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PERSISTENT HYPERINSULINAEMIC HYPOGLYCAEMIA IN A SIX-WEEK OLD NIGERIAN BOY: CLINICAL PRESENTATION AND MANAGEMENT CHALLENGES IN A DEVELOPING COUNTRY.

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ABSTRACT

This paper reported a case of a six-week old Nigeria boy with persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) who presented with typical clinical and laboratory features and in whom some management challenges commonly seen in developing countries were encountered. The clinical diagnostic features included: at the time of hypoglycaemia (blood glucose level 1.6 mmol/L), serum insulin level of 6 mU/ml; absence of ketonuria and acidosis; and elevated level of serum C-peptide and a high glucose infusion rate (12 mg/kg/day) with persistence of the hypoglycaemia. Management challenges encountered included non-availablity of a long-acting somatostatin analog (octereotide) for treatment, lack of investigative facility for distingiuishing between diffuse beta-cell hyperplasia and focal beta-cell microadenoma, paucity of surgical expertise for pancreatectomy and lack of fund to pay for medical treatment abroad in the event of referral.

INTRODUCTION

Persistent hypoglycaemia refers to a low blood glucose persisting or reoccurring over a period of five to seven days and warrants an endocrinologic consultation.[1] The criteria for diagnosis of endogenous hyperinsulinism include: in the presence of hypoglycaemia, serum insulin level above 5 mU/ml ; absence of ketonuria and acidosis; elevated serum C-peptide(an insulin-related product); and a glucose infusion rate greater than 10 mg/kg/min in neonates/early infancy necessary for maintenance of normoglycaemia.[2-4] The hypoglycaemia is usually permanent, both in the fasting and post-prandial states.[3]In the literature, some school of thought set even more stringent criteria for defining hyperinsulinism. They argue that any value of serum insulin concentration above 2 mU/ml in the presence of hypoglycaemia is abnormal.[2] Indeed insulin level should be undetectable at the time of hypoglycaemia.[3] Many authorities agree that the need for measurement of blood levels of other substrates and counterregulatory hormones is unnecessary, if these criteria are met.[1,2]

Unregulated insulin secretion by the pancreatic beta cells result in hyperinsulinaemic hypoglycaemia. Persistent hyperinsulinaemic hypoglycaemia of infancy (also referred to as congenital hyperinsulinism[3]) is a genetic disorder with familial and sporadic forms.[2,3] It is a heterogeneous disorder, both clinically and genetically, and its response to medical and surgical therapy is also variable.[3-6] Some patients with persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) have genetic abnormalities of the sulfonylurea receptor or other genetic defects that alter the function of the ATP-sensitive potassium channel that regulates insulin secretion.[7,8] The estimated incidence of PHHI is 1 in 50,000 live births, with a higher incidence in populations where consanguinity is common.[3]

The differential diagnosis of endogenous hyperinsulinism include diffuse beta-cell hyperplasia or focal beta-cell microadenomas with the former being more common.[2,3] Insulin-secreting macroadenomas are rare in childhood.[2,3]

Although most children with PHHI present in the neonatal period, the age of onset vary from birth to 18 months.[2,3] Hypoglycaemia is less common after the newborn period but its recognition still remains important in the postneonatal period. Hyperinsulinism is the commonest cause of persistent hypoglycaemia in early infancy.[2,10] The common presenting clinical features of PHHI include episodes of weakness (wilting spells), colour changes, jitteriness and frank seizures. Additional clinical features include the need for high rates of exogenous glucose infusion to prevent hypoglycaemia (often at rates greater than 10 mg/kg/min; 6 ml/kg/hour) and absence of ketonaemia (ketonuria) or acidosis.[2-4,7]

The purpose of this paper is to describe the clinical features in a six-week old Nigerian boy with persistent hyperinsulinaemic hypoglycaemia and highlight the management challenges encountered in the care of this infant.

