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A Study on Nesidioblastosis in Hyperinsulinemic Hypoglycemia

— Diagnosis, Treatment, and Neurologic Sequelae —

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The medical records of six cases of nesidioblastosis were examined to determine the diagnostic approach, treatment, and neurologic sequelae. All six patients were male, and their ages at the onset of the disease ranged from one day to six months (means 3.36±2.5 mo.). Initial clinical features were seizure, cyanosis, poor feeding, and apnea. Other subsequent symptoms were developmental delay, hyperactivity, and cold sweating. The Birth weight of the neonatal onset group was heavier than the postneonatal onset group (4.4±0.3 vs 3.26±0.04 kg). Before the diagnosis of hyperinsulinism, steroids of ACTH proved effective for seizure control. Initially, hyperinsulinemia (serum insulin > 10μU/ml) was detected in four cases, but another two cases also showed hyperinsulininsm by insulin/glucose(I/G) ratio > 0.3 during the fasting test. The glucagone response performed in 2 cases, showed normal and partial responses. Euglycemia was obtained by near total pancreatectomy (95% pancreatic resection)without malabsorption or persistent diabetes. In one case, nesidioblastoma coexisted with nesidioblastosis. Developmental delay was noted in three cases. In this group, the mean duration between symptom onset and operation was longer than the group without developmental delay (1.25±0.47 vs 0.38±0.19 yr).

Key Words: *Nesidioblastosis, Persistent hyperinsulinemic hypoglycemia, I/G ratio*

INTRODUCTION

Nesidioblastosis is one of the causes of persistent hyperinsulinemic hypoglycemia (PHH) in infancy and childhood. Since the hypoglycemia may be exceedingly difficult to control and associated with a high incidence of brain damage and subsequent mental retardation, it is a diagnostically important disease (Aynsley-Green et al., 1981).

We studied six recent cases of nesidioblastosis in order to obtain clinical information on the diagnostic approach, treatment, and neurologic sequelae.

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MATERIALS AND METHODS

The records of six children with histologic findings of nesidioblastosis were reviewed. They were admitted to Seoul National University Children's Hospital from January 1988 to February 1990 for evaluation of hypoglycemic seizure.

The clinical diagnesis of relative hgperinsalinism was based on the criteria of insulin level > 10 μU/ml dur ing hypoglycemia or insulin/glucose ratio > 0.3 during the fasting test consisted of simultaneous blood sam pling for insulin and glucose every hour from the time of the last feeding to the development of hypoglycemic symptoms, such as lethargy or seizure.

All six were checked by abdominal ultrasonography or computerized tomography to detect any pancreatic abnormality. EEG and brain CT were used to observe brain damage.

RESULTS

A. General symptomatology (Table 1)

① Age at onset ranged from one day to six months (mean 3.26 mo ±2.5). Sex distribution was male only.

② The birth weight of the neonatal onset group (Cases 4,5) was higher than the postneonatal onset group (4.4±0.3 kg vs. 3.26±0.04), but statistically insignificant by Mann-Whitney test ($p=0.11$).

③ The initial symptoms of the neonatal onset group were cyanosis, poor feeding, and apnea, but subsequently seizure appeared. The postneonatal onset group showed seizure initially, but developmental delay and hyperactivity at night were also noted.

B. Response to medical treatment before diagnosis (Table 2)

① Clinical seizure was terminated with steroids or ACTH therapy, but recurred after off-medication (Cases 1, 2, 3, 4).

② Usual anticonvulsants, such as phenobarbital, diphenylhydantoin, and valproate, had no effect on seizures (Cases 5, 6).

C. Diagnostic work-up (Table 3, Fig. 1)

① All cases except case 3 and 5 revealed an insulin level above 10 μU/ml during hypoglycemia, i.e., hyperinsulinemia.

② The level of I/G ratio during the fasting test increased above 0.3 in all cases, including Cases 3 and 5, i.e., hyperinsulinism.

③ In all cases, no evidence of morphologic abnormality in the panoreas was detected by abdominal ultrasonography or abdominal CT.

