PERSISTENT HYPERINSULINEMIC HYPOGLYCEMIA OF INFANCY

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Manuscript received May 27, 1997, Initial review completed August 4,1997, Revision accepted November 11,1997.

Objective *To study the nature and clinical course of persistent hyperinsulinemic hypoglycemia of infancy (PHHI) due to nesidioblastosis* ***Design*** *Clinical, laboratory and therapeutic evaluation of infants with this disorder and study the outcome* ***Setting*** *Hospital born neonates and infants referred from other hospitals* ***Subjects*** *Thirteen infants from 9 families inclusive of four pans of siblings referred within few hours of birth to 3 months of age, for seizures Mean birth weight was 3 68±0 45 kg Consanguinity documented in one sporadic and one familial case* ***Methods'*** *Clinical and laboratory evaluation by standard biochemical and radioimmunoassay techniques* ***Results:*** *The mean serum insulin level of 24 2±12.5 mlU/ml was in the normal range but inappi opnately high for the con evponding hypoglycemic blood sugar (23.1±9.1 mg/dl) value, with an I/G ratio of 1 36±0 97; as in hyperinsulinemia (normal <0.4) Investigations excluded other causes of persistent hypoglycemia A trial of TV/oral glucose, frequent carbohydrate rich feeds in all, oral diazoxide (10 to 20 mg/kg) in 9/13 cases along with subcutaneous octreotide (20 Hg/kg QID) in one helped, but pancreatic tesection (85 to 90%) zvas opted for in two (1 familial, 1 sporadic) Six infants including one with pancreatic resection succumbed to hypoglycemia (n=1) or fulminating infection (n=3) or brain damage Of the seven survivors, one familial case with pancreatic resection* is *ham damaged, and of the six on diazoxide therapy, one is slightly subnormal while one sporadic and three familial cases have done well One infant was lost to follow up Diazoxide could be withdrawn in two subjects (1 familial, 1 sporadic) by 8 years of age signifying maturation of islet cell function* ***Conclusion:*** *PHHI appropriately known as 'Islet cell dysmaturation syndrome' is a complex disorder posing problems in diagnosis and therapy The high familial incidence (77%), with intrafamilial variation in the severity, insulin levels in the normal range but inappropriately high for the blood glucose levels, normal C-peptide levels, with normal I/G ratio (<0.4) in 4/13 are some of the notable features of this study Severe recurrent infections in nearly 30%,* is *an unusual feature in this series and needs an indepth study The mortality (46%) and morbidity (43%) in survivors is high and calls for greater awareness, early diagnosis and genetic counselling as this disorder may be familial.*

Keywords' *Familial hyperinsulinemic hypoglycemia Hyperinsulinemic hypoglycemia in infants Nesidioblastosis*

PERSISTENT hyperinsulinemic hypoglycemia of infancy (PHHI), is a complex disorder often posing diagnostic problems and requiring aggressive therapeutic approach Hyperinsulinism probably accounts for 20% of all infants having persistent hypoglycemia(l) McQuarne in 1950s described it as a syndrome of persistent hypoglycemia of unknown cause of healthy infants resulting in brain damage due to late diagnosis and treatment(2).

The term 'Nesidioblastosis' (in Greek-

island) was coined by Laidlow(3) in 1938 but the specific histological findings in PHHI were first described in 1971(4). The nomenclature describing the pancreatic changes in these infants, such as beta or islet cell hyperplasia, microadenomatosis and focal or multiple islet cell adenomatosis is confusing. The term islet cell dysmaturation or dysplasia syndrome may be more appropriate than nesidioblastosis indicating a probable developmental or maturational defect of insulin secreting cells(5-7).

Sporadic occurrence of PHHI is well documented but the familial occurrence of nesidioblastosis in siblings, first reported by Woo *el al.* in 1976(8) is uncommon. A recent article refers to familial PHHI with sibling affection in 25 families, reported between 1976 to 1991(9). Here we report a series of 13 subjects with PHHI seen in the past 16 years with onset of symptoms in neonatal period or early infancy, of which eight are familial.

Subjects and Methods

In these 13 infants with recurrent episodes of hypoglycemia the diagnosis of primary (form of) congenital hyperinsulinism was confirmed by laboratory investigations. Infants with other forms of hypogly-cemias with specific metabolic/ endocrine derangements or hyperinsulinism associated with specific syndromes like Beckwith's or familial adenomatosis are excluded

Detailed history regarding the onset, duration and nature of hypoglycemic episodes and all details of birth history, family history, sibling affection and consanguinity, as well as physical examination findings were recorded. These patients have been followed up for a period ranging from few months to over fourteen years.