CASE REPORT

The patient was born in a secondary health-care facility in Benin City, Nigeria. His parents are Nigerians. The patient was the first child of the couple. The pregnancy, labour and delivery were uneventful. He weighed 3.0 kg at birth and was discharged from the hospital 72 hours after birth in accordance with the hospital's policy. The patient was apparently doing well until during the 5th week of postnatal life when he was noticed to be having episodes of weakness which was unrelated to time of the day. The episodes of weakness continued throughout the day. This was associated with poor suck, necessitating feeding with expressed breast milk by the mother at home. He first presented at the secondary health-care facility where he was born and was admitted as a case of septicaemia. He was placed on appropriate doses of intravenous antibiotics (cefotaxime and gentamycin) and maintenance intravenous fluid (4.3% dextrose in 0.18% saline). The episodes of weakness continued despite this modality of treatment. On the 4th day of admission he was noticed to be pale (haematocrit 34%) and shortly after he had a seizure, warranting his referral to the University of Benin Teaching Hospital (UBTH) for further evaluation and management.

Evaluation at the UBTH revealed no history of fetal distress, birth asphyxia or maternal alcohol ingestion. The mother did not have diabetes mellitus or acute fatty liver in pregnancy or HELLP syndrome (haemolysis, elevated liver enzyme, and low platelets). No history of neonatal jaundice, whether prolonged or not. There was no history suggestive of a temporal relationship with meals or caloric deprivation. Physical examination revealed a weight of 2.45 kg, normal occipitofrontal circumference and body temperature (37^0C). Jaundice and hepatomegaly were absent. The tongue was of normal size and there was no umbilical hernia or any dysmorphic feature, such as cleft lip/palate or microphallus or cryptorchidism. There was no abnormal pigmentation or abdominal mass. Laboratory investigation revealed a blood glucose of 1.5 mmol/L. The urea and electrolyte profile was within normal limits. Urinalysis revealed no ketonuria. A diagnosis of severe symptomatic hypoglycaemia of unknown cause was entertained. Standard protocol for treatment of severe symptomatic hypoglycaemia was instituted, using 10% dextrose in water (10% DW). [2,10] The rate of 10% DW infusion was increased at the rate of 2 mg/kg/min until a maximum of 12 mg/kg/min was reached[10] but hypoglycaemia still persisted (blood glucose fluctuating between 1.5 to 1.7 mmol/L). Intravenous hydrocortisone was added to his therapy but the hypoglycaemia still persisted. At this point, a diagnosis of persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) was entertained and fatty acid oxidation disorder and galactosaemia were considered as differentials, both being principal causes of nonketotic hypoglycaemia. Therapy with oral diazoxide (15 mg/kg/day) was instituted to correct the hypoglycaemia without success. Effort to procure glucagon or octreotide or human growth hormone was unsuccessful. Further investigations were performed. Urine tests for ketone and reducing substances (glucose and non-glucose) were negative. A critical sample (blood sample collected at the time of hypoglycaemia) revealed the following results: blood glucose 1.6 mmol/L (hypoglycaemia), serum insulin 6 mU/L (elevated), serum C-peptide 65 pg/dl (elevated), and free fatty acid 0.25 mmol/L (low). Results of thyroid function test were within normal limits. Abdominal ultrasonography was normal. Unfortunately, the patient died on the third day on admission in UBTH. The parents refused to give consent for autopsy.