④ Glucagon test was perfcrmed in Cases 1 and 2 with 0.3 μg/kg I.M. In case 1, the basal level of glucose 31 mg/dl increased to 69 at 10 min. and 89 at 30 min., showing a normal response. In case 2, the glucose levels were 31 mg/dl at 0 min., 49 at 15 min., 51 at 30 min., 51 at 45 min., and 41 at 30 min., showing a partial response.

D. Operation and postoperative problems (Table 4)

① All cases underwent near total pancreatectomy (95% resection).

② The ages at operation ranged from three months

Table 1. Patlents' Profiles and Clinical Symptoms

Case No.	Age at Onset	Sex	Birth Wt(kg)	Initial Symptoms	Other Symptoms
1	3mo.	M	3.3	Sz	Delayed development
2	6mo.	M	3.3	Sz	Night hyperactivity Delayed development
3	6mo.	M	3.24	Sz	
4	1day	M	4.7	Cyanosis Poor feeding	Sz
5	2day	M	4.1	Apnea Cyanosis	Sz Cold sweating
6	5mo.	M	3.2	Sz	

Sz: seizure

Table 2. Effects of Medical Treatment on Seizures

Case No.	History of Medical Treatment	Effects on Seizure
1	PD for 1mo.	(+) Only during medication
2	PD for 1mo. ACTH for 3 wk.	(+) Only during medication
3	ACTH	(+) Only during medication
4	Frequent feeding & hydrocortisone	Partial response
5	Pb	(−)
6	Pb, DPH, Valproate	(−)

PD: prednisone, Pb: phenobarbotal, DPH: diphenylhydantoin

Table 3. Results of Fasting Test

Insulin (μU/ml) / Glucose (mg/dl)	Time of Sampling							
	0	1hr.	2hr.	4hr.	6hr.	8hr.	10hr.	14hr.
Case 1	17.5	14.2	7.0					
	9	10	20					
Case 2	10.2	10.0	8.2	8.9	16.0	7.0	10.6	
	25	31	28	6	19	20	25	
Case 3	3.0	7.0	4.8	5.6	4.4	4.0	4.0	8.3
	62	34	24	24	4	4	4	4
Case 4	30.0	22.3	21.9					
	78	29	23					
Case 5	3.5	8.8	8.1	10.5	6.4	4.4		
	74	100	79	27	7	6		
Case 6	30.1							
	60							

Table 4. Surgery and Postoperative Problems

Case No.	Age at Surgery*	Malabsorption /sec. DM	Neurologic Abnormality /Development
1	1 10/12 yr.	-/-	Absent Sz, delayed speech
2	2 1/12 yr.	-/-	Normoglycemic Sz (persistent) delayed development
3	1 1/12 yr.	-/-	Hypoglycemic Sz to milk product, delayed development (speech)
4	3 mo.	-/transient	Uneventful, not delayed
5	8 mo.	-/-	Transient Sz, not delayed
6	8 mo.	-/transient	Uneventful, not delayed

*There was a near-total pancreatectomy in all patients.
sec. DM: secondary diabetes mellitus

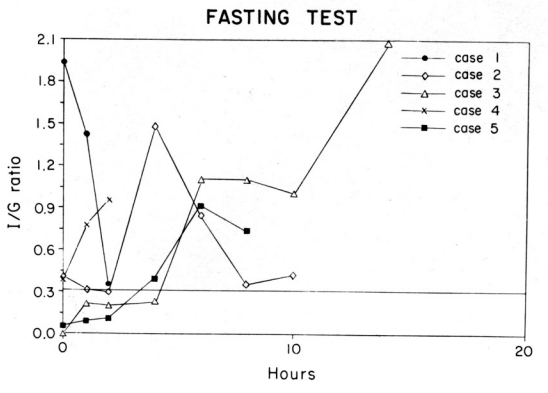

Fig. 1. The I/G ratio during the fasting test was raised above 0.3 in all five cases.

to 2 1/12 years (mean 1.1±0.66 yr).

