ORIGINAL ARTICLE

CLINICAL PROFILE AND OUTCOME OF PERSISTENT HYPERINSULINEMIC HYPOGLYCEMIA OF INFANCY

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Abstract

Aim: To study the clinical profile and outcome of persistent hyperinsulinemic hypoglycemia of infancy (PHHI).

Setting: Retrospective study done at a tertiary pediatric referral hospital at Chennai from January 2007 to March 2013.

Methods: Fifteen infants diagnosed to have PHHI were included in the study. Their genetic, biochemical and clinical outcome were analyzed.

Results: Seizures, lethargy and refusal of feeds were the initial presentation in these infants. Thirteen (86.6%) were term babies. Three (20%) were large for gestational age. Serum insulin levels were in the range from 3 to 54μIU/ml with a mean of 23+/-15.7μIU/ml. Among the 12 infants who underwent genetic evaluation, 4 (33%) had mutations in ABCC8 gene. Five (33%) infants underwent pancreatectomy for refractory hypoglycemia. All children with pancreatectomy had diffuse disease and on follow up three of them are euglycemic without any drugs, one infant is still on octreotide and one infant succumbed with sepsis 7 months later. Among the 8 children on medical therapy, 7 (87.5%) children are still on diazoxide and being followed up. Two (13.3%) children were lost to follow up. Nine (69%) children have attained age appropriate developmental milestones on follow up. Motor developmental delay, delayed speech, seizures and microcephaly were the neurological findings on follow up in 4(31%) children.

Conclusions: Majority of infants with PHHI were term appropriate for gestational age. ABCC8 mutations are encountered in 33% infants. Diazoxide responsive PHHI was common in the study group.

Keywords : PHHI, infancy, genetic mutations.

Introduction

Hypoglycemia is a medical emergency which needs prompt diagnosis and treatment, the failure of which may lead to brain damage. Hyperinsulinism is the most common cause of persistent hypoglycemia in infancy [persistent hyperinsulinemic hypoglycemia of infancy (PHHI)]. The incidence of PHHI is estimated at 1/50000 live births but it may be high as 1/2500 in countries with substantial consanguinity. (1) Recurrent episodes of hypoglycemia may expose children to high risk of irreversible brain damage leading on to mental retardation, cerebral palsy and epilepsy. (2-5). Hyperinsulinism is a heterogeneous genetic disorder with two main clinically indistinguishable histopathological lesions: diffuse and focal. Focal form is characterised by focal adenomatous hyperplasia of islet cells while the diffuse form involves hypertrophy of all the beta-cells of pancreas which results in unregulated hypersecretion of insulin. Gene mutations play a pivotal role in their etiology. (6,7) Molecular genetic analysis and 18F-fluoro-L-Dopa positron emission tomography (PET) can help to differentiate diffuse or focal forms of hyperinsulinemia of infancy (HI). (8,9) Treatment of hypoglycemia includes intravenous glucose or drugs like diazoxide, glucagon, octreotide, hydrocortisone and nifedipine. When medical therapy is ineffective, or when a focal HI is suspected, surgical treatment is offered. Surgical resection in focal HI is curative. By contrast, the outcome of diffuse HI after subtotal pancreatectomy is characterized by a long term risk of diabetes with variable time of onset. We present clinical profile and outcome of PHHI in our patients.

Methods & Materials

We discuss the experience of PHHI among South Indian infants from a pediatric tertiary care hospital in Chennai, Tamil Nadu. We conducted a retrospective case record review of children with PHHI during the period 2007 to 2013. A diagnosis of PHHI was made in children based on the following criteria: requirement of glucose infusion of >8mg/kg/min, laboratory blood glucose <3 mol/l with a detectable serum c-peptide or insulin levels, in the absence of ketosis or ketonuria, with or without elevated ammonia and/or a positive response to diazoxide or octreotide.

