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Further Studies of the Hypoglycemia in Children with the Exomphalos–Macroglossia–Gigantism Syndrome*

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INTRODUCTION

Beckwith and his associates(1) described the following features of a condition subsequently called the exomphalos–macroglossia–gigantism (EMG) syndrome: macroglossia; omphalocoele; visceromegaly; somatic gigantism and neonatal hypoglycemia. Combs *et al.*(2) studied two children with this syndrome and demonstrated that hyperinsulinism and polycythemia during infancy were also part of the syndrome. The facial abnormality was emphasized by Irving(3). Wiedemann and his co-workers(4,5) and Hooft *et al.*(6) suggested that the etiology of this syndrome was a nonprogressive abnormality of the diencephalon.

Three studies recently published(7–9) have summarized the information currently available in the literature and have highlighted the variability of the syndrome.

The current paper reports studies carried out in eight such children, three of whom had hypoglycemia. The changing nature of their hypoglycemia is documented, and hypoglycemia in the EMG syndrome is discussed.

PATIENTS STUDIED

The history and physical findings present at birth in the eight patients are shown in Table 1. Two of the patients (L.P. and P.R.) were partially discussed

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TABLE 1

HISTORY AND PHYSICAL FINDINGS AT BIRTH IN CHILDREN WITH EMG SYNDROME

Pt.	Sex	Family history: Hypoglycemia	Family history: Diabetes	EMG Syndrome	Gestational age Weeks	Birth measurements (percentiles): Hd. cir.	Ht.	Wt.	Signs: Viscero-megaly	Macro-glossia	Abnormal umbilicus	Poly-cythemia	Hemi-hyper-trophy	Midfacial hypo-plasia	Hypo-glycemic seizures
D.J.[a]	F	0	0	0	35	25	15	25	0	+	+	+	0	+	+
L.P.	F	0	+	0	40	50	90	90	+	+	+	0	+	+	+
D.G.	M	0	0	0	38	50	90	90	0	+	+	0	0	+	0
P.R.	M	0	0	0	38	80	90	90	0	+	+	+	0	0	+
K.B.	F	0	0	0	38	25	90	90	0	+	0	+	0	+	0
T.C.	F	0	0	+[b]	39	55	90	90	+	+	0	+	0	+	0
J.C.	M	0	+	0	39	15	50	50	+	+	0	0	+	+	0
G.T.	M	0	0	0	38	10	90	90	0	+	+	0	0	+	0

[a] One of twins.

[b] Three-year-old male cousin.

in a previous publication(2). With the exception of D.J., who was one of non-identical twins, all of the patients were born at term. Three had hypoglycemic seizures. Six of the eight were above the 90th percentile for both height and weight. In these six, the measurements of head circumference ranged from the 10th to the 80th percentile, thus, frequently giving the appearance of microcephaly. All eight had macroglossia, seven had midfacial hypoplasia, five had an abnormal umbilicus, and four were plethoric. As noted in Table 1, other abnormalities were less constant.

One patient (T.C.) had a cousin with this syndrome. None of the others had any additional family members known to have this condition.

One patient (S.F.) previously reported as having the EMG syndrome(2) must now be considered as having idiopathic hypoglycemia, since she neither had macroglossia nor an abnormal umbilicus. Therefore, this patient was not included in the current publication.

With the exception of G.T. who was Negro, all of the patients were Caucasian and none was retarded.

METHODS

All eight children were fasted for periods of 12–24 hr starting at 6 P.M. after having eaten a diet considered normal for the child's age for the 3 previous days (Table 2). During the fast period they were allowed only water to drink. The two children who demonstrated hyperinsulinism (D.J. and L.P.) were fasted on several occasions.

Intravenous glucose-tolerance tests were carried out in four patients (Table 3). These tests were done at 8–9 A.M. after 12 hr of fasting and subsequent to at least 3 days of a diet considered to be normal for the child's age. One gram of glucose per kg body weight in a 20% solution was administered in 3–5 min. Venous blood samples were obtained prior to and at 15–min intervals after glucose injection for the first hour and at hourly intervals for the next 5 hr.

Thirty micrograms of glucagon (Lilly Glucagon for injection) per kg body weight was injected intravenously for the glucagon–tolerance test. Venous blood samples were obtained at 15–min intervals for 1 hr. This test was performed at the completion of the glucose-tolerance test in four patients. Glucagon was also administered to all eight patients at the completion of the 12– to 24–hr fast.