③ Postoperatively, the malabsorption syndrome didn't develop in all cases.

④ Secondary diabetes after oral feeding developed in Cases 4 and 6, but they spontaneously subsided after three and six days of insulin therapy, respectively.

E. Pathologic findings (Table 5, Fig. 2, 3)

The removed pancreases measured from 5.5cm to 12.5cm in maximum cross, and weighed from 2 to 11.5gm. The pancrease grossly showed a gray-pink lobulated appearance as in the normal pancreas, except for two cases (Cases 2 and 4) where they were well-or poorly-circumscribed with no other findings.

Microscopically, there was diffuse ductuloendocrine hyperplasia in all cases. The Langerhans islets were

Table 5. Summary of Pathologic Features

Case No.	Specimen Size (cm)	Specimen Wt (gm)	Gross	Nesidioblastosis	Immunohisto-chemistry
1	8×1.7×1.4	9.4	Lobulated	Diffuse pinkish gray	B.A.S.PP
2	12.5×2.5×1.5	11.5	Ill-defined ovoid mass 2×1.5cm. in tail, dusky yellow	Diffuse and nodular	B.A.S
3	12×1.2	9.7	Pale gray-pink, lobulated	Diffuse	B.A.S
4	6.5×1.5×1.5	2.0	A round mass 0.8 cm. in tail well-circumscribed	Nesidioblastoma	B.A.S.PP
5	8×1×1	2.9	Diffuse lobulated	Diffuse	B.A.S
6	5×1.5×1.4	8.6	Diffuse lobulated, pinkish gray	Diffuse	B.A.S