Fifteen patients with PHHI were identified and included in the study group. The study parameters included disease history, biochemical investigations, molecular genetic analysis and follow up. History included presenting features, age at onset of hypoglycemia, gestational age, birth weight, family history and degree of consanguinity. Biochemical investigations included estimation of plasma glucose, serum insulin, serum cortisol, growth hormone, thyroid function tests, arterial blood gases, c- peptide levels, blood ketones, serum lactate, ammonia and urine ketones. Imaging modalities included ultrasonography of the abdomen. Gadolinium PET scanning and molecular genetic studies were performed wherever feasible. In children who had undergone pancreatic resection, histopathological reports were noted.

Affected children received dextrose bolus for correction of hypoglycemia followed by a glucose infusion ranging up to a maximum of 20mg/kg/min. Infants with PHHI received oral diazoxide in gradually increasing doses from 10 to 25 mg/kg/day in three divided doses. Somatostatin analogue (octreotide) had also been given in the dose of 5 to 20 μg/kg per day QID, given subcutaneously, in babies who had not maintained normoglycemia with adequate feeding, glucose infusions, hydrocortisone and diazoxide (25 mg/kg/day). Infants received nifedipine if refractory. Pancreatic resection (85 to 90%) had been offered when plasma glucose could not be maintained above 60 mg/dl despite the best of medical management.

Results

Male to female ratio was 1.5:1. The presenting

symptoms were seizures, lethargy and refusal of feeds in all patients. Age at onset varied from three hours of life to three months. Four children (26%) presented within 24 hours of life and another 4 (26%) presented within 72 hours and the remaining 7 (54%) babies had symptoms within first 3 months of life. Seven (46%) children were born of consanguineous marriage. History of similar complaints in siblings was noted in two families with one of them having a history of seven neonatal deaths prior to the two affected babies.

Thirteen infants (86%) were of term gestation while the other two (13%) were preterm. None of them was an infant of a diabetic mother. Birth weight in the study group varied from 2 kg to 3.74 kg with a mean of 2.9 +/-0.5kg. Three (20%) were large for gestational age. Blood sugar at admission ranged from 18mg/dl to 56mg/dl with the mean 32.2+/-7.5mg/dl. Serum insulin levels were in the range from 3 to 54μIU/ml with a mean of 23+/-15.7μIU/ml. Other parameters like urine ketones and blood ketones were negative. Serum cortisol levels and thyroid profile were in normal range for all patients. Hyperammonemia was encountered in 1 (6%) infant. Ultrasonography of the abdomen was normal. Gallium Dotanoc PET scan was done in 5 (33%) children. Three (60%) of them had evidence of diffuse uptake. Pancreatectomy was done in these three children and the histopathology confirmed the diffuse disease. Two other children underwent pancreatectomy for refractory hypoglycemia and had evidence of diffuse disease in the histopathology postoperatively.

During the acute phase, 10 (66.6%) children responded to diazoxide and octreotide therapy and 5 (33.3%) required additional nifedipine therapy. Five (33.3%) children underwent surgery with four requiring near total pancreatectomy and one subtotal pancreatectomy.

Biopsy samples revealed diffuse islet cell hyperplasia. Molecular genetic analysis by direct sequencing method was undertaken for 12 children (75%) to identify mutations in ABCC8, KCNJ11, INS, HNF4A, GCK and GLUD1. Four children had genetic mutation in ABCC8 gene. Among these one was a paternally derived heterozygous mutation and the Gadolinium scan was suggestive of a diffuse disease. Two had homozygous mutation with both parents being heterozygous and the other one was a heterozygous mutation which was also seen in the mother. The child with hyperammonemia tested negative for GLUD mutation.

One child who underwent pancreatectomy succumbed to severe sepsis after 7 months of surgery. She also had diabetes mellitus and required insulin for 3 months postoperatively. Of the fourteen children, two were lost to follow up, and the rest (12 children) were followed up at the clinic. Seven (58%) children are still on diazoxide, with normal development. The duration of diazoxide therapy varied from 3 months to 5 years. One child was on injectable octreotide for 2 years and is now off octreotide and is euglycemic. Among the children who underwent surgery, one infant is on octreotide at a dose of 15μg/kg/day. Nine of the 13 children (69%) who were followed up have attained developmental milestones appropriate for age with no neurological deficits. One child on diazoxide has mild speech delay, two children with pancreatectomy (40%) had developmental delay with, microcephaly and one child, post pancreatectomy (20%) developed recurrent seizures. Only 2 of the children (40%) with pancreatectomy were developmentally normal. Table 1 summarizes the clinical profile among individual patients.

