and low branched chain amino acid levels in blood when hypoglycaemic.
3. Glucose requirement of > 8 mg/kg/min
4. Glycaemic response to glucagon when hypoglycaemic

All our patients were diagnosed as hyperinsulinemia based on above criteria (I: G >1, GIR >8/16, no ketones)

Acute symptomatic hypoglycemia is managed with 10% dextrose 2ml/kg Intravenous bolus over 5-10 min followed by glucose infusion. Glucagon is added for emergency treatment of severe hypoglycemia.³ For hyperinsulinemia, diazoxide is first line of management¹ (Figure 4). With diazoxide sodium, water retention; and pulmonary hypertension necessitate preoperative echocardiography. Second line of drugs includes octreotide (acts as agonist to KATP channel and VGCC antagonist) and nifedipine (VGCC antagonist). Complications of octreotide include

diarrhea, abdominal distension, gall bladder stones as well as increased risk of paradoxical hyperglycemia and severe bradycardia intraoperatively.^{1,3} Nifedipine is associated with hypotension.¹



Fig. 3: Baby at time of discharge

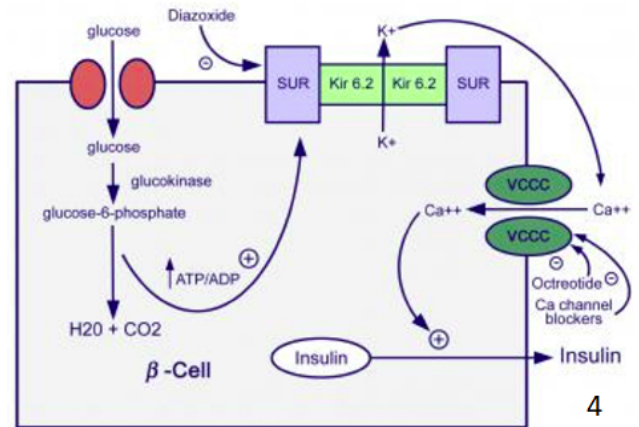


Fig. 4: Normal physiology- entry of glucose into beta cell of pancreas increases ATP/ADP ratio in turn causing closure of K_{ATP} channel leading to depolarization and opening of voltage gated calcium channel releasing stored insulin from the cells. Drug therapy acting on receptors thus decreasing insulin release

When medical management is ineffective, surgical treatment becomes imperative.³ Partial pancreatectomy for focal lesion and near total pancreatectomy for diffuse lesion is required. Preoperatively focused neurological examination to rule out hypoglycemia induced brain injury (HIBI) is essential.³ Routine investigations with special

emphasis on serum electrolytes should be done, as there is persistent hyperinsulinemia.

These children have macrosomia and short neck so we should anticipate difficult airway and venous access. Main anaesthetic consideration perioperatively is optimization of blood sugar and assessment of hydration. Glucose requirement may be more than 8-10ml/kg/hr, which can lead to dehydration due to free water deficit and glycosuria. Therefore, infusion rate and concentration should be kept as low as possible with continuation of drug therapy. Cessation of feeds increases I/V dextrose requirement and blood sugar monitoring frequency should be increased.

Intraoperatively to maintain euvoemia, dextrose solution should not exceed 4ml/kg/hr and if required only concentration of solution is changed. Anticipating major fluid shift, replacement by balanced salt solution of at least 8-10ml/kg/hr with blood replacement accordingly is advised.

Invasive monitoring is required as significant blood loss is anticipated. Aim is to maintain moderate hyperglycemia (100-140mg/dl). Half hourly monitoring of B.G. is recommended. High concentration of dextrose solution can lead to rebound hypoglycemia as excess glucose suppresses gluconeogenesis and glycogenolysis, while hyperglycemia observed while clamping of vessels is a transient event, so neither GIR is stopped nor insulin is given.⁷

Hypoglycemia predisposes the child to neuronal injury, so any period of hypoxemia during induction or haemodynamic instability can potentiate HIBI. Various interactions are associated with drug therapy of these patients of which most significant is between thiopentone and diazoxide. Both these drugs are highly protein bound, therefore may displace each other from the protein binding site leading to cardiovascular instability. Thus thiopentone is given slowly and in titrated doses with hemodynamic monitoring. We have used thiopentone in one of our cases without any untoward effects. Ketamine can be used as an alternative for induction. Inhalational agents decrease insulin release but effect is not clinically significant.

There have been controversies regarding the use of regional anaesthesia as it is believed to suppress stress response in turn causing hypoglycemia, however this response is not seen in patients with CHI. Conversely it may be advantageous for postoperative management of pain and hyperglycemia.⁶ We used epidural and caudal anaesthesia safely in our patients.

Patients with preoperative neurological involvement may require postoperative mechanical ventilation. Intensive monitoring along with neurological and blood sugar monitoring is mandatory in first 48hrs.

6. Conclusion

CHI although a rare condition can lead to permanent brain damage which mandates prompt diagnosis and aggressive

treatment. Pancreatectomy is a semi-emergency surgery that is performed to prevent hypoglycemia induced neuronal damage. Successful anaesthetic management of such cases requires comprehensive preoperative, intraoperative and postoperative management. Focus should be on maintaining adequate fluid balance, normoglycemia, and haemodynamic stability during the perioperative period.

7. Source of Funding

None.

8. Conflict of Interest

The authors declare no conflict of interest.

9. Ethical Approval

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000.

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