NEONATAL HYPOGLYCEMIA DUE TO NESIDIOBLASTOSIS — A CASE REPORT

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SYNOPSIS

A 2 week old baby was admitted with a history of persistent hypoglycemia and generalised convulsions since birth. The diagnosis of nesidioblastosis was established by demonstrating inappropriate elevation of serum insulin levels. Following initial medical therapy, subtotal pancreatectomy was carried out. The histology confirmed nesidioblastosis. Hypoglycemic episodes recurred at the 6th post-operative week. Total pancreatectomy was advised, but refused by the parents. The diagnostic and management difficulties of this case are discussed in the local context.

INTRODUCTION

The term nesidioblastosis was used by Laidlaw (1) in 1938 to describe the diffuse proliferation of pancreatic islet cells which is a known cause of hyperinsulinism and hypoglycemia in childhood. We describe below the first case seen at the University Hospital, Kuala Lumpur (UHKL).

CASE REPORT

P.N., a female infant weighing 4.65 kg was born in the Ipoh General Hospital to non-consanguinous parents, at 37 weeks of gestation. The mother had a normal vaginal delivery. Shortly after birth, the baby developed mild respiratory distress and hypoglycaemia with plasma glucose concentration of 0.6 mmol/l (lower limit of normal is 2.2 mmol/l). She was given two-hourly feeds and a 15% Dextrose infusion. This failed to correct the hypoglycaemia which was associated with apnoeic attacks, sweating and generalised fits. She was further treated with intravenous hydrocortisone and oral diazoxide prior to referral to the UHKL. She was seen here at the age of 2 weeks for further investigation.

In UHKL her hypoglycaemia persisted despite treatment with continuous intravenous glucose infusion, two-hourly feeds with added sugar, intravenous hydrocortisone (8 mg/kg) and oral diazoxide (21 mg/Kg/day). There was no clinical history of maternal diabetes mellitus. On examination, she was lethargic, cyanosed and had intermittent focal fits of the upper limbs. Her weight was 4.68 Kg which was above the 90th percentile on the Boston growth charts. She had no dysmorphic features, but the skull circumference was 33.5 cms, which was below the 3rd percentile. The liver was enlarged, being palpable 4 cms below the costal margin. Cardiovascular and respiratory systems were normal. She was hypotonic but had brisk reflexes.

Ultrasonographic examination of the abdomen showed an enlarged liver with normal echotexture. The kidneys and pancreas were normal. Computerised tomographic (CT) scan of the abdomen failed to reveal any lesions in the pancreas. Chemical pathological investigation showed plasma glucose = 1.3 mmol/l, blood urea = 1.1 mmol/l (reference range 1.4 – 5.4 mmol/l), sodium = 130 mmol/l (reference range = 132 – 142 mmol/1), potassium = 4.5 mmol/l (reference range = 4 – 6.2 mmol/l) and total serum calcium 2.1 mmol/l (reference range = 2.0 – 2.5). There was absence of ketone bodies, reducing substances and aminoacids in the urine, and the blood lactate level was 2 mmol/l (reference range = 0.5 – 2.0). While on diazoxide, her fasting plasma insulin level was inappropriately high at 51 mU/l (measured using double antibody solid phase system of Pharmacia insulin RIA kit calibrated against WHO human insulin research standard A 66/304, Pharmacia Diagnostic, Uppsala, Sweden) in the presence of hypoglycaemia of 1.9 mmol/l. The "amended insulin glucose ratio" (AIGR) was $>$ 200 (normal is $<$ 30) (2). After intravenous glucose (1 g/kg) the plasma glucose increased to 9.7 mmol/l at 60 min with plasma insulin level of 22 mU/l (AIGR = 15). Peak plasma glucose level was observed at 120 min. The plasma insulin level increased to 240 mU/l (plasma glucose = 0.9 mmol/l; AGIR $>$ 200) after withdrawal of diazoxide (Fig. 1) for 2 days. Glucagon stimulation test (1 mg) showed a normal increment of plasma glucose of 1.7 mmol/l. With the above findings a diagnosis of nesidioblastosis was made and a 95% subtotal pancreatectomy was performed on the baby at the age of 38 days. The pancreas measured 6.5 × 1.2 cms. Histology showed diffuse proliferation of the islet cells with micronodule formation. The cells were of moderate size with central nuclei and abundant cytoplasm (Fig. 2). The features were similar to those described by others (3,4). Liver biopsy showed inappropriate presence of glycogen.