Laboratory investigations included estimation of plasma glucose conentrations during acute symptomatic hypoglycemic episode or testing after 4 to 8 hours of fasting depending on the age, while monitoring blood sugar (less than 30 mg/dl within first 3 days in full terms and <40 mg/dl thereafter, was considered significant). Simultaneous blood sugar and insulin levels were estimated on more than three occasions in majority of infants during hypoglycemia. Serum insulin, C-peptide, serum acetone, free fatty acid levels and serum growth hormone, cortisol and thyroid hormones were also tested during hypoglycemia. Insulin/glucose (I/G) ratio exceeding 0.3(1), 0.5(10) or 0.4(11) (0.4 - in this study) constitutes one of the important parameters for diagnosis of hyprinsulinemia. Routine biochemical investigations such as serum calcium, phosphorus, alkaline phosphatase, serum electrolytes, blood gases and serum creatinine were also tested in all. Urine was tested for acetone in all, and urine for metabolic disorders and serum lactic acid were tested in four cases. A glycemic response to IV glucagon (30 μg/ kg) with a rise in blood glucose exceeding 30 mg/dl above the basal value, 30 mintues after symptomatic or fasting hypoglycemia also indicates hyperinsu-linemia with adequate glycogen stores. This was tested in 10/13 infants. Imaging studies like CT Scan and MRI became available later; hence imaging of pancreas was carried out in four cases. Histopathologic studies on pancreas were carried out in two cases who underwent pancreatic resection (85 to 90%).

Standard biochemical techniques were utilized for all biochemical estimations including glucose. Hormonal assays were carried out soon after blood collection by standard radioimmunoassay (RIA) kits and the serum insulin levels were measured by specific RIA with a sensitivity of 2 mU/ml.

Resected pancreatic tissue was studied by Hematoxylin Eosin stain. Glucohemostix was used for frequent monitoring of blood glucose levels during hospitalization and for home monitoring. The parents were instructed to monitor blood sugar, use glucagon injection when needed, and were made aware of the clinical symptoms of hypoglycemia.

Patients admitted with acute hypoglycemic episodes were infused with 10% to 20% glucose on admission, with a rate of administration which had to be increased from 10 to 15 mg/kg/min (15 to 20% glucose solution with central venous catheter) for maintaining normoglycemia (>60mg/dl not exceeding 120/150 mg/dl) suggesting hyperinsulinism as the underlying cause. Eolus doses of 25% glucose, 2ml/kg were used sparingly. The rate and concentration of glucose infusion and the total quantity of fluid and electrolytes administered had to be monitored carefully while maintaining normoglycemia.

Once the diagnosis was ascertained in 2 to 3 days, oral diazoxide was administered in gradually increasing doses from 10 to 25 mg/kg/day in three divided doses, based on periodic blood sugar monitoring (diazoxide became available to us by mid 1980s). Somatostatin analogue (octreotide) became available recently and was used in the dose of 5 to 20 Hg/kg per day QID, given subcutaneously in the most recent patient, as diazoxide (25 mg/kg/day), alone, adequate feeding and glucose infusions did not maintain normoglycemia. Anticonvulsants and hydrocortisone were used only initially, and glucagon injection when necessary. Orally, carbohydrate rich frequent feeding was encouraged (breast milk or 2:1 diluted milk to curtail leucine intake with additional sugar, and arrow root kanji or raw corn starch (in older infants) to maintain stable blood sugar levels. Chlorthiazide was used mainly to counter the fluid retention caused by diazoxide.

Pancreatic resection (85 to 90%) was offered when plasma glucose could not be maintained above 50 to 60 mg/dl despite adequate trial (8-10 days) with drugs and feeding, necessitating frequent glucose infusions or when medical therapy was unacceptable because of frequent monitoring and management problems or socioeconomic constraints. All implications of surgical intervention, mortality, morbidity, final outcome and the success and failure of initial surgical therapy requiring a second surgery with near total pancreatic resection were explained to the parents. The fact that surgery may not be the endpoint of management, monitoring and glycemic drugs may still be needed, and the future possibility of developing diabetes mellitus and exocrine pancreatic insufficiency were explained.

Results

This series comprised of 13 patients with 6 female and 7 male infants of 9 families from amongst a total of 21 children born in these families. Some of the important features are listed in *Table I.* Eight of these 13 were familial cases (four pairs of siblings) involving both the sexes in two families, and two sisters and two brothers in each of the other two families, suggesting a possible autosomal recessive inheritance. All the infants were born of nondiabetic mothers close to full term after normal pregnancy and delivery with birth weights ranging between 3 to 4.5 kg (mean±SD = 3.68±0.45 kg). History of consanguinity was obtained in one familial and one nonfamilial cases.

