Persistent hyperinsulinemic hypoglycemia of infancy in 38 children

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ABSTRACT

Objectives: To describe the clinical, biochemical, radiological and electrophysiological features of 38 Saudi children with persistent hyperinsulinemic hypoglycemia of infancy that have been followed since 1983.

Methods: Data from 38 patients followed at King Faisal Specialist Hospital and Research Centre, Riyadh, Kingdom of Saudi Arabia from 1983 through to 2002 was retrospectively analyzed. Persistent hyperinsulinemic hypoglycemia of infancy was diagnosed on the basis of high intravenous glucose requirement, high insulin to glucose ratio, negative urinary ketones and normal tandem mass spectrometry. The patients were assessed radiologically by brain magnetic resonance imaging, computed tomography, or both and electrophysiologically by brain stem auditory evoked potential, visual evoked response and electroencephalogram. The patients who failed medical therapy had subtotal pancreatectomy.

Results: The patients were severely hypoglycemic and intolerant to fast. Hypoglycemic convulsion was the most commonly presenting complaint. Eighteen patients were developmentally delayed and 14 of them had brain atrophy. All patients, except nine, did not respond to medical treatment and had surgery. Four pancreatectomized patients developed diabetes and 2 had malabsorption. One patient was treated medically during childhood and developed diabetes and weight gain during adolescence.

Conclusion: Persistent hyperinsulinemic hypoglycemia of infancy is a relatively common and serious disease among Saudi children. Early medical intervention is necessary to avoid neurological damage in our patients who are severely hypoglycemic and medical therapy unresponsive. Surgically and probably medically treated patients are at high risk of developing diabetes that could be the natural outcome of this disease.

Saudi Med J 2003; Vol. 24 (8): 890-894

Persistent hyperinsulinemic hypoglycemia of infancy (PHHI), formerly known as nesidioblastosis, is a glucose metabolism disorder characterized by profound hypoglycemia and inappropriate secretion of insulin.[1] The incidence of PHHI in the general population is 1:50,000 live births in which most of the cases are sporadic.[2] However in countries with substantial inbreeding such as the Kingdom of Saudi Arabia (KSA) and where most of the familial cases are present, the incidence may be as high as 1:2500.[3] Familiar forms may be caused by recessive or dominant defects in the sulfonylurea receptors (SUR1) gene;[4] the potassium inward rectifying receptors (Kir6.2) gene;[5] the glutamate dehydrogenase gene[6] or the glucokinase gene.[7] Affected children run the risk of severe neurological damage unless immediate and adequate steps are taken.[8] Treatment with diazoxide, somatostatin analogue, or both is not always effective especially in familial cases, which may necessitate an alternative intervention such as pancreatectomy.[9] Several case studies describing the clinical and the molecular basis of this disease have been reported, however the data on the long term outcome is limited. In this study we report our long-term clinical experience with 38 children with PHHI followed at King

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Received 17th March 2003. Accepted for publication in final form 12th May 2003.

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Faisal Specialist hospital and Research Center, Riyadh, KSA from 1983.

Methods. We retrospectively evaluated the records of 38 Saudi children (23 girls, 15 boys) with PHHI diagnosed between 1983 and 2002. Persistent hyperinsulinemic hypoglycemia of infancy was diagnosed on the basis of an intravenous glucose requirement of 12mg/kg/min or more to maintain euglycemia, insulin (μU/ml) to glucose (mg/dl) ratio of 0.3 or more while the patient is hypoglycemic, a 30-minute glucose increment of 30mg/dl or more in response to intramuscular/subcutaneous 0.5 mg glucagon, negative urinary ketones and normal blood spot acylcarnitine profile determined by tandem mass spectrometry (MS). The method of tandem MS was introduced after April 1994. Growth hormone (GH), cortisol, adrenocorticotrophic hormone (ACTH), insulin, lactate and urinary ketones were measured during hypoglycemia. Growth hormone level of 20 mU/L and cortisol level of 500 nmol/l or more were considered normal. Growth hormone, cortisol, ACTH, insulin levels were measured by radioimmunoassay, glucose by glucose oxidase method and urinary ketones by chemistrip (IRIStrips, Roche). The patients were assessed radiologically by brain magnetic resonance imaging (MRI), computed tomography (CT), or both and electrophysiologically by brain stem auditory evoked potential (BEAP), visual evoked response (VER) and electroencephalogram (EEG). Echocardiogram was performed in patients in whom a cardiac disease was suspected. Our management policy was to treat medically, surgically, or both to maintain a blood glucose level of 70mg/dl or more post, at least, an 8 hour fast in neonates or 12 hour fast in older children. Medical therapy was the first choice; diazoxide was the first-line drug (maximum dose 25mg/kg/day), followed by octreotide (maximum dose 40mcg/kg/day). If medical therapy failed (lack of response or development of side effects), subtotal (95%) pancreatectomy was the initial surgical resection, if failed, another cycle of medical therapy was tried before near total (98%) pancreatectomy was performed. Histological reports of 15 patients were available for review. Histologically, pancreases were divided in 2 groups; focal and diffuse. Focal forms were diagnosed based on the presence of a localized excessive proliferation of islet cells in otherwise, normal pancreas, however in diffuse form the diagnosis was based on the appearance of diffuse islet cell hyperplasia. No pre-operative localizing procedures for focal lesions were performed.