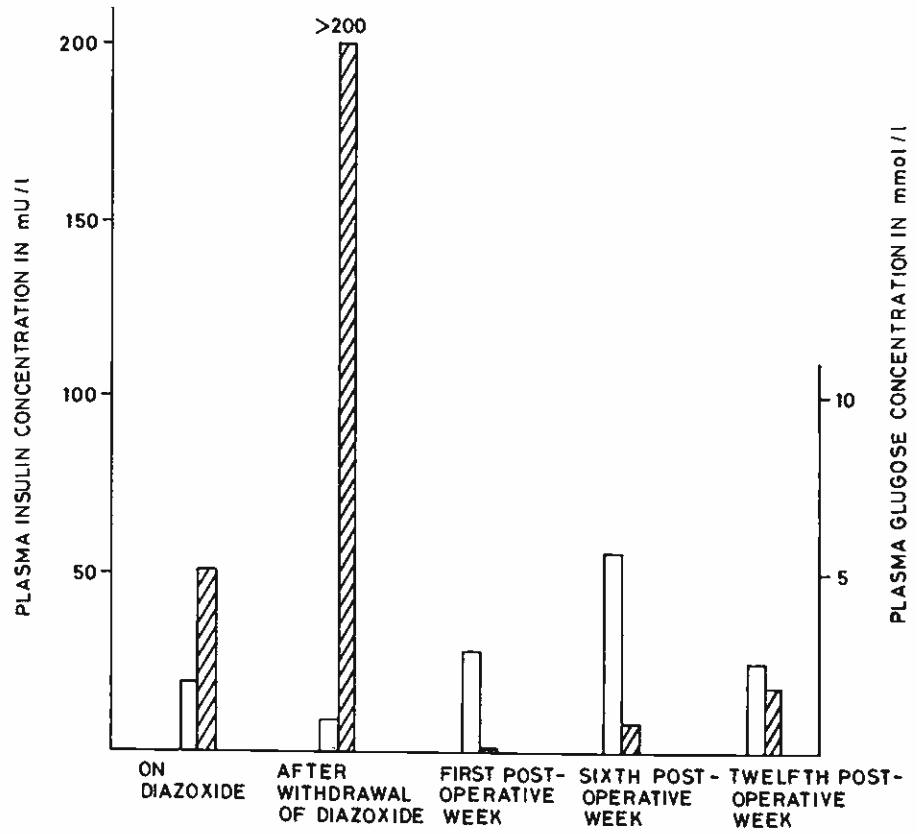

FIGURE 1. The change of plasma glucose ▭ and serum insulin ▨ levels over the period studied.