The age at onset of clinical symptoms varied from within few hours of birth to 3 months; within 24 hours of birth in five neonates, by 3 to 7 days in five more, and

in 3 infants by 2-3 months *(Table I)* The age at referral ranged between few hours of birth to 15 months Intrafamilial variation in the age at onset and severity of the disease was noted in one pair of siblings (Nos. 9 and 10) with the elder sibling succumbing with severe hypoglycemia within 24 hours of birth and the younger one manifesting at 3 months.

Clinical manifestations included listlessness, cyanotic spells, pauses of apnea or grunting respiration, feeding problems, irritability, staring spells and hypotheimia Recurrent generalized seizures was the commonest presenting complaint in all Five of these 13 infants *(Table I,* Nos. 2, 5, 6,10,13) presenting within few hours of birth were large and plethoric, with respiratory grunting in three, resembling infants of diabetic mothers (IDM) No other clinical signs were noted in any of these infants and prior to referral two to ten hypoglycemic episodes were reported with recorded low blood sugar levels of between 0 to 30 mg/dl Five of them were described as glucose responsive

There was wide variation in the serum insulin levels (10 to 60 uU/ml) in the same infant during various episodes of hypoglycemia in a minimum of three or more samples obtained m these infants The values listed in *Table I* are those where simultaneous insulin, GH, cortisol, serum FFA and acetone were tested during one of these hypoglycemic episodes with a mean blood sugar value of 23 1+9 1 mg/dl (range - 10 to 40 mg/dl) with simultaneous mean serum insulin level of 24 2±12 5 jiU/ml (range 6 to 40 uU/ml) Thus insulin levels during the hypoglycemic episode listed in *Table I,* were not high (normal 5 to 35 uU/ml) but were inappropriate for the low blood sugar levels The mean Insulin/Glucose (I/G) ratio was high 1 36±0 97 (range 0 16 to 3, *Table 1)* The I/G ratio in hyperinsulinemic state exceeds 0.3 to 0.5(1,10) with a cut off of 0.4 being used by others(11,12) Three of the four infants in this series with I/G ratios < 0.4 were familial cases (Nos. 9,11,12) who responded to diazoxide and feeding and the fourth infant (No. 13) was confirmed to have nesidioblastosis on pancreatic resection after initial success with diazoxide and octreotide In the neonates presenting with hypoglycemia, requirement of glucose infusions > 10 mg/kg/ minute or more to maintain normogly-cemia (60 to 150 mg/dl), was also indicative of hyperrnsulinemic hypoglycemia The C-peptide levels tested in 8/13 were in the normal laboratory range (1 to 3 ng/ml), with a mean of 1.4±0.7 ng/ml The free fatty acid levels are low in hyperinsulinemia with no acetonemia, no acetonuria, and absence of acidosis and lacticacidemia(1) The FFA was in the low normal range (normal 100 to 560 mEq/L) with a mean level of 223.5 ± 34 mEq/L in these infants Serum acetone levels in 8/13 were normal (0.3 to 2 mg/dl) with blood lactic acid levels in the normal range (5.7 to 22 mg/dl) There was no acetonuria and no other abnormality on urinary screening for other metabolic problems Serum glucagon estimated in two patients (Nos. 1 and 11) was little above the normal range of 45 to 200 pg/ml (300 pg/ml and 430 pg/ml), indicating no deficiency of this hormone All other biochemical parameters were normal The glycemic response at 30 minutes to IV glucagon (30 ug/kg), with the rise in blood glucose exceeding 30 mg/dl (40 to 65 mg/dl) above the basal hypoglycemic value in 10/13 tested, also favoured hyperlnsulinemic hypoglycemia.

Hormonal studies, serum growth hormone (10 to 14 ng/ml) and serum cortisol (18 to 26 µg/dl) tested in 10/13, revealed no abnormality and were in the upper