Results. All children were products of full term pregnancies except 5 who were preterms. All except 7 were born vaginally. Seven patients were born via cesarean section; 2 of them had cephalopelvic disproportion. The birth weight ranged from 2.5-4.5kg (median 3.5kg). Twelve patients had a birth weight of more than 4kg. On referral to our center, head circumference measurements were available in 20 patients and ranged from -1.5 SD to +0.5SD. Three mothers were gestationally diabetic and 2 mothers had type 2 diabetes that were treated with insulin during pregnancy. The parents were first-degree cousins in 17 families, second-degree cousins in 7 and far relatives in 5. One family had 7 affected children, and 3 families had 2 siblings with PHHI. The current age of patients ranged from 4 months to 17 years (median 5 years), the age of first documented hypoglycemia ranged from a few hours to one year (median one day), the age at which the diagnosis was made ranged from 10 days to 3 years (median 2 months). Hypoglycemic convulsion was the most commonly presenting complaint, which was observed in 28 children followed by sweating, lethargy, tremor and apnea in 20 patients. All patients were severely hypoglycemic and intolerant to fast. The median fasting tolerance time needed for hypoglycemia to occur was 90 minutes (range from 30 minutes to 2 hours). All patients had inappropriately raised plasma insulin concentrations for the level of glycemia and required high rates of glucose infusion (more than 12mg/kg/min, range from 14-20mg/kg/min). Insulin level ranged from 18-106 μU/ml (mean 36) which was collected during hypoglycemia (blood glucose less than 40mg/dl). Insulin (μU/ml) to glucose (mg/dl) ratio ranged from 0.5 to 3.8 (mean 2.3). All patients had negative urinary ketones, normal GH, cortisol and ACTH levels, which were collected during hypoglycemia. Twenty-three patients were referred to our center after April 1994 and had normal acylcarnitine profile by tandem MS which excluded fatty acid oxidation defects. Thirty-two patients received intramuscular or subcutaneous glucagon injection 30mg/kg (which was approximated to 0.5mg in the majority of them) as a therapeutic measure of hypoglycemia and to confirm the diagnosis of hyperinsulinism. All patients except 2 had a normal hyperglycemic response of more than 30mg/dl increment in glucose level 30-minute post injection (range from 35-65mg/dl). Ammonia level was evaluated in 14 patients and found to be elevated in one.

Brain imaging (MRI, CT or both) was performed in 20 patients who had recurrent hypoglycemic convulsions, developmental delay, or both. The imaging studies were normal in 6 children and showed varying degrees of brain atrophy in the remaining patients. Four patients had multicystic brain changes with cortical atrophy and secondary ventricular dilatation, 6 had periventricular leukomalacia and 4 had delayed myelination. Brain stem auditory evoked potential was performed in 11 children with recurrent hypoglycemic convulsion and speech delay. Brain stem auditory evoked potential results showed that 8 patients had decreased auditory stimulus latency and 3 patients had no response. Nine patients with clinical evidence of impaired visual acuity had VER study, which showed, delayed visual conduction time in 7 patients and absent

response in 2. Electroencephalogram was performed in 19 children with a history of hypoglycemic convulsion and delayed development. It showed slow disorganized background activity indicative of diffuse cerebral dysfunction in all patients and diffuse multifocal epileptiform discharges in 4 patients. A systolic murmur was heard in 12 patients. Echocardiogram showed an increased interventricular septal thickness in 6 and bicuspid aortic valve in 2. The remaining patients had normal results.

