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Congenital hyperinsulinism in a Nigerian infant: A case report and review of literature

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ABSTRACT

Congenital hyperinsulinism, a rare genetic disorder characterized by excess insulin secretion even during hypoglycemic episodes, has two histological subtypes; diffuse and focal. Genotypes denote which of the two subtypes presents, and this is the first case being reported in Nigeria. The aims of this study were to report the first case of genetically confirmed compound heterozygote inheritance for two non-sense mutations in the ABCC8 gene in a Nigerian child and her family. A full-term average weight (7.5 lb) female baby presented with severe hyperinsulinemic hypoglycemia [HH] after birth and failed medical treatment with dextrose infusion. She had several hypoglycemic seizure episodes and spastic diplegic cerebral palsy, despite frequent feeding. Following physiotherapy, her spasticity was regressing and she was also able to say polysyllabic words. Genetic testing done 2 years after birth showed that her father was heterozygous for the ABCC8 non-sense mutation, P.W143*, and her mother was heterozygous for the P.Q416* ABCC8 mutation. This report shows the need for quick and early genetic testing for rare disorders and the possibility of collaboration with more specialized genetic laboratories. When diagnosed, diffuse or focal diazoxide unresponsive hypoglycemia may be treated by partial or complete pancreatectomy with the potential complication of diabetes mellitus later in life.

Keywords: Congenital hyperinsulinism, Nigeria, Genetic testing, hypoglycemia

INTRODUCTION

Congenital hyperinsulinism (CHI), though a rare condition, is the most frequent cause of persistent hypoglycemia in newborns and infants.[1-3] This condition has various forms dependent on their histopathologic features, and responsiveness to different types of therapy (including medications and surgery) and the molecular etiology.[4] The most common type of CHI is the inactivation mutation in one of two adjacent genes located on chromosome 11p15.1: ABCC8 and KCNJ11. These genes encode the sulfonylurea receptor 1 and Kir 6.2 proteins, which form the ATP-sensitive plasma membrane potassium (K_{ATP}) channel in pancreatic β-cells.[5-7] The loss of this channel activity results in the membrane of the pancreatic β-cells remaining permanently depolarized causing a constant release of insulin, ultimately leading to hypoglycemia in these children. Two main forms of KATP channel mutations have been recorded; one is recessive and the other is dominant.

Recessive mutations result in proteins that remain on the surface of the cell membrane and can cause either focal (affecting only a part of the pancreas) or diffuse (affecting the entire pancreas) CHI.[8,9] While diffuse CHI is caused by inheritance of biallelic recessive mutations, focal CHI is caused by transmission of a paternal monoallelic recessive mutation with an

embryonic somatic loss of maternal 11p15.1.[10] The other common type of CHI is the activating mutation of glutamate dehydrogenase enzyme gene (GLUD1 on chromosome 10), which causes hyperinsulinism (HI)/hyperammonemia syndrome.[11,12] These mutations impair the regulation of amino acid-stimulated insulin secretion leading to fasting hypoglycemia and leucine sensitive hypoglycemia.[10] Other rarer forms of HI exist and most of them are diazoxide responsive like the GLUD1 mutations.

In this case study, we report the phenotype and genotype of the first case of genetically diagnosed HI in Nigeria, and her immediate family's genotype. We also report methods available for making the diagnosis when genetic studies are unavailable, and management processes available in resource-limited settings like Nigeria.

CASE REPORT

The patient is a 2-year 5-month-old female who was delivered at term to a 38-year-old para 3 mother and a 51-year-old father, who are non-consanguineous. At birth, she had normal physical signs, 7.5 Ib weight, 50 cm body length and 35 cm head circumference. She had good Apgar scores of 9 and 10 at 1 and 5 min, respectively. She was hypoglycemic with a routine random blood glucose level of 2.6 mmol/L. Neonatal convulsions started soon after, which were initially aborted with diazepam 0.3 mg/kg, but became refractory to conventional anticonvulsants, including carbamazepine and phenobarbital. A clinical diagnosis of neonatal hypoglycemic convulsion was made after a random blood glucose revealed abnormally low levels, and she was started on intravenous (IV) glucose and oral feeds. Her blood glucose never stabilized and she required a high-dose IV dextrose infusion at 20 mg/kg/min. She was eventually discharged from the special care baby unit to the clinic after assessment by the pediatric endocrinology unit and counseling of the mother to feed the child as often as every 2 h to prevent hypoglycemia.

She continued to have hypoglycemic convulsions. She was treated with combination of carbamazepine, phenobarbital and oral glucose as the health-care team could not obtain glucagon, diazoxide, or growth hormone analogue (octreotide) because they were unavailable in Nigerian pharmacies and could not be obtained from foreign pharmacies without insurance. Her blood glucose fluctuated widely between 1.2 and 11.5 mmol/L, as her mother fed her frequently as she was anxious of the hypoglycemic convulsion.

The follow-up visit at 6 months revealed a small head with head lag and fixed hyperextension of the ankle joints. She was unable to babble, but she had good social smile. An additional diagnosis of cerebral palsy with spastic paraplegia was made and she started physiotherapy. Two years after making the clinical diagnosis and giving genetic counseling to the parents and obtaining their consent, samples for genetic testing were sent to University of Exeter Medical School Molecular genetics laboratory. The results revealed compound non-sense mutations of the ABCC 8 gene, p.W143*, and p.Q416* inherited from both parents.