DISCUSSION

In this patient, the diagnosis of persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) was based on clinical features and laboratory findings. This six-week old boy presented initially with recurrent episodes of weakness (wilting spells) and poor suck and later colour change (pallor) followed by seizure. These signs and symptoms are typical of hypoglycaemia in early infancy.[2-4] The signs and symptoms persisted for up to 7 days (despite high rate of infusion of 10% dextrose in water), qualifying it as persistent.[1] The results of the "critical sample" which revealed low blood glucose, elevated serum insulin, low plasma ketone (evidenced by absence of ketonuria) and low plasma free fatty acid levels. The elevated level of C-peptide and absence of acidosis are further evidence of endogenous hyperinsulinaemic hypoglycaemia in this patient. Epidemiologically, PHHI is the commonest cause of persistent or recurrent hypoglycaemia presenting in early weeks or months of life.[2,3,9] This patient presented in early infancy (age of 5 t0 6 weeks). The differential diagnosis in this patient include fatty acid oxidation disorder (FAOD) and galactosaemia; the two major causes of hypoketotic hypoglycaemia in infancy. With regard to FAOD, the negative history of maternal acute liver in pregnancy and HELLP syndrome,[11] low plasma free fatty acid level, absence of ketonuria and acidosis made this consideration less likely. In addition, most patients with medium-chain acyl-CoA dehydrogenase (MCAD) type of fatty acid oxidation disorder (commonest form of FAOD) have their first episode of hypoglycaemia between the age of 3 months and 3 years and the episodes of hypoglycaemia are usually associated with a history of fasting.[12] The index patient was 6 weeks old and hypoglycaemia persisted despite frequent feeding and high rate of glucose infusion, both features being against the diagnosis of FAOD. Galactosaemia usually presents in the second half of the first week of life with evidence of liver failure (hyperbilirubinaemia, disorders of coagulation, hypoglycaemia), vomiting, diarrhorea, hepatomegaly after initiation of milk feeding but none of these clinical features (except hypoglycaemia) was present in the index patient. More importantly, absence of reducing substance in the urine was against the diagnosis of galactosaemia. Insulin-secreting mesenchymal tumour (a cause of hyperinsulin-like hypoglycaemia) was unlikely because of absence of abdominal mass on physical examination and confirmed by normal abdominal ultrasonography. PHHI, itself, may be due to diffuse beta-cell hyperplasia or focal beta-cell microadenomas.[2-4] Insulin-secreting macroadenomas are rare in childhood. [2] However, in this patient we could not determine the specific cause of the PHHI because of lack of investigative facility in our hospital. This is not surprising as experts on this subject have acknowledged the difficulty in distinguishing between diffuse beta-cell hyperplasia and focal beta-cell microadenomas, a distinction requiring [18F]-DOPA positron emission tomography,[2-4,13] and an investigative procedure currently unavailable in Nigeria.

For the purpose of this discussion, the management challenges in this patient will be categorized

into two: diagnosis and therapy. The major diagnostic challenge was our inability to distinguish between diffuse beta-cell hyperplasia and focal beta-cell microadenoma, a distinction that heavily influences the surgical management.[2-4] Therapy with diazoxide having failed, the next stage in the management was to consider surgery (partial or near-total pancreatectomy),[3,4] if the patient had lived longer. An objective which we could not have achieved because of lack of the appropriate investigative facility. The lack of response to diazoxide therapy observed in the index patient is not surprising, as some studies have reported similar experience. Indeed, they reported that 55-60% of diazoxide-unresponsive PHHI are focal forms, whereas 40-45% are diffuse forms, in Western countries.[14] Considering the two principal differential diagnoses, fatty acid oxidation disorder and galactosaemia, the laboratory facilities for their confirmation are scarce in Nigeria, and perhaps other developing countries. Their confirmatory tests require determination of urine dicarboxylic acid level and assay of relevant enzymes in cultured fibroblasts in the case of FAOD.[11,12] With regard to galactosaemia, the confirmatory test involves determination of the level of galactose-1-phosphate uridyl transferase in the erythrocytes.[12,13] The refusal by the patient's parents to give consent for autopsy represented a lost opportunity to reach a histopathological diagnosis. This scenario is common in Nigeria, and perhaps most African countries, because of some traditional beliefs regarding reincarnation. The principal therapeutic challenge was non-availability of long-acting somatostatin analog (octereotide) used as a temporizing agent for variable periods before sub-total pancreatectomy. In Nigeria, like in most developing countries, there is the issue of availability of the necessary surgical expertise for pancreatectomy in a six-week old infant. Furthermore, wide-spread poverty in our society make referral to technologically advanced countries, possessing the required medical expertise, a nonexistent option. [15]

In conclusion, although this six-week old male infant presented with typical clinical features of PHHI, some management challenges commonly seen in developing countries were encountered during the course of his medical care in the hospital.

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