All patients were treated medically initially with intravenous glucose infusion and frequent feeding supplemented with complex carbohydrates (Polycose/corn starch). Ten to 20 mg/kg/day of diazoxide (median 15mg/kg/d) divided 3 times a day was used in 35 patients. Three patients required 20-25mg/kg/day of diazoxide to control blood glucose, which was complicated with weight gain and fluid retention. Side effects of diazoxide such as hypertrichosis were observed in 20 patients, leukopenia (absolute neutrophil count less than 1500) in 4 and thrombocytopenia (platelets count less that 20,000) in 3. The duration of treatment with diazoxide ranged from one week to 4 years (median 15 months). Octreotide was first used in 1992 as a second line drug therapy. Twenty-two patients were treated with octreotide as an adjunctive therapy to diazoxide. Five to 40 mcg/kg/day of octreotide was used (median 15mcg/kg/day). The duration of octreotide treatment ranged from one week to 5 years (median 18 months). All patients, except 9, did not show a response to medical therapy and had subtotal pancreatectomy. Seven out these 9 medical therapy responders presented after the first year of age. Eight patients had transient hyperglycemia immediately post-operatively which lasted for one to 2 days. No insulin therapy was required for postoperative hyperglycemia. Two patients continued to have recurrent hypoglycemia and had a second surgery (near total pancreatectomy). Two patients were treated with nifedipine (0.5mg/kg/day) with no hyperglycemic response and 12 patients were tried on hydrocortisone as a temporary therapeutic measure prior to referral to our center. Histological reports of the resected pancreata were available for review in 15 patients. They were reported to be normal in 9 patients, focal in 2 and diffuse in 4. No electron microscopical evaluation of the nuclear size was performed.

The patients, in this series, have been followed for a median duration of 7 years (ranged from 4 months to 17 years). Four children died, 2 of them died with septic shock and 2 died following hypoglycemic seizure. Six patients were lost to follow up. Five patients among those who had pancreatectomy were older than 12 years (range from 13 to 17 years). Four out of these 5 patients were diabetic; 2 of them were persistently hyperglycemic and required insulin therapy. Two patients had steatorrhea with positive stool fat globules and started on pancreas capsules. No pancreozymin-secretin stimulation test was performed. One patient had an ammonia level of 280 µmol/l (0-55). He was suspected to have activation mutation of glutamate dehydrogenase, however, no genetic study was conducted. He failed the medical treatment and had surgery. He was treated with sodium benzoate and arginine for hyperammonemia. Another patient was diagnosed with leukocyte adhesion defect and had bone marrow transplant. A patient with neonatal PHHI was treated with diazoxide and octreotide until the age of 10 years when these 2 medications were stopped. At the age of 14, she developed diabetes and weight gain. She had an insulin level of 10µU/ml and C-peptide level of 0.16nmol/l at a serum glucose level of 350mg/dl. Anti glutamic acid decarboxylase, insulin and islet cell antibodies were negative. Her blood sugar ranged from 200-300mg/dl, which responded to metformin 250 mg twice a day.

Eighteen patients were developmentally delayed, 4 were blind and deaf. Intelligence quotient was assessed in 8 patients with neonatal PHHI, which ranged from 43 to 84. All patients except 3 had a normal height velocity, and their height ranged from 2 SD to 0.5 SD below the mean. The 3 patients with subnormal height (height on 3SD below the mean) were initially treated with hydrocortisone in the referral hospitals and currently on octreotide and diazoxide. One patient attained the final, and his height is 155 cm.

Discussion. Persistent hyperinsulinemic hypoglycemia of infancy is the most frequent cause of severe persistent hypoglycemia in infancy and childhood. Several studies have defined the syndrome at the molecular, genetic and clinical level. However, long-term follow up data is limited. In this report, we describe the clinical, biochemical, radiological and electrophysiological features of this syndrome in 38 children who have been followed in one institution over the last 2 decades.