TABLE I *Clinical, Laboratory and Follow up Data on 13 Infants with PHHI*

Sr No	Sex	Age at onset	Birth (kg)	Glucose (mg/dl)	Insulin (3-30 µU/ml)	I/G	Therapy	Outcome
1	F	2 5 mo	3 5	18	16	0 88	Diazoxide 5 yrs Anticonvulsants	Mild MR, Seizures Off diazoxide - 7 yrs
2	M	8 h	3 85	13	40	3 1	Hydrocortisone Anticonvulsants	MR, Seizures Expired - 11 yrs
3	F	2 mo	3 0	29	40	1 38	Diazoxide	Normal at 4 5 yrs Diazoxide Continuing
4	M	12 h	3 2	20	30	1 5	Diazoxide	Follow up 1 yr - N
5	F	3 days	4 2	12	40	3 3	Hydrocortisone Anticonvulsants	Expired - 3 weeks Sepsis
6	M	7 days	4 5	20	30	1 5	Hydrocortisone Anticonvulsants	MR, Seizures Expired - 11 yrs
7	F	2 days	3 8	23	39 8	1 93	Diazoxide 90% pancreatectomy	MR Seizures Alive- 5 yrs Euglycemic
8	F	1 day	3 5	18	20	1 1	Diazoxide Response +	Repeated infections Expired - 3 mo
9	F	3 mo	3 6	30	8 1	0 27	Diazoxide Response good	Diazoxide - Normal at 5 yrs
10	M	6 h	4 2	10	30	2 0	Glucose Hydrocortisone	Expired - 24 h
11	M	4 days	3 5	36	6	0 6	Diazoxide Response good	Normal - 14 yrs Off diazoxide - 6 yrs
12	M	3 days	4 0	40*	14 4	0 36	Diazoxide Good response	Normal at 6 yrs Diazoxide continued
13	M	7 h	3 0	31	10 3	0 33	Diazoxide + Octreotide 90% Pancreatectomy	Expired at 4 mo Repeated infection Sepsis

* Subsequent blood sugar 20 to 30 mg/dl with seizures
Nos (5-6), (7-8), (9-10), (11-12) were sibling pairs

MR - Mental Retardation

normal range during hypoglycemia, indicating normal counter regulatory hormone response. Thyroid hormones (9/13 tested) were in the normal range. MRI/CT imaging in 4 cases did not reveal any abnormality.

After tiding over the acute episode with adequate glucose infusions, frequent carbohydrate rich feeds (breast feeds with sugar water and arrow root kanji in between the feeds, or 2:1 milk and kanji) with additional sugar as tolerated were introduced. Oral diazoxide therapy (10 mg/kg/day divided into three doses) was initiated on confirmation of the diagnosis within 2-3 days in 10 of these thirteen infants and seemed effective as the dose was stepped upto 15 to 20 mg/kg in all except No. 13. Three of the earliest cases were diagnosed prior to the availability of diazoxide (Nos. 2,5,6). One of the familial cases (No. 7) finally opted for surgery because of the cost of diazoxide therapy. The most recent patient (No. 13) could not be adequately controlled with diazoxide upto 20 mg/kg and adequate feeding but responded very well with addition of subcutaneous octreotide (20 µg/kg/day QID). With octreotide the dose of diazoxide could be reduced to 10 mg/kg/day. Surgical intervention rejected by parents earlier was finally opted for at 8 weeks, as medical therapy was prohibitively expensive. Chlorthiazide 1.5 to 3 mg/kg/day on alternate days was given for fluid retention caused by diazoxide, not so much for its glycemic effect.

XThe pancreatic tissue from two patients with near 85% to 90% resection showed typical findings of nesidioblastosis, hypertrophy and hyperplasia of islets of Langerhans with large islets and variation in islet cell size, disorganization of islet structure including single, scattered islet cells in the exocrine parenchyma and proliferation of new islets from ductular epithelium.

Six of these 13 children succumbed to the disease or associated complications and consequences *(Table I);* one newborn within 24 hours of birth (No. 10) and two of brain damage and seizures (Nos. 2, 6) at a later age prior to the availability of diazoxide. Three infants (Nos. 5, 8,13) died of fulminating infection, one prior to availability of diazoxide, one while controlled with diazoxide and one of them (No. 13) 2 months after pancreatic resection while remaining normoglycemic with diazoxide (reduced to 5 mg/kg). Of the 7 survivors all except one had received medical therapy. Two children have mental subnormalcy, minimal in one (No. 1) and severe in one familial case (No. 7) with subtotal pan-createctomy who is now 5 years old and euglycemic *(Table I)*. Three familial cases (Nos. 9,11,12) and one sporadic case (No. 3) followed up for 4 to 14 years are surviving and developmentally normal with diazoxide at d appropriate feeding care. Hypertrichosis of varying severity was noted in all with individual differences in hair growth on equivalent dose. Repeated respiratory and gastrointestinal infections occurred in one of them (No. 9) upto 2 years of age when diazoxide requirement was high. In the oldest of these patients now 13 and 14 years old (Nos. 1 and 11 -familial case) diazoxide was gradually withdrawn by 8 to 9 years of age. Beyond the age of 2 years, smaller doses of diazoxide (3 to 5 mg/kg) seem to maintain normoglycemia, but longer periods of fasting are not well tolerated.

