Synalbumin Insulin Antagonism in Idiopathic Hypoglycemia of Infancy

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SUMMARY

Infantile idiopathic hypoglycemia appears to be an early manifestation of an inherited metabolic defect that leads to diabetes mellitus. Eight children with this form of hypoglycemia were studied for the presence of synalbumin insulin antagonism. All had diabetes in one or both parental families. Two of the children had normal antagonist levels before and after they developed chemical diabetes. A third child was tested twice after she was found to have chemical diabetes, and on each occasion had normal antagonist levels. Rather than a causa sine qua non for the development of diabetes, or a constant feature of the disorder, excess synalbumin insulin antagonism appears to be a variable expression of a more fundamental metabolic abnormality in essential diabetes mellitus. DIABETES *17*:557-59, September, 1968.

We have recently reported that idiopathic hypoglycemia of infancy can be an early manifestation of familial diabetes mellitus.[1] This report was based on the following findings: (1) the development of diabetic glucose tolerance in several children with a history of idiopathic hypoglycemia; (2) relative glucose intolerance in affected children compared to their unaffected siblings; (3) a frequency of diabetes mellitus in families of these patients comparable to that in families of known diabetic children; (4) in several instances, ascertainment through the hypoglycemic child of previously unknown diabetes in parental families.

Because of this association with diabetes mellitus, we decided to measure levels of plasma synalbumin insulin antagonism[2,3] in children with a history of idiopathic hypoglycemia.

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METHODS

The subjects were eight affected children. In all of them hypoglycemic seizures began between three and eighteen months of age. Medical progress of the patients was followed for six months in the youngest of the group to thirteen years in the oldest. Three of the children who have had partial or complete remission of their symptoms and are not on continuous therapy have developed diabetic glucose tolerance tests over a period of months or years (figure 1).

Fasting blood samples were obtained from patients and fifteen of their parents. Plasma insulin levels were determined by a modification of the radioimmunoassay method of Yalow and Berson.[4] All subjects underwent oral glucose tolerance tests after a three-day period during which they ate a diet rich in carbohydrate. Capillary blood was analyzed for sugar concentration. Details of the method used and criteria for diagnosing diabetic glucose tolerance are in our previous report.[1] Tests for the synalbumin insulin antagonist were performed on trichloroacetic acid/ethanol extracts of fasting blood.[2,5] The initial children's specimens were analyzed in our laboratory; repeat specimens obtained eight months to one year later were analyzed in the laboratory of Dr. John Vallance-Owen. In all cases 1.25 per cent of extract was tested for its effect on glucose uptake of rat hemidiaphragms incubated in glucose-balanced salt solution containing 1,000 μU. insulin per milliliter. In addition, extracts from two children who were being treated for continuous hypoglycemia were tested at physiologic blood concentration (3.75 per cent).

RESULTS

None of the eight children tested was found to have increased synalbumin insulin antagonism, despite the presence of diabetes in all their families (table 1). This contrasts with results reported in testing adult diabetic patients[5] and diabetic children and their siblings.[6] It should be noted, as previously reported,[5] that the protein

TABLE 1

Fasting blood sugar and insulin concentrations, with results of testing for glucose tolerance and synalbumin insulin antagonism, in eight children with idiopathic hypoglycemia.

Subject	Sex	Age (years)	Diabetes in parental family	Fasting blood sugar (mg. per 100 ml.)	GTT	Insulin (μU./ml.)	Excess synalbumin
NN.	F	13	Conjugal	82	Diabetic	36	No
		14		88	Diabetic	—	No
G.N.	M	12½	Maternal	95	Normal	3	No
D.H.	F	7	Paternal	92	Normal	66	No
W.F.	M	6	Paternal	71	Normal	2	No
		6 8/12		52	Diabetic	—	No
B.L.	M	4	Conjugal	39	—*	8	No
J.B.	F	4	Paternal	51	Normal	1	No
A.R.	M	3	Conjugal	28	—*	1	No
C.G.	M	9/12	Maternal	68	Flat	4	No
		1½		92	Diabetic	—	No

*Patient on treatment with zinc glucagon to prevent continuous hypoglycemia. Glucose tolerance affected by therapy.