Discussion

Congenital hyperinsulinism (CHI) or persistent hyperinsulinemic hypoglycaemia of infancy or islet cell hyperplasia is a heterogeneous disorder of unregulated excessive secretion of insulin with variable age at onset from birth to childhood. (2) It is characterised by non-ketotic non-acidemic severe hypoglycemia with depressed fatty acid level consequent to its inhibitory action on counter regulatory hormones. (3) The incidence of PHHI in the general population increases in areas with consanguinity. In our study of 15 infants, 7 infants were born to varying degrees of consanguinity. Findings similar to ours were seen by Thornton et al who studied twenty five families with affected siblings being reported in 15 cases. Consanguinity plays a major role in familial occurrence. (1) So far mutations in eight genes have been identified- ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A and UCP2. (10) Of these, mutations in ABCC8 (encoding SUR1, subunit of a potassium channel in the beta-cell) and KCNJ11 (encoding Kir6.2, subunit of the same potassium channel) genes are the most common cause (12-14) characterised by diffuse form of PHHI which is unresponsive to diazoxide therapy. (6,7) GLUD1 mutations have been associated with leucine hyper responsiveness with hypoglycaemia following feeds and hyperammonemia. (10,14-16)

Measurement of serum ammonia as a screening tool may add to the diagnostic work up of hyperinsulinemic hyperammonemia syndrome. (HI-HA) Focal forms are genetically heterogeneous which may involve the combination of a paternally-inherited ABCC8 or KCNJ11 mutation and a paternal isodisomy of the 11p15 region, which is specific to the islets cells within the focal lesion. Genetic analysis and 18F-fluoro-L-DOPA positron emission tomography (PET) may help to differentiate diffuse or focal forms of HI which are clinically indistinguishable. (8,9) However, 40-50% of the patients are still genetically unexplained (17) especially the focal forms of hyperinsulinism. PHHI can be dominantly or recessively inherited or may occur de novo. Focal forms are usually sporadic. A number of syndromes can be associated with PHHI including Beckwith wiedemann syndrome (18) or congenital disorders of glycosylation syndromes type Ia and Ib, Kabuki and Soto's syndrome (19).

Recurrent, generalized seizures was the commonest presenting feature in this series, followed by lethargy and refusal of feeds. Similar observations were made in a study by Desai et al in Mumbai (20).

The aim of treatment is to maintain normoglycemia and prevent hypoglycemia related brain damage. Three treatment modalities were considered to maintain

Table 1: Clinical profile of all patients

Case	Gender	Age at presentation	Consanguinity	Birth weight (kg)	Positive family history	Blood glucose (mg%)	Insulin Micu/ml	Insulin/glucose	PET CT	Diazoxide responsive	Gene mutation	Outcome	Follow up
1	Male	3 hours	No	2.1	No	26	47.5	1.82	-	Yes	-	improved	Lost to follow up
2	Male	72 hours	Yes	3.25	yes	31	37.4	0.63	-	No	-	improved	microcephaly, developmental delay, seizures
3	Male	13 days	Yes	3.1	Yes	36	18.5	0.33	-	No	-	died	-
4	Male	3 hours	No	2	No	35	12.6	0.36	-	Yes	No	improved	Lost to follow up
5	Male	4 days	Yes	3.3	No	22	15.3	0.69	normal	No	ABCC8	died	microcephaly, developmental delay, diabetes mellitus
6	Male	3 months	Yes	2.8	No	35	6.2	0.17	diffuse	Yes	No	improved	Normal development
7	Female	3 months	No	2.5	Yes	38	54.1	1.42	-	Yes	No	improved	Normal development
8	Male	3 months	No	3	Yes	36	10.7	0.3	-	Yes	No	improved	Normal development
9	Female	2 days	No	3.74	No	22	36.1	1.66	diffuse	No	No	improved	Normal development
10	Male	20 days	Yes	3.25	No	23	15.3	0.7	-	Yes	No	improved	Delayed speech
11	Female	2 days	No	3.05	No	30	6	0.5	normal	Yes	No	improved	Normal development
12	Female	24 hours	Yes	2.8	No	18	32.7	1.8	-	Yes	ABCC8	improved	Normal development
13	Female	33 days	No	2.75	No	39	19	0.47	diffuse	No	ABCC8	improved	Normal development
14	Female	3 days	Yes	3.2	No	35	30.1	0.7	-	-	ABCC8	improved	Normal development
15	Male	24 hours	No	2.8	No	38	3	0.07	-	-	No	improved	Normal development

