Beta Cell Nesidioblastosis

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Abstract. Two patients with severe hypoglycemia since birth are described. In both hyperinsulinism was demonstrated during spontaneous hypoglycemic attacks or could be provoked by various tolerance tests. In case I considerable obesity and psychomotor retardation was present at the age of one year whereas in case II weight gain was normal and development unaffected.

Immunofluorescence microscopic and electron microscopic examination of the pancreas after subtotal pancreatectomy revealed diffuse islet cell hyperplasia with nesidioblastosis in case I and β-cell nesidioblastosis in case II. The hyperplastic and nesidioblastotic areas consisted mainly of β-cells. In addition, an accumulation of somatostatin producing cells was observed in case I, and some cells were found with ultrastructural signs of both endocrine and exocrine function.

In both cases, pancreatic insulin release was inhibited by a prolonged somatostatin infusion. The results of tolerance tests did not allow a diagnosis of the underlying pancreatic lesion. In case II, leucine-sensitive hypoglycemia detected soon after birth, was present even after subtotal pancreatic resection.

Therapeutic trials with diazoxide in case I and a leucine-restricted diet in case II were only of temporary benefit. After subtotal pancreatectomy there was clinical improvement in both cases, but case II still needs a leucine-restricted diet. The familial occurrence of persistent hypoglycemia in both cases suggests that β-cell nesidioblastosis may be a hereditary disorder.


Introduction

Persistent hyperinsulinism seems to be a rare cause of hypoglycemia in neonates, infants and children, and there are only few reports which give complete clinicopathological studies (Flanagan et al., 1961; Perheentupa et al., 1967; Rawlinson

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** With support of the Landesamt für Forschung des Landes Nordrhein-Westfalen
Investigation of the causes of hyperinsulinism has revealed single or multiple pancreatic adenomata (Garces et al., 1960; Robinson et al., 1971; Schwartz and Zwiren, 1971; Rawlinson and Christiansen, 1973; Klöppel et al., 1975; Babinet et al., 1975), diffuse hyperplasia of the \( \beta \)-cells (Haworth and Coodin, 1960; Misugi et al., 1970; Pagliara et al., 1973; Klöppel et al., 1974; Crowder et al., 1976) and nesidioblastosis (Brown and Young, 1970; Yakovac et al., 1971; Grampa et al., 1974).

Nesidioblastosis, a term introduced by Laidlaw (1938), seems to be not uncommon in infants. This entity comprises postnatal formation of \( \beta \)-cells, presumably from cells of the pancreatic ductules (Brown and Still, 1969; Yakovac et al., 1971) as it occurs in early fetal life when the normal islet-cells originate from the periductular epithelium (Falin, 1967). Experimental studies in animals, as well as clinical observations in man, have shown that some nesidioblastosis can be induced by prolonged infusions of carbohydrates (Elliot et al., 1961) and by certain drugs (Franckson et al., 1953; Herman et al., 1964), e.g. sulfonylurea (Bunnag et al., 1966).

Hyperinsulinism in infants may be accompanied by abnormal sensitivity to leucine.

Very little is known about the relationship between the anatomical basis of hyperinsulinism and the clinical symptomatology, e.g. leucine sensitivity, or the response to therapy. Therefore, the clinical, pathological and ultrastructural findings in two children with \( \beta \)-cell nesidioblastosis who had severe hypoglycemia from birth are described. One of these infants was leucine-sensitive.

**Probands**

*Case I.* L.S., a girl, born May 1st 1975, is the third child of apparently healthy unrelated parents. There is no diabetes mellitus or blood-group incompatibility in the family. A brother, now seven years old, is well. The second child, a sister, died at 3 days after several convulsions caused by intractable hypoglycemia.

Pregnancy and birth of L.S. were uneventful and her birth weight was 3700 g. The Apgar score was 10 at 1 min. On the second day of life several attacks of cyanosis and convulsions caused by low blood glucose concentrations (minimum value 7 mg/dl) were observed. Despite intravenous administration of glucose, the blood glucose level remained low. However, the amount given was relatively low (8—10 g/kg/day). Several intravenous injections of dexa-methasone were without benefit. Glucagon injection (1 mg intramuscularly) induced a transient rise of the blood glucose to 85 mg/100 ml but this was followed by a decrease to 10 mg/100 ml after 30 min. On the seventh day of life the child was referred to the University Children's Hospital C at Düsseldorf. On admission, physical examination revealed slight picrocyanosis and some tremor of the hands. There was no hepatomegaly. The tendon reflexes were normal, but muscle hypotonia was present.

Laboratory investigations revealed normal values for acid-base status, serum electrolytes (including calcium and magnesium), blood lactate, pyruvate, acetocetate and \( \beta \)-hydroxybutyrate. There was no urinary excretion of ketones or sugars. The urinary excretion of amino acids was normal. The blood glucose decreased to 13 mg/100 ml despite intravenous infusion of glucose up to 25 g/kg/day. The highest plasma insulin concentration was 31 \( \mu \)U/ml at a time when the blood glucose level was 34 mg/100 ml. Therapy with diazoxide (8 mg/kg/day) was