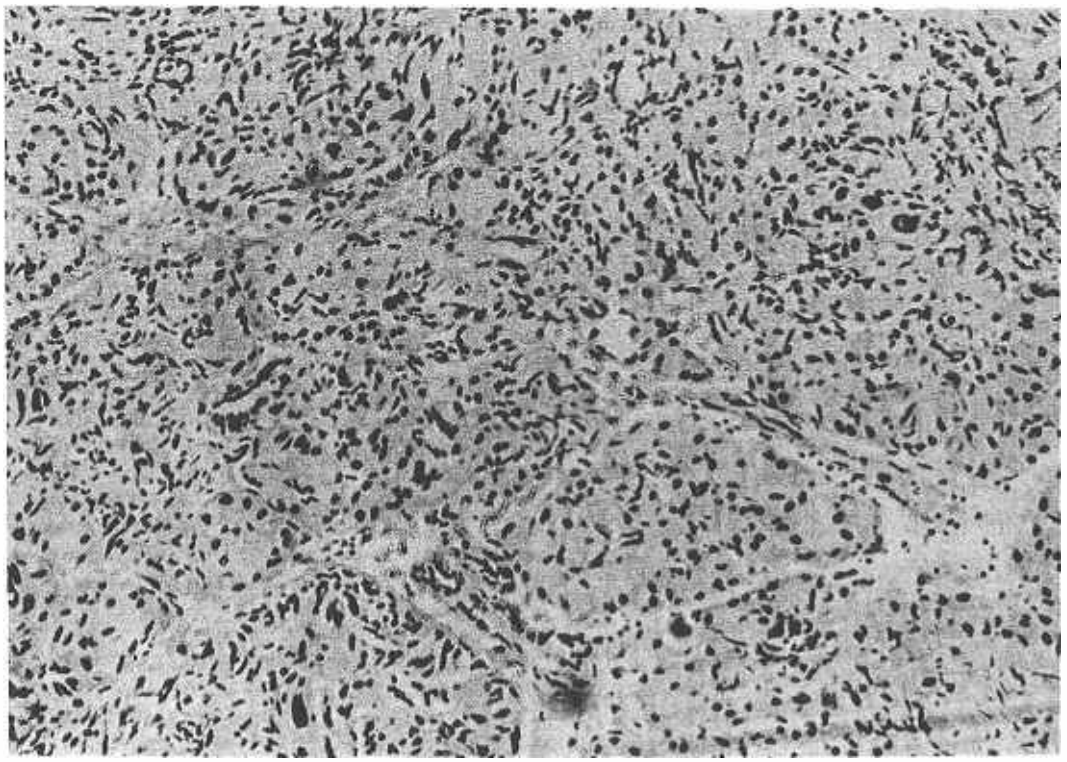

FIGURE 2. Diffuse proliferation of islet cells. Hematoxylin and eosin stain X200.

On the first post-operative days she developed hyperglycaemia (with peak plasma glucose of 24.9 mmol/l) and was treated with small doses (1 – 2 units) of soluble insulin. Her plasma glucose was subsequently stabilised at 2.8 mmol/l. The plasma insulin was undetectable one week after the operation. However, hypoglycaemia episodes recurred in the 6th post-operative week. The plasma insulin level was 17.4 mU/l (plasma glucose level = 2.5 mmol/l; AIGR = 116) in the twelfth post-operative week. She was further treated with diazoxide 50 mg b.d. and somatostatin (1 mg/Kg/dose 8 hourly for 10 days) which failed to control her hypoglycaemia. A total pancreatectomy was advised but was unacceptable to the parents. The child defaulted subsequent follow-up. Throughout the period of hospitalisation, the development of the child was delayed. Her mental age at 7 months was equivalent to that of a 3 month child on the Denver Development Scale.

DISCUSSION

Persistent hypoglycaemia is an uncommon finding in neonate and inappropriate insulin secretion accounts for 20 – 33% of such cases (5,6). The underlying hyperinsulinism is usually due to nesidioblastosis which consists of diffuse proliferation of islet cells originating from the duct epithelium (1). This first reported case of nesidioblastosis from Malaysia shows the typical clinical, chemical pathological and histological features classically described (1,2,4,5,6). The clinical diagnosis depends considerably on accurate glucose and insulin measurements. The expression of insulin and glucose results in AIGR provides a sensitive index of insulin secretion relative to glucose level. The AIGR decreased after glucose loading while the patient was on diazoxide therapy. This probably was due to active inhibition of insulin response to glycaemic stimulation (7,8). The subsequent post-operative increase of AIGR possibly indicates recurrence of inappropriate insulin secretion from the pancreatic remnant. This has been documented in 50% of infants after initial subtotal pancreatectomy (9). The normal glucagon stimulation test, suggests inappropriate storage of liver glycogen (10) and this was supported by the histological finding. This could account for the hepatomegaly observed clinically.

As insulin measurement is an important component of diagnostic investigations in nesidioblastosis, a simplified rapid and economic method of transport of serum specimen (11) to the regional laboratory for insulin assay could make the service readily accessible to most patients in developing countries. The use of non-isotopic immunoassay methodology (12) further help to devolute the services to peripheral laboratories, thus enabling early diagnosis of the condition so that effective therapy can be instituted at the earliest possible date. A rapid, accurate, and precise method for glucose analysis is an absolute necessity for therapeutic monitoring of this condition.

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