A neonate with resistant and prolonged hypoglycemia

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ABSTRACT
A case of resistant hypoglycemia in a newborn is presented and the evaluation and management of this rare condition is discussed.

Baby was born premature at 34 weeks gestational age and was diagnosed with grade 3 respiratory distress syndrome. He was ventilated and received 2 doses of Survanta. Baby had hypoglycemic episodes from the first day as detected by glucometer and confirmed by laboratory test on venous blood. Baby needed glucose infusion rate up to 13 mg/kg/min by 5th day along with feeds to maintain sugar levels. Hypoglycemic episodes continued despite high glucose infusion rate, full feeds and hydrocortisone. Hence, he was diagnosed as a case of resistant and prolonged hypoglycemia and started on intravenous octreotide. Blood glucose was maintained on intravenous octreotide and glucose infusion rate could be decreased to 7 mg/kg/min. Baby's serum insulin level was very high (317 µU/ml) with corresponding blood glucose of 48 mg/dl. There is a family history of resistant hypoglycemia in one of his cousin sister and history of consanguinity between his parents. Genetic test was done which showed nonsense mutation of ABCC8 gene confirming diagnosis of autosomal recessive congenital hyperinsulinism. Plan is to do subtotal pancreatectomy to decrease insulin level.

Resistant and prolonged hypoglycemia in a neonate is defined as a hypoglycemia persisting despite glucose infusion rates of 12 mg/kg/min for more than 24 hours and hypoglycemia persisting beyond 7 days of life respectively. Our case had resistant and prolonged hypoglycemia secondary to hyperinsulinism. His blood sugars were under control with the help of hydrocortisone and octreotide in addition to glucose infusion and feeding. Genetic tests were carried out in view of family history of similar presentation in the cousin sister and history of consanguinity in his parents. It confirmed the diagnosis of autosomal recessive congenital hyperinsulinism and he carries same mutation as his affected cousin sister (homozygous mutation in ABCC8 gene). He underwent subtotal pancreatectomy one month back. He is now 5 months old and is on injection octreotide and gastrostomy feeds.

Keywords: Refractory Neonatal Hypoglycemia, Congenital Hyperinsulinism, ABCC8 Gene Mutation.
INTRODUCTION
Hypoglycemia is a common metabolic problem in newborn babies\textsuperscript{1,2}. Most of the time neonatal hypoglycemia is transient and mild and occurs within first several hours after birth\textsuperscript{1}. This can be considered as physiological and is due to transition from intrauterine existence to extra uterine life\textsuperscript{1}. Neonatal hypoglycemia is also commonly seen in infants of diabetic mother, premature and small for gestational age babies and IUGR babies\textsuperscript{1}. It is very important to recognize and treat any hypoglycemia promptly to prevent neurological morbidity in the long term\textsuperscript{1,2}. This is because newborn brain is almost exclusively dependant on glucose for its energy metabolism. Rarely, hypoglycemia is refractory and prolonged\textsuperscript{3,4}. This requires careful investigations and aggressive treatment to identify the cause and to prevent any neurological morbidity\textsuperscript{4}. In these cases various drugs like hydrocortisone, octreotide & diazoxide might be used to maintain normal blood glucose level\textsuperscript{4}. We are presenting one such case of persistent hypoglycemia.

CASE REPORT
Preterm baby, 34 weeks gestational age, large for gestational age with birth weight of 2.31 Kg was born on 01/06/14 by emergency caesarian section. The parents of the baby were German nationals of Afghanistan origin and were from Hazara community. The indication for emergency caesarian section was antepartum hemorrhage secondary to placenta previa and transverse lie. Baby developed grunting and respiratory distress soon after birth. Hence, he was admitted in the NICU of GMC hospital. X-ray chest showed grade 3 respiratory distress syndrome. The baby was ventilated and received 2 doses of Survanta. Baby was then weaned and extubated on 3\textsuperscript{rd} day of life. Baby had hypoglycemic episodes from the first day of life as detected by glucometer with the help of reagent strips and also confirmed by laboratory analysis of venous blood sample. Orogastric tube feeds were started on 3\textsuperscript{rd} day and increased to full feeds by 10\textsuperscript{th} day of life. In addition to feeds, high dose of intravenous glucose infusion was required with glucose infusion rate reaching 13 mg/kg/min by 5\textsuperscript{th} day of life. Despite high dose of glucose infusion and full feeds, hypoglycemic episodes continued. Some of the episodes were symptomatic and were associated with lethargy and poor feeding.