Discussion

Hyperinsulinism is the single most important cause of persistent hypoglycemia in infants beyond the first few days after birth. The congenital nature of this disorder is suspected after appropriate clinical and laboratory evaluation and by exclusion of other clinical conditions associated with

persistent hypoglycemia Prior to 1975 the diagnosis of islet cell adenoma was frequent which is now superceded by nesidioblastosis(12) The incidence of PHHI is relatively low in most countries, 1 in 50,000 live births(13) but as high as 1 in 2675 in Saudi Arabian population with 51% rate of consanguineous marriages(14) Beyond a few case reports, the Indian pediatric literature(15-17) has very little documented information on this subject and familial occurrence is not reported.

The familial variety of PHHI though uncommon is now well recognized Thornton *et al* refer to twenty five families with sibling affection in 15 reports while adding five of their own with multiplex families(9) One of the largest reported kindred had 4 affected siblings with PHHI from amongst a total of 13 siblings(7) The present series of 13 infants includes 8 cases (61 5%) of the familial form PHHI is now believed to be an autosomal recessive condition with similar features in both sporadic and familial cases which cannot be distinguished from each other on clinical or pathological grounds(6,9,14,18) Consanguinity plays a major role in familial occurrence(14) In the present small series there was no difference in consanguinity amongst the familial and sporadic groups

The histopathology of the endocrine pancreas of neonates and infants suffering from PHHI is varied The variety of pancreatic lesions range from typical islet cell adenomas, islet cell hyperplasia with fetal type budding from pancreatic ducts, beta cell adenomatosis and nesidioblastosis(4) The underlying pathogenesis is believed to be similar, independent of the type of histopathologic changes, with no consistency of histologic changes within a family indicating that the abnormality of regulation of beta cells rather than the specific histologic changes that are genetically determined(9) Purely functional hyperinsulinism with a normal appearing pancreas is thus a theoretical possibility(9) The term "Islet cell dysmaturahon" or "beta cell dysregulation" syndrome may adequately include the various histopathologic changes(19,20)

The disease most commonly presents with severe hypoglycemia in a few hours of birth, with the onset of symptoms within the first three postnatal months in 75% of patients, onset of symptoms above the age of one year is rare(l,20,21) Recurrent, generalized seizures was the commonest presenting, feature in this series, manifesting within the first week of birth in *77%* Infants presenting in the neonatal period are reported to have more diffuse pathologic findings, more severe illness, tend to be larger and were classified as 'infant giants' in the past(22) Affected infants cluster in the upper percentiles for weight at birth, indicative of lntrauterine hyperinsulinism(l) Almost all infants in this series were large at birth Some degree of rntrafamilial variability as regards age at onset and severity of the disorder is described(20,22,23) as also noted in this series In view of the published reports and our own experience, history of similar disorder in a previous sibling is important(l,21,23) PHHI is also implicated in sudden infant death syndrome(24)

The variable clinical and laboratory manifestations of nesidioblastosis, often make the diagnosis quite difficult The various laboratory parameters helpful in diagnosis of PHHI are instability of blood glucose levels over short periods of fasting and requirement of glucose infusions at a rate exceeding 10 mg/kg/min, insulin concentration greater than 10 μ,U/ml during hypoglycemia, I/G ratio exceeding 0 3 to 0.5, and a rise in blood glucose level exceeding 30 mg/dl above the basal hypoglycemic level with glucagon (1,10,11,21)

All the criteria may not be fulfilled in all the patients unless several samples are obtained(l,10,21,23). The other supportive criteria are listed in *Table II.* Thus a constellation of clinical and laboratory parameters are necessary to confirm the diagnosis.

A number of criteria listed in *Table II* were applicable in these infants. Histopathologic examination of resected pancreatic tissue in two infants was characteristic. Other biochemical and hormonal studies were normal. There is general concensus that imaging studies are not helpful. The insulin levels ranging between 6 to 40 mlU/ml (24.2±12.5 mlU/ml) were in the laboratory range (5 to 35 (lU/ml) but high for the corresponding blood sugar values (12 to 40 mg/dl). In contrast to insulinomas where insulin production and/or C-peptide are significantly more, nesidioblastosis may have only mildly excessive insulin secretion despite profound hypoglycemia(23). As observed, high insulin levels are not consistently encountered even in the same patient during every episode of hypoglycemia(l,23). Levels of insulin above 5 μU/ml in presence of hypoglycemia are considered suspicious and more than 10 μU/ml favor hyperinsulinemic state(l,21,25). Others consider any measurable insulin with a blood glucose less than 40 mg/dl as abnormal and favoring hyerinsulinemia(10). A burst of insulin release may induce hypoglycemia but insulin level may rapidly return to a normal range before elevation of insulin is documented(25). Several samples may be required for diagnosis; insulin levels in relation to glucose levels are considered important(1, 11,19, 23). The insulin/glucose ratio equal to or exceeding 0.4 (0.3 to 0.5) is very helpful(l,10,11) but may not be consistently high as also observed in this series in three of the familial cases (Nos. 11,12,13) and the infant with pancreatic resection confirmed to have nesidioblastosis (No. 13). C-peptide levels may also be normal; proinsulin estimation was not possible. The role of insulin precursors like proinsulin causing hypoglycemia has been discussed in some studies(l). These instances illustrate the difficulties in arriving at a diagnosis. It is thus important not to always expect higher than normal levels of insulin while diagnosing PHHI. Relative deficiency of other hormones, glucagon and in particular somatostatin may also contribute to hypoglycemia(21,23).