B: beta cell, A: alpha cell, S: somatostatin, PP: pancreatic polypeptide

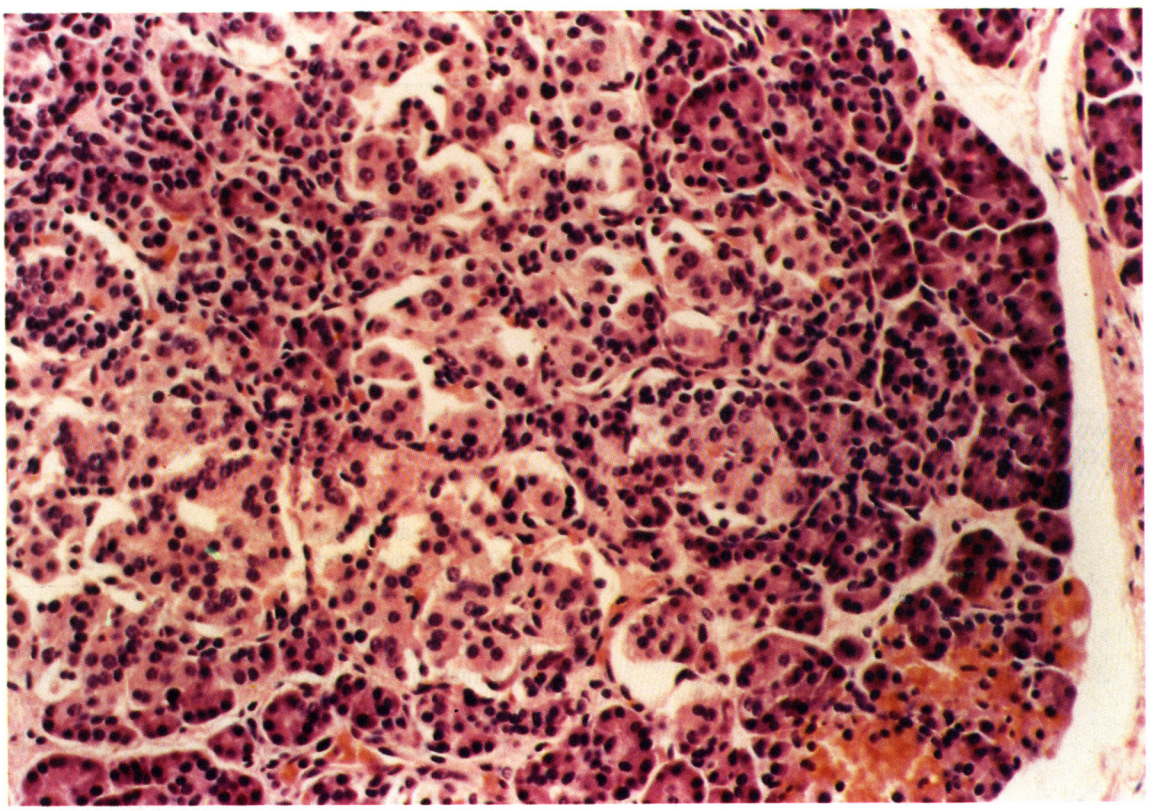

Fig. 2. The tumor nodule is composed of various sized lobules of pancreatic tissue, in which islet cell proliferation takes place with peripheral normal-appearing acinar elements. The islet cells are a pattern of anastomosing ribbons and cords (H & E ×200, from Case 4).

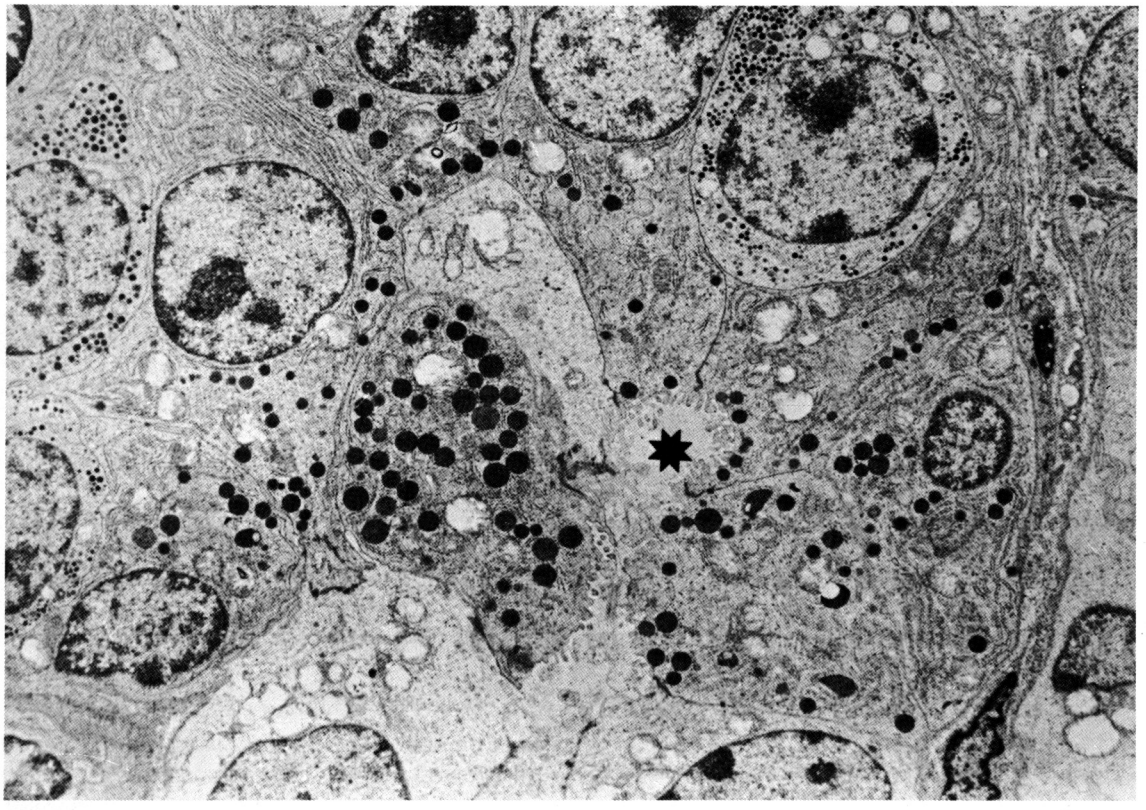

Fig. 3. An ultrathin section of acinus shows a well-formed lumen (asterisk) with microvilli along with acinar cells containing zymogen granules in which several islet cells are embedded (EM, from Case 4).

