www.jmscr.igmpublication.org
Impact Factor (SJIF): 6.379
Index Copernicus Value: 71.58
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v6i2.167

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Hyperinsulinemic Hypoglycemia: Masquerading as a Case of Seizure Disorder

Authors
Gupta Akanksha[1], Singhal Deepika[2], Rustagi Vaishakhi[3], Chopra Saurabh[4]
[1]Consultant PICU, [2]Senior Consultant PICU, [3]Pediatric Endocrinologist, [4]Pediatric Neutrologist
Pediatric Critical Care Unit, Max Superspeciality Hospital,Vaishali, NCR

Abstract
Hypoglycemia is one of the most important acquired causes of neurodevelopmental delay in neonates as well as infants and children. We present a case of 20 months old toddler with congenital hyperinsulinemic hypoglycemia presenting with abnormal oromotor movements who was being treated as a case of seizure disorder,was managed with Glucose infusion and diazoxide. Only high index of suspicion and early and aggressive management of hypoglycemia is the key to good neurological outcome.
Keywords: *Hyperinsulinemic hypoglycemia, developmental delay, hypoglycemia.*

Case Report

20 months old male child presented to the casualty with complaints of multiple episodes of lethargy followed by excessive cry along with abnormal movement of lips for 3 days. Most of the episodes occured in the morning. There was no history of fever, vomiting, diarrhea, feed refusal, rashes, ear discharge, cyanosis, loss of consciousness or trauma. He had past history of recurrent similar episodes (4 episodes) between 8-17 months of age for which child was on valproate (30 mg/kg/day) since the age of 8 months. Records of previous blood sugar values were not available. He was a preterm 35 weeker, appropriate for gestational age with a birth weight of 2.5 kg. Neonatal period was uneventful and he was developmentally normal. On examination child was irritable, no pallor, icterus, cyanosis, clubbing, lymphadenopathy, edema, facial dysmorphism, midline deformity in face, cataract, skin normal, hydration fair, no neurocutaneous markers or hyperpigmentation, vital parameters were stable. Anthropometry was normal. Systemic examination was normal. Laboratory reports showed random blood sugar (RBS)- 31 mg/dl, hemogram was normal. Sepsis screen was negative, renal function and liver function were normal. Child was having low RBS even after fluids and oral feeds so Glucose infusion was started at 6 mg/kg/min. In view of hypoglycemia and recurrent history critical sample and metabolic screen was sent. GIR requirements had to be stepped up upto 8 mg/kg/min. Pediatric neurology and endocrinology opinion were taken. Magnetic Resonance Imaging brain, ultrasound abdomen were normal. Initial reports were suggestive of hyperinsulinemia so a starvation test was planned, critical sample was resent. Critical sample reports showed, insulin 6.74 uIU/ml, growth hormone and cortisol were appropriately

increased. Glucagon challenge test was done which showed an increment of blood sugars by more than 30 mg% confirming our diagnosis of Persistent Hyperinsulinemic hypoglycemia in infancy.

Classical response to glucagon on glucose value favoured diagnosis of hyperinsulinemia. The child was started on diazoxide at 15 mg/kg/day. He maintained sugars on 15 mg/kg/day of diazoxide. Genetic studies did not detect a mutation. Gradually the dose has been tapered, and the child is maintaining normal blood sugars on 10 mg/kg/day of diazoxide.

Discussion

Our case was peculiar because of hypoglycemia presenting as lethargy followed by abnormal oromotor twitching and shrill unconsolable cry which was misdiagnosed as seizure disorder and started on anti epileptics. Blood sugar level should always be checked in any bizarre neurological presentation.

The incidence of hypoglycemia in children older than 6 months in a large urban emergency department is 0.034%[(1)]. Hypoglycemia is most common in the immediate post neonatal period. Repeated episodes can blunt neurogenic responses to subsequent hypoglycemic episodes .This leads to reduced or absent awareness of hypoglycemia and impairs hepatic glucose release, perpetuating hypoglycemia known as Hypoglycemia associated autonomic failure HAAF[(2)]. Whenever possible, specimens (a "critical sample") for identifying the etiology of hypoglycemia should be obtained at the time of spontaneous presentation and before treatment. Other test like c-peptide, blood gas, acyl carnitine profile, Tandem Mass Spectroscopy, Gas Chromatography Mass Spectroscopy may be required to delineate etiology.

In the absence of a "critical sample," a provocative fasting test is the most informative method for identifying the etiology of hypoglycemia disorders[(3)].

Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in infancy[(4)]. It comprises a group of different genetic disorders with the common finding of recurrent episodes of hyperinsulinemic hypoglycemia due to an inappropriate secretion of insulin by the pancreatic β-cells. The estimated incidence of HI is 1/50, 000 live births (up to 1/2, 500 in Saudi Arabia because of a high rate of consanguinity). Mutations in the ABCC8 and KCNJ11 genes are the most common causes of HI and account for 40 to 45% of all cases (82% of diazoxide- unresponsive patients[4]), whereas mutations have been identified on six other genes in approximately 5 to 10% of the cases. The genetic etiology for the remaining 45-55% of patients is still unknown[(5)]. Fifty five to sixty percent of diazoxideunresponsive HI are focal forms, whereas 40-45% are diffuse forms, in western countries. When closed, the KATP channel depolarizes the plasma membrane leading to insulin secretion. In this group of HI, two clinically indistinguishable histopathological lesions have been described: the focal and the diffuse HI (both mostly resistant to diazoxide). Patients with a paternal mutation in ABCC8 and KCNJ11 (or those with no mutations in these genes) potentially have focal disease Presentation may be in neonatal period with severe hypoglycemia or in infancy or sometimes later in life. The treatment of hyperinsulinemic hypoglycemia involves medical therapy and surgery in some cases. The mainstay of initial medical treatment is the provision of adequate carbohydrate to maintain normoglycemia i.e. blood sugar level between 3.5-6 mmol/L (65-106mg/dl). Symptomatic hypoglycemia should be managed with mini bolus of 10% dextrose @ 2 ml/kg, higher dextrose concentration should be avoided to prevent rebound hypoglycemia by further stimulating insulin secretion. Glucagon is primarily used for management of acute symptomatic hypoglycemia either as subcutaneous injection at dose of 0.5-1 mg or as continuous intravenous infusion at dose of 1-20 mcg/kg/hour. Hydrocortisone can also be used in acute cases. For long term management,

diazoxide a KATP channel agonist, is the mainstay of medical treatment in prolonged hyperinsulinemic hypoglycemia. It prevents cell membrane depolarization and inhibits insulin secretion by keeping KATP channels open. It is given orally in the dose of 5-20 mg/kg/day in 3 divided doses. Fluid retention, hypertrichosis are common side effects, which reverts after cessation of therapy. Diazoxide responsiveness is noted when infant can fast appropriately for age, maintains normal glucose levels and shows rise in serum fatty acids and ketone bodies at the end of fast[6]. Octreotide, a somatostatin analogue causing inhibition of insulin release is used in resistant cases[7]. The use of once a month long acting release lanreotide as an alternative to octreotide pump treatment is promising[8]. Recent advances have shown the effectiveness of
the mammalian target of rapamycin (mTOR) inhibitor, Sirolimus and GLP-1 receptor antagonist Extendin (9-39) in infants with severe diffuse form of hyperinsulinemic hypoglycemia that had been unresponsive to maximal doses of diazoxide and octreotide [9,10]. Further molecular genetic testing for mutations should be done when patient is unresponsive to diazoxide. It helps differentiate focal and diffuse lesion. 18F-DOPA PET should be done in whom the genetic testing is inconclusive or in favour of a focal lesion. The diffuse from may require a near total pancreate-ctomy (with the risk of diabetes mellitus and pancreatic exocrine insufficiency) whereas the focal form will only require a focal lesionectomy. Post surgery these patients should be monitored for growth, neurological/ psychomotor development, diabetes mellitus, pancreas exocrine function.

References

1. Daly LP,Osterhoudt KC,Weinzimer SA. Presenting features of idiopathic ketotic hypoglycemia. J Emerg Med.2003;25 (1):39-43.
2. Cryer P. Diverse Causes of Hypoglycemia-Associated Autonomic Failure in Diabetes. N Engl J Med. 2004;350(22):2272-2279.
3. Bonnefont J, Specola N, Vassault A, Lombes A, Ogier H, de Klerk J et al. The fasting test in paediatrics: Application to the diagnosis of pathological hypo- and hyperketotic states. Eur J Pediatrics.1990;150(2):80-85.
4. Bellannı-Chantelot C , Saint-Martin C, Ribeiro MJ et al. ABCC8 and KCNJ11 molecular spectrum of 109 patients with diazoxide- unresponsive congenital hyperinsulinism. J Med Genet. 2010;47 (11):752-759.
5. Flanagan SE, Kapoor RR, Hussain K. Genetics of congenital hyperinsulinemic hypoglycemia. Semin Pediatr Surg. 2011;20(1):13-17.
6. Senniappan S, Arya VB, Hussain K. The molecular mechanisms, diagnosis and management of congenital hyperinsulinism. Indian J Endocr Metab. 2013;17:19-30.
7. Kim-Hanh Le QS, Jean-Baptiste A, Asmaa M, Saint-Martin C, Bellannı-Chantelot C, Valayannopoulos, et al. Successful treatment of congenital hyperinsulinism with long-acting release octreotide. Eur J Endocrino. 2012;166:333-9.
8. Kuhnen P, Marquard J, Ernert A, Meissner T, Raile K, Wannenmacher G, et al. Long-term lanreotide treatment in six patients with congenital hyperinsulinism. Horm Res Paediatr.2012;78(2):106–12.
9. Senniappan S, Alexandrescu S, Tatevian N, Shah P, Arya V, Flanagan S, et al. Sirolimus therapy in infants with severe hyperinsulinemic hypoglycemia. N Engl J Med. 2014;370:1131-7.