Blood samples were evaluated for glucose, using the glucose oxidase method(10); immunoreactive insulin (IRI), using a double–antibody radioimmunoassay method(11); and growth hormone (HGH), using a similar radioimmunoassay(12).

RESULTS

The blood glucose and IRI levels during the 12– to 24–hr periods of fasting are shown in Table 2. Two patients (D.J. and L.P.) had spontaneous hypogly-

cemia and fasting insulin levels above 40 μU/ml during the first year of life. (In our laboratory the average 12–hr fasting control IRI value for seven children, 4–16 months of age, is 14.3 $\pm$ 2.3 μU/ml.) Subsequently they had hypoglycemia only when fasted and at that time neither of these children had elevated levels of IRI. Hypoglycemia was noted in one other patient (P.R.). When tested at 2 months of age he developed hypoglycemia after 20 hr of fasting; however, IRI was not elevated. The other five had no symptoms of hypoglycemia and were able to sustain a 24–hr fast without developing low blood–glucose levels.

Glucose– and glucagon–tolerance tests are shown in Table 3. Low blood–glucose levels were present within 3 hr after glucose administration in four of the five tests. In the fifth test (G.T.) blood glucose levels never fell below 56 mg per 100 ml. The previously noted insulin levels above 40 μU/ml in D.J. and L.P.

TABLE 2

BLOOD GLUCOSE AND SERUM INSULIN LEVELS DURING 12- TO 24-HOUR PERIODS OF FASTING IN PATIENTS WITH EMG SYNDROME

Pt.	Age (months)	Test[a]	Hours 12	14	16	18	20	22	24
	3	BG	48	45	41	38	38	38	
	4	BG	54						
		IRI	44						
D.J.	6	BG	13	10	40	48	68	51	40
	11	BG	70	77	48	43	24+	35	9
	40	BG		65		53		27+*	
		IRI		2		3		0	
	3	BG	34						
		IRI	80						
L.P.	12	BG	57						
		IRI	60						
	20	BG	93	85	81	44	28	10	
	32	BG	50	17					
		IRI		5					
D.G.	92	BG	73						87
		IRI	2						0
P.R.	2	BG	63	46		45	35	38*	
		IRI	4						
K.B.	140	BG	65		74		79		63
		IRI	7		3		2		1
T.C.	26	BG	67			63			55
		IRI	6			2			1
J.C.	14	BG	87			69			68
		IRI	4			2			2
G.T.	3	BG	50			47			55
		IRI	9			2			8

[a] BG = blood glucose (mg/100 ml); IRI = immunoreactive insulin (μU/ml); * = seizures; + = ketonuria.

are seen here again. Neither P.R. nor G.T. had elevated IRI levels. HGH concentrations were slightly elevated in the three patients (four tests) in whom it was measured (normal fasting HGH levels are 0-3 ng/ml(13)). However, in each case there was a normal fall in HGH concentrations after glucose administration.

All four patients had significantly elevated blood–glucose levels after glucagon administration.

DISCUSSION

Hypoglycemia and associated hyperinsulinism have been noted in the first descriptions of the EMG syndrome(1,2). Subsequently it has become evident that this is not invariably seen in all such patients. It is Beckwith's current impression that only one third to one half of infants with this syndrome will have neonatal hypoglycemia(7). Including the current study, approximately 59 such patients have been described by various authors(1,3,4,6–9,14–18). Since many of these patients have not had blood glucose measured, and since in those patients in whom this has been done, the measurement has been carried out at various ages, it is very difficult to give an accurate percentage for the occurrence of hypoglycemia in this syndrome. Nevertheless, low blood–glucose levels have been documented in 10 patients(1,6,9,14,16,18). However, the variability of this finding is seen in the additional documentation of normal blood–glucose concentrations in 15 children with this syndrome(4,6–9).