poorly delimited. Two cases that had grossly appearing nodular lesions, revealed basically the same histological features as the remaining cases. However, one case (Case 4) showed exaggerated nesidioblastosis inside the nodule. No capsular formation was seen. Immunohistochemistry to demonstrate beta, alpha, delta, and pancreatic polypeptide (PP) cells showed a mixed pattern, although the majority were beta cells. Cells with PP were rare. Electron microscopy showed frequent intermediate cells in the region where ductuloendocrine hyperplasia was seen light microscopically.

F. Developmental and neurological problems (Table 1, 4, 6, 7)

① Cases 1 and 2 with preexisting developmental delay showed persistent delay postoperatively, but Case 3, who has no detectable delay preoperatively, showed speech delay postoperatively.

② Seizure terminated completely in Cases 1, 4 and 6 after operation. Case 5 also recoverd from seizures after brief episodes.

③ Persistent postoperative seizures were noted in Cases 2 and 3. Seizure control was incomplete in Case 2, even with anticonvulsant (carbamazepin). Case 3 occasionally showed hypoglycemic seizure on milk product feeding, especially cheese.

④ While cases with normal preoperative EEG and brain CT showed persistent seizure postoperatively (Cases 2, 3), cases with preoperative EEG findings of diffuse cerebral dysfunction didn't develop seizure postoperatively (Cases 4, 5), and a normalized EEG was obtained postoperatively in Case 5.

⑤ The duration between the onset of symptoms and the age at operation in the developmentally delayed group was longer than the group without delay postoperatively (Table 7) but statistically insignificant by Mann-Whitney test ($P=0.19$).

DISCUSSION

There is no unified morphologic nomenclature and corresponding clinical classification concerning PHH

Table 6. Preoperative and Postoperative EEG and Brain CT Scan Findings

Case	Preoperative		Postoperative	
No.	EEG	B-CT	EEG	B-CT
1	Partial Sz	WNL	NC	NC
2	WNL	WNL	WNL	WNL
3	WNL	WNL	NC	NC
4	Diffuse cerebral dysfunction	Diffuse brain atrophy	NC	NC
5	Diffuse carebral dysfunotion	WNL	WNL	NC
6	WNL	WNL	WNL	NC

NC: not checked, WNL: within normal limit

Table 7. Duration between symptom Onset and Operation

Developmental Delay	Case No.	Duration between Symptom Onset and Operation
(+)	1, 2, 3	1.25±0.47 yr.
(−)	4, 5, 6	0.38±0.19 yr.

p=0.19 by Mann-Whitney test

in infancy.

Laidlaw first used the term nesidioblast, meaning "islet builder" in 1938. He described the differentiated cells that emerged from the duct epithelium to build an islet. When a tumor is formed from the cell, it is called, a nesidioblastoma, and diffuse or disseminated proliferation of the cell was called nesidioblastosis (Laidlaw, 1938). Heitz uses the term "multifocal ductuloinsular proliferation" to describe extensive proliferation of endocrine cells in contact with the ductular structure (Heitz et al., 1977). Gabby proposes the term "islet cell dysmaturation syndrome" to describe the ß-cell abnormality with hyperinsulinism ranging from adenoma to nesidioblastosis (Cabbot et al., 1978).

This hyperinsulinemic hypoglycemia from nesidioblastosis is reported not only in infants but also in adults (Klöppel et al., 1988; Fong et al., 1988; Albers et al., 1988). In Korea, there were two case reports-one of a neonate and one of an adult (Kim et al., 1986; Kim et al., 1985).