Therefore, drugs like hydrocortisone and octreotide were started to maintain normal blood glucose level. Also, baby was investigated for the causes of refractory hypoglycemia. On taking detailed history, we found that there is a history of consanguineous marriage between the parents. Additionally, one of the cousin sister of the patient had similar medical history of refractory hypoglycemia and she underwent pancreactomy in early infancy following which she was apparently cured. She is now 5 years old and is apparently doing well. Serum insulin levels were very high i.e. 317 µU/ml for the corresponding glucose level of 48 mg/dl. Serum ammonia, cortisol and lactate levels were normal. Venous blood gas did not show any acidosis. Sepsis work up was normal. This suggested diagnosis of hyperinsulinemic hypoglycemia. Injection octreotide was given intravenously and dose adjusted to maintain normoglycemia. After starting octreotide, sugar levels were maintained and glucose infusion rate could be reduced to 7 mg/kg/min. Baby was shifted to tertiary centre NICU for further management.

Genetic work up was done at the referral hospital. It was found that patient’s cousin sister, who had undergone pancreactomy for refractory hypoglycemia in early infancy, carries a pathogenic homozygous nonsense mutation of ABCC8 gene p.R705. Hence, patient and his family members were tested for the same mutation. Patient is homozygous for the same ABCC8 nonsense mutation, p.R705. His both parents and one of his sister is heterozygous for the same mutation whereas the other sister is normal and does not carry
the mutation. He underwent near-total pancreatectomy, the procedure in which 95% of his pancreas was removed, 1 month back in the same hospital (Al Qasmi Hospital, Sharjah). The patient is now 5 months old and still admitted in the same hospital. He is on injection octreotide and gastrostomy feeds. He has suffered severe neurological morbidity and has marked developmental delay because of hypoglycemic brain injury.

**DISCUSSION**

Persistent hyperinsulinemic hypoglycemia of infancy, also known as congenital hyperinsulinism, is one of the causes of refractory and persistent hypoglycemia. Genetic mutations are identified in 50% of these patients whereas in the remaining 50%, no known genetic mutation has been identified. The commonest mutation is ABCC8 gene mutation which occurs in about 40% of cases with known genetic mutation. Incidence varies from 1 in 50,000 to 1 in 2,500 in communities where consanguineous unions are common. Age of presentation is from birth to 18 months, but most patient presents immediately after birth.

It occurs in 2 forms: diffuse and focal. In focal form, the islet abnormality is located in one or more focal areas whereas in diffuse form there is diffuse abnormality of islet cells leading to hypersecretion of insulin. Diffuse forms are either autosomal dominant or autosomal recessive. Focal forms have non mendelian mode of inheritance. It is due to mutation of maternal allele in embryonic cells in certain areas of pancreas in a patient who has inherited mutated paternal allele. This lead to loss of heterozygocity in focal areas derived from clonal cells with the mutated maternal allele. It is clinically important to differentiate between focal and diffuse form. Resection of one or more focal lesions leads to lifelong cure. On the other hand, diffuse form requires near-total pancreatectomy in most cases. Even after this procedure, medical management is generally required to control hypoglycemia for several years. The average period from surgery to cure is about 4.7 years. There is a long term risk of development of diabetes mellitus even after conservative pancreas surgery.

**REFERENCES**