TABLE 3

BLOOD GLUCOSE, SERUM INSULIN, AND GROWTH HORMONE AFTER GLUCOSE AND GLUCAGON ADMINISTRATION IN PATIENTS WITH EMG SYNDROME

Pt.	Age (months)	Test[a]	Interval after IV glucose (min) 0	5	15	30	60	120	180	240	300	360	Interval after IM glucagon (min) 15	30	45	60
D.J.	4	BG	54	128	65	72	43	52	53	46	49	46	65	79	78	
		IRI	44	88	75	44										
		HGH	5		1											
L.P.	3	BG	34	395		86	12	10	29	10	17	22	80	109	97	75
		IRI	80	400			87									
		HGH	4	2		2	3									
	12	BG	57		279	125	42	48	67	48	49	65	95	124	139	127
		IRI	60		120	83	63									
		HGH	7		4	9	7									
P.R.	2	BG	63	419	358	211	99	50	34	15	21	33	90	120	110	
		IRI	4	32	21	15										
G.T.	3	BG	76	374	255	182	65	56		76		80	93	120	97	73
		IRI	8	30	24	18	10									
		HGH	4		3	3	0									

[a] BG = blood glucose (mg/100 ml); IRI = immunoreactive insulin (μU/ml); HGH = growth hormone (ng/ml).

Only two other groups of workers have measured insulin in these children(1,2,18) giving a total of five documented cases of hyperinsulinemia. To these data must be added the significant number of such patients who have had hyperplasia of the Islets of Langerhans. Thirteen of the 22 patients who have come to autopsy have had this finding(3,7,8,9,15) and although insulin levels were not measured, the possibility of hyperinsulinism is distinct. Despite the few data, it would appear that hyperinsulinism is a significant factor in many of these patients.

As has been noted above, not all of these patients have hypoglycemia. In addition, it is likely that not all of these patients with hypoglycemia have hyperinsulinism. In our study one patient (P.R.) had significant hypoglycemia without hyperinsulinism at 7 weeks of age. The demonstration of low blood glucose in these patients does not warrant the assumption that serum insulin levels are high if such measurements are not made.

In the two patients in this study with neonatal hyperinsulinemic hypoglycemia, insulin levels were high during the first year of life. Subsequently, these patients developed low blood glucose values only when fasted for 12–24 hr. This sporadic hypoglycemia was not associated with elevated insulin levels and disappeared spontaneously between 3 and 5 years of age.

Many of these large newborn infants with marked polycythemia developed into mildly microcephalic, nonplethoric children without the previously noted somatic gigantism. Excess insulin has been shown to be associated with polycythemia(19) and to act as an excellent stimulus for growth(20). Thus, the possibility exists that both the neonatal findings as well as the subsequent changes in growth pattern can be explained on the basis of hyperinsulinism during intrauterine, neonatal, and early childhood development.

The responses to glucose administration were variable (Table 3) and therefore difficult to explain. Three of the four patients tested (D.J., L.P., and P.R.) developed hypoglycemia during the glucose–tolerance tests. Glucose utilization was extremely rapid in D.J. Fifteen minutes after the glucose injection her blood–glucose was only 65 mg per 100 ml. L.P., whose low blood glucose was first seen 1 hr after glucose administration, may have had a reactive or stimulative rather than fasting hypoglycemia. P.R. had a blood glucose value of 34 mg per 100 ml 3 hr after glucose administration. Since this value was obtained after 15 hr of fasting, and since this patient had a blood glucose value of 46 mg per 100 ml after 14 hr of fasting on another occasion (Table 2) this patient's low blood glucose most likely represents fasting hypoglycemia.

Since there was a significant increase in blood glucose in each patient given glucagon (Table 3), it would appear that these patients have no abnormality in glycogen synthesis and release.

Several investigators have suggested that the etiology of this condition is a nonprogressive dysfunction of the hypothalamus(4–6). Our findings do not yield direct evidence to corroborate this thesis. However, in light of the work of Cornblath *et al.*(21) showing that central nervous system lesions could alter the blood glucose, free fatty acid, and insulin responses to an intravenous glucose

load in macaque monkeys, the transient abnormality in the control of carbohydrate homeostasis which occurs in these children may be indirect evidence of central nervous system malfunction. This malfunction appears to involve hyperinsulinism initially and subsequently involves other mechanisms which are, as yet, poorly understood. It has been suggested that the central nervous system may play a role in the control of glucagon secretion(22). With this possibility in mind, the inability to demonstrate any serum glucagon in one patient with the EMG syndrome(18) may represent still another aspect of malfunction in central nervous system control of carbohydrate homeostasis. The potential importance of this syndrome as an aid to the understanding of such central nervous system function as well as carbohydrate homeostasis in hypoglycemic states certainly warrants careful study of each of these hypoglycemic patients from birth until that time when they can sustain a 24–hr fast without the development of low blood glucose.

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