Brown first reported the association of nesidioblastosis with severe infantile hypoglycemia and stresses leucine as a releaser of insulin and an inducer of ß-cell neoformation (Brown et al., 1970). Yakovac stresses that excess production of insulin is an important feature of this disease (Yakovac et al., 1977), but thereafter Heitz reports additional abnormalities in the distribution and number of glucagon, somatostatin, and pancreatic polypeptide cells by immunohistochemical method (Heitz wt al., 1977). Bishop demonstrates a decrease of pancreatic somatostatin in neonatal nesidioblastosis resulting in a distinct alteration of islet cell function (Bishop et al., 1980). It is suggested that hyperinsulinism in this disorder may not be the sole hormonal abnormality, but rather that this disease is one of a generalized disturbance of islet cell function (Schwartz et al., 1980). Considering our Cases 3 and 5, which had hyperinsulinism without hyperinsulinemia, the hypoglycemia was supposed to result from a decrease of other pancreatic hormones.

The etiology of the histological abnormality in nesidioblastosis is unknown. During normal pancreatic embryogenesis, primary islands originate from the primitive ducts of the pancreas beginning in the eighth week of gestation, reaching their maturity in the fifth month, then degenerating thereafter. The secondary islands, constituting the pancreatic islands, arise from the cells of the terminal ducts at the third month of gestation and are located within the lobules among the acini (Like et al., 1972; Liu et al., 1962). The phenomena of budding off from the ductular epithelium in nesidoblastosis and the spatial relationship of the different cells observed strongly resemble the same features during embryogenesis. This suggests that nesidoblastosis may be the result of "inappropriate control" during the earliest phase of the develop-

ment of the endocrine pancreas (Heitz et al., 1977). Dahms describes two histologic subgroups in PHH. Those in Group 1 younger than eight months of age had diffuse hyperplasia of islets of Langerhans as well as nesidioblastosis. Group 2, which ranged from three to fifteen years of age, had more subtle nesidioblastosis alone. Dhams regards nesidioblastosis in Group 1 as an exaggeration of the physiologic process, while that in Group 2 reflected either an abnormal prolongation or recurrence of this physiologic process (Dahms et al., 1980). The possibility of autosomal recessive inheritance was suggested in familial occurrence (Woo et al., 1976; Schwartz et al., 1979). While autosomal dominance inheritance was suggested in reporting nesidioblastosis in families with multiple endocrine adenomatosis (MEA), and nesidioblastosis might be the basic pathology in the variable involvement of other endocrine glands in MEA (Vance et al., 1969). These above reports suggest that PHH in nesidioblastosis results from inappropriate control during the embryogenesis of the endocrine pancreas probably due to a genetic defect or environmental factors. We couldn't find any genetic traits, but occasional hypoglycemic seizures during milk product feeding in Case 3 sug gested that the role of environmental factors is an important one in its pathogenesis. Also, a higher birth weight in the neonatal onset group suggested the pathologic process beginning from intrauterine life.

Clinical manifestation of nesidioblastosis is due to persistent hypoglycemia. Early onset symptoms are seizure, apnea, lethargy, twitching, sweating, and tachycardia. Late onset symptoms are developmental delay, hyperactivity, behavior disturbance, abdominal pain, sweating, tachycardia, nervousness, hunger, mental confusion, and coma (Campbell et al., 1983; Goode et al., 1986; Mayer et al., 1981). The physical character of these patients is general adiposity, like an infant of a diabetic mother (Aynsley-Green et al., 1981). It was true of neonatal onset group in our cases. Occasionally, nesidioblastosis was discovered in an unexpected neonatal death (Polak et al., 1976). Nesidioblastosis, reported as a pancreatic abnormality in 36% of SIDS (Sudden Infant Death Syndrome) is regarded as one of the causes of SIDS (Cox et al., 1976).