The choice of therapy remains controversial as no single modality of treatment has proved uniformly effective *(Table III).* The major goal of therapy is to prevent brain damage by stabilizing blood glucose. The treatment modalities are directed towards suppressing insulin secretion (diazoxide, low protein diet, epinephrine, diphenylhydantoin, chlorthiazide and somatostatin or its analogues), using drugs antagonizing the effects of insulin on tissues (glucocorticoids, epinephrine, glucagon) and reduction of beta cell mass by surgical resection. Diazoxide continues to remain the treatment of choice for those who respond adequately. It may prove ineffective in infants who present from birth(5,6,21,23). Some cases have been successfully treated with octreotide which has been preferred over surgical resection(26) but results are not uniform(27) and therapy is expensive and cumbersome. Along with diazoxide, octreotide proved effective in one infant of this series but the cost of therapy precluded its continuation. Its long term effects are yet to be established.

Surgery viewed as an unphysiologic blind procedure is usually the last resort when medical therapy is ineffective more than 50% of times(6). In the past 25 years, 95% pancreatectomy has become the mainstay of therapy for PHHI at most centers

TABLE *Il-Chmcal and Laboratory Evidences Helpful in Diagnosis ofPHHI*

A Clinical

* Large babies born of normal mothers
* Absence of heaptomgely or any other abnormalities
* H/o hypoglycemia in previous sibling

B Important Laboratory Criteria

* Instability of blood glucose levels - Rapid onset of hypoglycemia with fasting
  Glucose infusion rate exceeding 10 mg/kg/mm (upto 15 to 30 mg) for maintaining normoglycemia (> 60 mg/dl)
* Serum insulin levels with hypoglycemia > 5 μu/mL suspicious, > 10 diagnostic
* Insulin-glucose ratio during hypoglycemia*> 0.3 to 0.5

C Other Suggestive and Supportive Evidences at Time of Hypoglycemia

* Low serum ketones, FFA and P-hydroxy butyric acid and absence of acetonuria and acidosis
* Brisk rise in plasma glucose > 30 mg/dl from baseline hypoglycemic level with glucagon (30ng/kg-IV)
* Elevated C peptide and/or Proinsulin
* Restoration of normoglycemia with diazoxide and/or somatostatin

These criteria have been formulated from several references on PHHI No single criterion by itself can be diagnostic
* For the present series I/G ratio of >0 4 (11) has been considered.

when the onset of the disorder is in the neonatal period(5,6,12,28) One third of these infants may still remain hypoglycemic requiring total pancreatic resection with its attendant mortality and morbidity(28) The true risks of late onset exocrine insufficiency is not known and diabetes mellitus after 95% pancreatectomy occurs in 69 to 75% of children requiring life long therapy with rnsulin(28,29) The pathophysiology of diabetes is being debated but beta cell failure as the end stage of PHHI with the onset of diabetes hastened by pancreatecomy is also postulated(26) Serious neurological sequelae have some what reduced with effective and early control(28) Though avoidance of hypoglycemia is paramount more conservative approach is now proposed and pancreatic resection recommended only when hypoglycemia cannot be controlled medically, by diet and oral medication(26,28-30) This is also in view of lack of significant complications with octreotide and diazoxide and the possibility of spontaneous remission described between the ages of 2 to 14 years as the endocrine pancreatic cells mature(l,7,26,31)

In the present series (6/13) 46% succumbed to the disease or associated complications and consequences Of the 7 survivors treated medically, two have outgrown their need for diazoxide and two need smaller doses Susceptibility to severe infections not reported by others, is an important feature of this study Diazoxide is reported to produce leukocyte and IgG alterations Whether immunological incompetence is an associated feature of this