normoglycemia, namely opposing the insulin action via glucagon, hydrocortisone or preventing the secretion of insulin from beta-cells by diazoxide or octreotide and nifedipine or reducing the beta-cell mass by resection in failure of above two measures. Diazoxide is the main treatment of choice for PHHI. It prevents insulin secretion by acting on the pancreatic beta-cell KATP channel and has the effect of opening the channel (keeping the beta-cell membrane in a hyperpolarized state). (3) Side effects include hypertrichosis and fluid retention. Chlorthiazide is usually added for diuretic effect. Diazoxide may prove ineffective in infants who present from birth especially in ABCC8 and KCNJ11 mutation as they involve the SUR1 subunits. Octreotide is a somatostatin analogue primarily used to tide over crisis situation. It prevents exocytosis of insulin from beta-cells. (21) Subcutaneous or intravenous octreotide inhibits first-phase insulin secretion and attenuates insulin responses to activated Gs-protein coupled receptors (such as the glucagon like peptide-1 receptor). Main side effect of octreotide is vomiting, diarrhea and tachyphylaxis. Few cases of necrotising enterocolitis have been reported. (22) One infant in our series had persistent vomiting and hypertrichosis due to diazoxide.

Surgery is the treatment modality in case of failure of drug therapy in a genetically confirmed diffuse disease with ABCC8 or KCNJ11 mutations or PET showing focal involvement. Resection of the segment involving the lesion may potentially cure the disease in case of focal form while near total pancreatectomy with the removal of 85 to 90 percent of pancreas is the

treatment of choice in case of diffuse form of PHHI. (23-25) One third of these infants may still remain hypoglycemic requiring total pancreatic resection with its attendant mortality and morbidity. The true risk of late onset exocrine insufficiency is not known and diabetes mellitus after 95% pancreatectomy occurs in 69% of children requiring lifelong therapy with insulin. (26) One infant in our series developed hyperglycemia after 3 weeks of pancreatectomy requiring exogenous insulin.

The study does have few limitations like the use of Ga- Dotanoc PET scan as an imaging modality in contrast to 18 F Dopa PET scan (27) which is recommended for diagnosing focal PHHI. 18F Dopa is not available at present in our country. Usefulness of Dotanoc scan in PHHI needs to be studied. But for a few case reports, not much details are available on Dotanoc PET scan in children with PHHI (28). Also a formal neuro-developmental assessment has been planned in all these children during follow up as this might bring out minor developmental issues.

Conclusion

Most of neonates with PHHI are born as full term. Diazoxide responsive PHHI is common in this study population. ABCC8 mutations are encountered in 33% of children with PHHI. Genetic and imaging studies may have a significant role in the management of PHHI. Dotanoc PET scan as an alternative in the absence of 18F Dopa PET scan needs to be studied for its utility in PHHI. Developmental delay and other neurological problems are encountered more commonly in children refractory to medical therapy.

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Previous publications in relevance to this article:

The above data is a part of the multicentric study conducted in India and the genetic aspects of that multicentric study paper has been submitted and are under the process. This paper describes the clinical aspects of the single site at Institute of Child Health and Hospital for Children, Chennai

Conflict of Interest : none

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