Persistent hyperinsulinemic hypoglycemia of infancy is a rare inherited disease and most of the cases are sporadic, but in an inbred country such as KSA where more than 50% of mating is consanguineous, the familial cases are common. In our series, one family had 7 affected siblings and 4 families had more than one affected child. The patients in our group were severely hypoglycemic and intolerant to fast. Hypoglycemic convulsion was the commonest presenting complaint. The mean insulin level was 36 µm/ml with a mean insulin to glucose ratio of 2.3 which is relatively higher than the levels reported in other studies.[10,11]

Neonatal PHHI is a major risk factor of severe mental retardation and epilepsy. These infants are especially vulnerable because they do not produce ketone bodies during hypoglycemia. Familial cases with SUR mutation may be at additional neurological risk. The SUR is expressed in the brain and defects in this receptor may interfere with brain development.[12] Menni et al[13] retrospectively studied 90 patients with PHHI and

found that 21% had psychomotor retardation and 13% had epilepsy.[13] In our series, 73% of the patients had hypoglycemic convulsion and 47% were developmentally delayed. A high percentage of developmental delay and epilepsy in our group might be related to the severity of hypoglycemia, unresponsiveness to medical therapy and late referral. This syndrome carries a high risk of mortality and morbidity in survivors which was estimated to be as high as 45%.[10] Four patients died in our group, 2 of them with sepsis. Severe and recurrent infections were observed in 30% of patients with PHHI in an Indian report.[10] This unusual and recently observed phenomenon mandates further study.

Medical therapy with diazoxide and octreotide has been successful in several series of patients,[14,15] however 29 patients in our group who presented during the neonatal period did not show a response. We observed that late infantile cases had a better response to medical therapy than neonatal cases. This observation was reported by others.[14] Saudi patients who may harbor SUR1/Kir6.2 mutations are severely hyperinsulinemic, early presenters, and diazoxide/octreotide unresponsive.

Several studies have suggested that partial pancreatectomy endangers future islet cell function. The incidence of diabetes increases with age and correlates with the extent of surgical resection.[10,16,17] However, there was no report of occurrence of overt diabetes in medically treated patients.[18] One patient, in our series, was treated medically with diazoxide and octreotide until the age of 10 years. At the age of 14, she developed non-autoimmune insulin insufficiency diabetes. Transgenic mice engineered to express a dominant negative form of Kir6.2 or mice with KATP deficiency developed hyperinsulinemic hypoglycemia followed by hypoinsulinemic hyperglycemia. Diabetes in these transgenic mice was thought to be due to sustained unregulated calcium influx and premature β cell apoptosis (burnout phenomenon).[19-21] Development of diabetes in our non-pancreatectomized PHHI patient may suggest that patients with PHHI will naturally develop diabetes whether they were treated medically or surgically or even if they are left untreated. Seino et al[22] reported another possible predisposing factor to hyperglycemia in PHHI patients. They showed that hyperglycemia in Kir6.2 knockout mice was more evident with age, and increasing weight.[22,23] They also suggested that Kir6.2 knockout mouse provides a model of type 2 diabetes and both the genetic defect in glucose-induced insulin secretion and the acquired insulin resistance due to environmental factors is necessary to develop diabetes in Kir6.2 knock out mouse. Diabetes in the above described patient was induced by weight gain and obesity. She responded to metformin, which may suggest that her diabetes is due to insulin resistance induced by weight gain and insulin insufficiency. This patient could be the human example of the Kir6.2 knockout mouse model. We recommend, based on this human clinical evidence, weight control in aged PHHI patients to decease the incidence of diabetes. Another possible contributing factor to the development of diabetes in this patient is the use of octreotide, which was reported to be Beta-cell apoptogenic.[24]

Partial pancreatectomy does not only affect the endocrine function of the pancreas but also the exocrine function. Previous studies[25,26] showed that the majority of pancreatectomized PHHI children had subclinical exocrine pancreatic insufficiency and the risk may increase with age and correlates with the extent of surgical resection. Two of our patients had clinical evidence of malabsorption that were treated with pancreatic enzyme supplement.

Growth was a concern in medically treated patients with octreotide or surgically treated patients. Some reports showed that these patients have defective linear growth with subnormal insulin-like growth factor-I level. Although they have normal growth hormone response to provocation.[27] In our series, 35 patients had normal height velocity and their heights were within the 2 standard deviations.

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