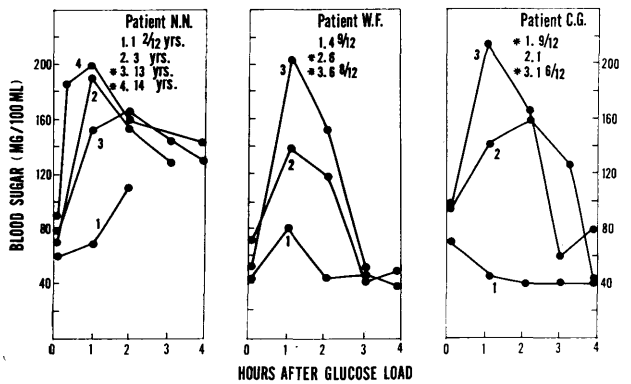

FIG. 1. Evolution of glucose tolerance in three patients with histories of idiopathic hypoglycemia of infancy. Capillary blood sugar concentrations were measured. *Indicates times at which tests for synalbumin insulin antagonism were performed. In no case was excessive antagonism found.

extracts in the absence of insulin had no significant stimulatory effect on basal glucose uptake; thus, there was no interference with possible inhibition of insulin effect.

Of fifteen parents tested, three had increased concentrations of the insulin antagonist. These included the father of N.N. and the mother of G.N.; each parent had a family history of diabetes mellitus. N.N.'s father had diabetic glucose tolerance; G.N.'s mother, normal tolerance. One parent with diabetic glucose tolerance, the father of B.L., did not have excess insulin antagonism on two separate assays. Detailed family histories of diabetes and results of glucose tolerance tests in parents and other relatives are in our previous report.[1]

Patients W.F. and C.G., who did not have increased insulin antagonism during the time their glucose tolerance was normal, developed diabetic glucose tolerances shortly thereafter (figure 1). Repeat assays for increased insulin antagonism after the children were found to have diabetic glucose tolerance remained negative. Patient N.N., whose glucose tolerance tests were abnormal at ages three, thirteen and fourteen had normal synalbumin insulin antagonism when tested on the latter two occasions (figure 1).

Two children, B.L. and A.R., were still having recurrent hypoglycemic episodes. Their "albumin" fractions (1.25 per cent) demonstrated no inhibition of insulin activity on the rat hemidiaphragm (table 1). At 3.75 per cent, however, their fractions significantly inhibited the insulin effect (greater than 40 per cent inhibition in both cases). This is a normal finding.[3,5,7] Thus, there was no evidence of a *decrease* in the insulin antagonist concentration measured in vitro to account for their hypoglycemia in the presence of normal plasma insulin concentrations (table 1).

Fasting plasma insulin levels of all subjects were normal range. Mean concentrations were 15.3 μU./ml. $\pm$ 8.0 SEM for the eight children and 9.3 μU./ml. $\pm$ 2.9 SEM for their fifteen tested parents. The difference between the means was insignificant. Two children (B.L. and A.R.) had fasting hypoglycemia when tested (39 and 28 mg. per 100 ml. respectively); both had plasma insulin levels in the low normal range (8 and 1 μU./ml. respectively). These findings confirm previous reports of normal plasma insulin concentrations in most patients with idiopathic hypoglycemia of infancy.[8]

DISCUSSION

Vallance-Owen suggested that excessive synalbumin insulin antagonism in an individual can be regarded as a biochemical marker of essential diabetes mellitus without reference to carbohydrate metabolism.[3] He postulated genetic transmission of this biochemical marker. It has not yet been ascertained whether such increased insulin antagonism is present at birth or develops later as the result of an unidentified metabolic stimulus.

The eight children with idiopathic hypoglycemia of infancy whom we have studied were all from families in which diabetes mellitus was present.[1] Three of the children have developed diabetic glucose tolerance (figure 1), two of them during the course of study. In neither of these two patients was excessive synalbumin antagonism found shortly before the appearance of chemical diabetes. When the test was repeated after chemical diabetes was discovered, excessive insulin antagonism was still absent. These observations indicate that such antagonism does not necessarily precede the development of other manifestations of the diabetic trait (such as infantile hypoglycemia). In the third child, abnormal glucose tolerance preceded the finding of normal synalbumin antagonism by years; both abnormal glucose tolerance and normal synalbumin were found on repeat examination. This is in accord with recently published reports in which it has been noted that increased synalbumin, though found in most adult and juvenile diabetic subjects who have been tested, has not been found in all.[5-7] It appears that such insulin antagonism is not the fundamental abnormality in diabetes mellitus, but is rather a variable expression of this still elusive insulin abnormality.

ACKNOWLEDGMENT

We wish to thank Dr. David M. Kipnis of the Washington University School of Medicine, St. Louis, for performing the plasma insulin assays; and Dr. John Vallance-Owen of Queen's University of Belfast, Northern Ireland, for performing one of the two series of assays for insulin antagonism on the children with histories of hypoglycemia.

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