She has not had a positron electron tomography (PET) scan done to locate site of disease. She has been maintained on high caloric diet with anticonvulsants. She is gaining weight and height as is now above the 95th percentile in both parameters, but her head circumference has remained below the 50th percentile for age and sex. Arrangements are still on going to obtain a PET scan and possible pancreatectomy to prevent hypoglycemic episodes.

Molecular genetics

Following genetic counseling and consent from her parents, whole blood samples were taken from the patient and her parents and placed in potassium ethylene diacetic acid bottles, 5 milliliters each. Samples were taken and immediately placed in an ice-pack container and sent to University of Exeter Medical School Molecular genetics laboratory, in London through courier. DNA was extracted from the peripheral leukocytes using standard methods and analysis of coding and flanking intronic regions of the ABCC8 and KCNJ11 genes (NM_000525.3, NM_001287174.1) by Sanger sequencing, were undertaken.

Ethical approval

After counseling and ethical approval was obtained from the Research and Ethics Committee of the University of Port Harcourt Teaching Hospital for the study, the parents of our patient gave consent to present their case.

RESULTS

The results of genetic studies for the family are as presented in Table 1 and show inheritance of compound heterozygote of 2 ABCC8 non-sense mutations inherited from each parent at different loci of their genes.

DISCUSSION

The clinical features of CHI are well-documented and the most striking feature is the severe refractory hypoglycemia the children presenting within the neonatal period.[1-3] This patient had similar presentation for which prompt clinical diagnosis was made. Convulsions can persist well into adult life causing epilepsy for many children that are not treated early. Epilepsy develops due to irreversible brain damage from prolonged and persistent anoxic-ischemic processes during the early life episodes. Treatment with diazoxide is possible

Table 1: Genetic results of patient and parents with the consequences of the mutations noted in the genes.

Mutation details	Index patient	Mother	Father
Gene	ABCC8	ABCC8	ABCC8
Location	Exon 4 and Exon 8	Exon 8	Exon 4
DNA descriptions	c.428G>A/c.1246C>T	c.1246C>T	c.428G>A
Protein description	p.Trp143Ter/p.Gln416Ter (p.W143*/p.Q416*)	p.Gln416Ter (p.Q416*)	p.Trp143Ter (p.W143*)
Consequence	Non-sense	Non-sense	Non-sense

for many diazoxide-responsive CHI children. However, patients with recessive mutation of the K_{ATP} gene, like our patient, are unresponsive to diazoxide making it invariable for total or partial pancreatectomy. Some children also respond to octreotide, which is a growth hormone analog, but there have been reports of necrotizing enterocolitis in children receiving this drug for prolonged periods.[13-15]

The processes of treating neonatal hypoglycemia are documented and physicians may need not go beyond dextrose infusion for successful management of most neonates. In CHI, however, diazoxide, octreotide, and hydrocortisone may be employed in the treatment regimen. When all these treatments fail, partial or total pancreatectomy should be considered and performed. Diazoxide is the first drug of choice in the treatment for CHI and it is the only oral medication available. It acts as an agonist of the SUR-1, opening up the K_{ATP} channel, thereby inhibiting the secretion of insulin. There may be need to increase the dose of diazoxide from the recommended 5 mg/kg to the maximum 15 mg/kg/day, if hypoglycemia persists after 3 days. Diazoxide responsive patients can be safely discharged home on the medication with home glucose monitoring. Octreotide is effective in the short-term management of refractory hypoglycemia; however, the tachyphylaxis it induces and the need for multiple injections limits its use. It has also been associated with fatal necrotizing enterocolitis (NEC), so the benefits of use in infants should be weighed against the risk of NEC.[13-15] None of these options were available to our patient as the medications and procedures were not available in the country.

The option of pancreatectomy is limited to refractory hypoglycemia and this complication can be a total or partial pancreatectomy depending on whether the disease is focal or diffuse.[16] It is therefore necessary to have a PET computed tomography scan done to localize the disease.[17,18] This procedure is very expensive and not yet available in Nigeria. The risk of developing diabetes mellitus is very high so this procedure is reserved only for the diazoxide refractory patients who have life-threatening convulsions and should be performed by experienced surgeons to avert complications. Possible complications include common bile duct injury, splenic injury, small bowel adhesions, and intussusceptions.

Making a molecular diagnosis of CHI is not possible in most of Africa, so samples need to be transported to specialized research laboratories in Europe and America.[19-21] This was relatively easy with our patient after successfully completing the procedures for transport of biological samples. After signing a material transport authorization with the ministry of health and obtaining permission from the parents, the courier to London arrived within a day and results were made available within 3 weeks. Many other materials for other investigations have been successfully transported to and from Europe. Until the processes, procedure, and equipment are made available in Africa or regionally, the means of diagnosis for rare diseases, such as CHI, should be explored by African countries for timely diagnosis and treatment of clinical cases.

CONCLUSION

This report has been able to detail the clinical course and complications of CHI in a girl in Nigeria who inherited two non-sense mutations in the ABCC8 gene from different exons from both parents. Early referral of the patient to the pediatric endocrinologists made it possible to make diagnosis and start treatment, though the standard imaging modalities, genetic analysis, and medications are not available in Nigeria. It is noteworthy that our collaboration with European and American physicians improved the outcome and prognosis of our patient.

Data availability

The patient data and clinical course with investigation results are available in the medical records and upon request to the corresponding author.

Authors' contributions

YIE and JT were responsible for the management of this patient and also prepared the manuscript for publication.

Declaration of patient consent

Patient consent is not required as the patient identity is not disclosed or compromised.

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None.

Conflicts of interest

There are no conflicts of interest

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