A level of insulin greater than 10 μU/ml in the presence of hypoglycemia is abnormal (Pagliara et al., 1973) and suggests hyperinsulinemia. Occasionally, hypoglycemia may be accompanied by a normal plasma insulin level. In such circumstances, the insulin/glucose ratio (I/G ratio) may be helpful. An I/G ratio over 0.3 is generally indicative of hyperinsulinism (Fajans et al., 1976: Sherwin et al., 1987). Ansley et al. lists important diagnostic points for hyperinsulinism as follows: ① inappropriately raised plasma insulin concentration for blood glucose level ② glucose infusion rate > 15 mg/kg/min to maintain blood glucose level > 36 mg/dl ③ low blood ketone body during hypoglycemia and ④ glycemic response to glucagone despite hypoglycemia (Aynsley-Green et al., 1981; Stanley et al., 1976). The striking and prolonged effect of somatostatin in an infant with nesidioblastosis was reported (Hirsh et al., 1977). It may proved to be a useful diagnostic test. Except for Case 3 and 5, others revealed hyperinsulinemia, but with the fasting test all our cases revealed an I/G ratio above 0.3. So the fasting test was very useful in detecting hyperinsulinism.

At present, one cannot clinically distinguish, on the basis of plasma insulin response to fasting and provocative stimulating agent, the entities of ß-cell adenoma, ß-cell hyperplasia, nesidioblastosis, and functional ß-cell secretory disorder (Pagliara et al., 1973: Crowder et al., 1976).

To prevent brain damage from a hypoglycemic seizure, one must vigorously correct the blood glucose concentration. Glucose infusion of even high rates was insufficient to restore normoglycemia (Aynsley-Green et al., 1981). To suppress insulin secretion, diazoxide, epinephrine, DPH and somatostatin were used. Diazoxide is used in a dosage range of 10-15 mg per kg of body weight. Side effects consist of hypertrichosis, advancement of bone age, mild hyperuricemia, and IgG deficiency (Pagliara et al., 1973; Goode et al., 1986). Somatostatin has an inhibitory effect on insulin release, and because somatostatin deficiency is a feature of nesidioblastosis, this hormone administration is theoretically logical (Hirsh et al., 1977; Bishop et al., 1980). But this hormone inhibits other endocrine systems, and long-term effects of prolonged treatment are unknown. To antagonize the effects of insulin on tissue, glucagon, epinephrine, and glucocorticoid were tried. Glucagon has only a transient effect but is useful in an emergency (Aynsley-Green et al., 1981). Because established pharmacologic management is not recognized, pancreatectomy should be considered when medical treatment fails to control symptoms or succeeds only at the expense of serious and significant side effects (Hamilton et al., 1967; Crowder et al., 1976; Thomas et al., 1977). Considering the medical records of our cases, while steroid or ACTH therapy could control hypoglycemic seizures, other conventional anticonvulsants couldn't control the seizures. An ACTH responsive seizure without a typical EEG finding of infantile spasm should be suspected to have PHH.

There was a large overlap in the extent of pancreatectomy necessary to achieve euglycemia. Some recommended that oral diazoxide be tried preoperatively, and if there is good or partial response, an 80% pancreatectomy should be attempted. An aggressive >90% pancreatic resection should be reserved for non-responders to medical therapy (Fong et al., 1989). But others recommended near total pancreatectomy as a primary procedure, because approximately 25% of all patients undergoing standard subtotal pancreatectomy for hyperinsulinism secondary to diffuse pancreatic disease have persistent hypoglycemia (Krammer et al., 1982). We performed near total pancreatectomy (95%) in all our cases, which brought about euglycemia without complications related to pancreatectomy, such as malabsorption or diabetes.

The patients who were regarded as mentally retarded had a slightly earlier mean age of the onset of symptoms and a longer mean interval between the onset and the operation (Thomas et al., 1977). So there is no justification for prolonged therapeutic trials during which the patient is permitted to have repeated hypoglycemic attacks. An aggressive approach to management of this disorder is required if permanent neurologic damage is to be minimized (Campbell et al., 1983). Also in our cases, the relationship between developmental delay and the duration of uncontrolled hypoglycemic symptoms revealed that early aggressive therapy, including surgery, is necessary in PHH in infancy.

In conclusion, nesidioblastosis should be considered one of the causes of PHH, and, the fasting test is diagnostically significant in hyperinsulinism, if the I/G ratio is above 0.3 even without hyperinsulinemia. An early near-total panoreatectomy is recommended to control hypoglycemic seizures and subsequently to prevent brain damage.

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