TABLE III—*Therapeutic Approaches*

* Glucose infusions 10 to 30 mg/kg/mm as required
  Central vein for 20% glucose Check on
  total fluid and electrolytes
* Institute oral feeding
  Adequate calories, carbohydrate rich, sugar and corn starch
  Low in protein especially leucine - frequent feeds
* Other emergency measures - like glucagon or hydrocortisone
* Trial with Diazoxide after confirmation of diagnosis
  10 to 20 mg/kg/day in three divided doses
  Trial for 3-5 days but not too long
* If no response, to add
  Inj Octreotide 5 (µg/kg every 6 hours SC Maximum
  upto 40 µg/kg daily in 3 to 6 doses SC
* If no success then pancreatectomy 95%
* Before surgery omit diazoxide to minimize fluid retention
  Use of glucagon infusion so as to maintain blood glucose at 60 mg/dl (0.5 to 1.5 mg continuous drip)
* Post operative hypoglycemia - Remtroduce Diazoxide, Octreotide
* Near total resection if no response

disorder and is related to diazoxide therapy needs indepth studies

The familial nature of this disorder may be more common than previously realized as observed in this series A mutation in the sulfonylurea receptor gene (SUR) mapped to chromosome Ilpl5 1 is reported in some patients with familial PHHI, resulting in a continuous intracellular signal to release insulin(32,33) As a result of this abnormality, ^{K}ATP channels which are critical for the regulation of insulin secretion are dysfunctional, the beta cells remain active inspite of low blood glucose because of continuous depolarization of the membrane with an influx of extracellular "calcium" and the release of insulin from storage granules(32-35) A possible therapeutic role of calcium channel blockade is hence suggested(34) Diazoxide requires a normal SUR gene for its action, hence it may prove ineffective in Familial PHHI with SUR mutations and ^{K}ATP defects(35), though it proved effective in 3 of our familial cases Only one abnormality that of potassium channel, is clearly defined in familial PHHI, others may be recognized in the near future(32,33,35)

The clinical and histologic data provide no evidence of a distinct familial and sporadic types of PHHI(9) Whether heterogeneity exists m the pathogenesis and underlying molecular mechanisms of familial and sporadic forms of PHHI with a common denominator of persistent hypoglycemia due to inappropriate or excessive insulin secretion, will need further study Judging from the several reports of familial

cases and our own experience, it may be prudent to advise the parents of an affected infant, of the one-in-four risk for subsequent children, till definitive genetic markers become available for predicting an affected fetus or neonate

Acknowledgements

We are grateful to the Medical Director of Sir H N Hospital Bombay, for his kind permission to publish this study We are grateful to all the pediatricians for their kind referral of these patients We are grateful to Dr V S Wamgankar and Dr V Rege for the surgical care and to all our residents who maintained round the clock vigilance on these infants

REFERENCES

1 Stanley CA, Baker L Hypennsulimsm in infants and children Diagnosis and therapy Adv Pediatr 1976, 23 315-355

2 McQuarne I Idiopathic spontaneously occuring hypoglycemia in infants Clini cal significance of problem and treatment Am J Dis Child 1954, 87 399-428

3 Laidlow GF Nesidioblastoma, the islet tumour of the pancreas Am J Pathol 1938, 14 125-139

4 Yakovac WC, Baker L, Hummeler K Beta cell nesidioblastosis in idiopathic hypoglycemia m infancy J Pediatr 1971, 79 226-231

5 Daneman D, Ehrhch RM The engima of persistant hypennsulmemic hypoglycemia of infancy J Pediatr 1993, 123 573-575

6 Baker L, Thornton PS, Stanley CA Management of hypennsulimsm in infants J Pediatr 1991,119 755-757

7 Horev Z, Moshe IPP, Levey P, Daneman D Familial hypennsulimsm Successful conservative management J Pediatr 1991, 119 717-720

3 Woo D, Scopes JW, Polak JM Idiopathic hypoglycemia in sibs with morphologic evidence of nesidioblastosis of the pancreas Arch Dis Child 1976, 51 528-531.

9 Thornton PS, Sumner AE, Ruchelli ED, Spielman RS, Baker L, Stanley CA Familial and sporadic hyperinsulinism Histopathologic findings and segregation analysis support a single autosomal disorder J Pediatr 1991,119 721-724

10 LaFranchi S Hypoglycemia of infancy and childhood Pediatr Clin North Am 1987,34 959-980

11 An tunes JD, Geffner M, Lippe BM, Landaw EM Childhood hypoglycemia Differentiating hyperinsulinemic from nonhypennsulinemic causes J Pediatr 1990,116 105-108.

12 Spitz L, Bhargava RK, Grant DB, Leonard JV Surgical treatment of hyperinsuliaemic hypoglycemia in infancy and childhood Arch Dis Child 1981, 56 496-508

13 Bruining GJ. Recent advances in hyperinsulinism and the pathogenesis of diabetes mellitus Current Op Pediatr 1990, 2 758-765.

14 Mathew RM, Young JM, Abu Osba YK Persistent neonatal hyperinuslinism Clin Pediatr 1988, 27 148-151

15 Daga SR, Talwalkar VC, Modadam Y, Nagle SB Beta cell nesidioblastosis Indian Pediatr 1986, 23 213-215

16 Singhi S, Narang A, Banerjee CK, Bhakoo ON Nesidioblastosis in newborn Indian Pediatr 1989,26 403-406

17 Merchant RH, Murthy A, Chitale A, Kapur V Nesidioblastosis Ultrastructural and immunohistochemical observations Indian Pediatr 1992, 29 1417-1420

18 Woolf DA, Leonard JV, Trembath RC, Pembrey ME, Grant DB Nesidioblastosis Evidence for autosomal recessive inheritance Arch Dis Child 1991, 66 529-530.

19 Kloppel G, Heitz PU Persistent hyperinsulinemic hypoglycemia in infancy *In*

Pancreatic Pathology Eds Klopel G, Heitz P U Edinburgh, Churchill Livingstone, 1984, pp 193-205

20 Gabbay HK. Case records of the Masachusettes General Hospital Case 30 N Engl J Med 1978, 299 241-248

21 Aynsley Green A, Polak JM, Bloom SR, Gough MH, Keeling J, Aschcroft SJH Nesidioblastosis of the pancreas, definition of the syndrome and the management of the severe neonatal hypermsulinemic hypoglycemia Arch Dis Child, 1981, 56 496-508

22 Hansson G, Reden B Familial neonatal hypoglycemia A syndrome resembling foetopathia diabetica Acta Pediatr 1963, 52 145-147

23 Schwart7 ^S, Rich BH, Lucky AW, Straus FH II, Gonen BB, Wolfsdorf MD, *et al* Familial nesidioblastosis Severe neonatal hypoglycemia in two families J Pediatr 1979,95 44-53

24 Polak JM, Wigglesworth JS Islet cell hyperplasia and sudden infant death Lancet 1976, 2 570-571

25 Sperling MA, Fmegold DN Hypoglycemia in infants *In* Pediatnc Endocrinology Ed Sperling MA Philadelphia, W B Saunders Co, 1996, pp 71-93

26 Glaser B, Hirsch HJ, Landau H Persistent hypermsulmemic hypoglycemia of infancy Long term octreohde treatment with out pancreatectomy J Pediatr 1993, 123 644-650

27 Thornton PS, Alter A, Levitt Katz LE, Baker L, Stanley CA Short and long term use of octreotide in the treatment of congenital hyperinsulinism J Pediatr 1993, 123 637-643

28 Shilyansky J, Fisher S, Cutz E, Perlman K, Filler RM 95% pancreatectomy the procedure of choice for treatment of persistent hyperinsulinemic hypoglycemia of the neonate J Pediatr Surgery 1997, 32 342-346.

29 Leibowitz G, Glaser B, Higazi AA, Salameh M, Cercasi E, Landau H Hyper-lnsulinemic hypoglycemia of infancy (nesidioblastosis) in clinical remission High incidence of diabetes mellitus and persistent beta cell dysfunction at long term follow up J Clin Endocnnol Metab 1995, 80 386-392

30 Filler RM, Weinberg MJ, Cutz E, Shilyansky J, Fischers, Perlmank K Current status of pancreatectomy for persistent ldiopathic neonatal hypoglycemia due to islet cell dysplasia Prog Pediatr Surg l991, 26 60-75

31 Grant DB, Dunger DE, Burns EC Long term treatment with diazoxide in childhood hyperinsulinism Acta Endocnnol Suppl 1986, 279 340-345

32 Thomas PM, Cote GJ, Wohlik N, Hadad B, Mathew PM, Rabi W, *et al* Mutations in the sulfonylurea receptor gene in familial persistent hyperinsulinemic hypoglycemia of infancy Science 1995, 268 426-429

33 Dunne MJ, Kane C, Shepherd RM, Sanchez JA, James RF, Johnson PR, *et al* Familial persistent hyperinsulinemic hypoglycemia of infancy and mutations in the sulfonylurea receptor 1997, 336 703-706

34 Lindley KJ, Dunne MJ, Kane C, Shepherd RM, Squires PE, James RFL, *et al* Ionic control of beta cell function in nesidioblastosis A possible therapeutic role for calcium channel blockade Arch Dis Child 1996, 74 373-378

35 Stanely CA Hyperinsulinism in infants and children Pediatr Clin North Am 1997,44 363 372