Insulinoma in Childhood

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Abstract

A 9-year-old boy with convulsions is herein described. He was diagnosed and treated for epilepsy and insufficient adrenal function for four years with no response. Hypoglycemia from hyperinsulinism was found and the source of the hyperinsulinism was a tumor of the tail of the pancreas - located by computerized tomographic scan and magnetic resonance imaging. Distal pancreatectomy was performed with good results. Histology of the tumor showed islet cell tumors with capsular invasion. For this type of patient, long-term follow-up should include: prevention of metastasis or recurrence, and testing for multiple endocrine neoplasia type 1.

Key word : Insulinoma, Islet Cell Adenoma, Hypoglycemia, Pancreatic Tumor, Hyperinsulinism

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J Med Assoc Thai 2001; 84: 136-142**

Pancreatic islet cell tumors, insulinoma, occurs rarely in children. The estimated incidence of all age-groups was one case per 250,000 patient-years[1]. It may occur sporadically, or associated (4-10% of cases) with multiple endocrine neoplasia 1 (MEN 1)[1-5]. Diagnosis is generally made by finding coincident hypoglycemia during fasting with inappropriately elevated serum insulin, C peptide or proinsulin concentrations. Multicentric pancreatic tumors are frequently found in MEN 1 [2,3]. Most (99%) of the tumors occur in the substance of the pancreas. Ectopic insulinomas have

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been found in areas of pancreatic heterotopia, including the wall of the duodenum, the porta hepatis, and the vicinity of the pancreas. Only 5 to 10 per cent of insulinomas are malignant and metastasize to surrounding tissues[1,3,4]. This paper reports the case of a nine-year-old boy with convulsions from hypoglycemia induced by solitary insulinoma of the pancreas.

CASE REPORT

For four years, a now nine-year-old boy (HN.ED 9254) from Roi Et province, came to the hospital with convulsions. He was diagnosed with epilepsy by the provincial hospital and was treated with oral phenobarbital. However, he still experienced frequent convulsions, especially in the morning. Two years previously, a private hospital found the boy to have hypoglycemia which responded well to intravenous glucose and hydrocortisone. Adrenal insufficiency was suspected, and prednisolone was prescribed (three tablets per day for two years). The boy was lethargic in the morning and was admitted to the private hospital many times with hypoglycemia. Finally, the boy was referred to our hospital with uncontrollable convulsions. (The family had no history of convulsions or hypoglycemia.)

The boy was short – in the third percentile. He was obese with Cushing's appearance (Fig. 1). No organomegaly was identified. There was normal prepubertal male genitalia, and neurological examination was normal. Laboratory investigations revealed a fasting blood glucose of 35 mg/dl, but negative urine ketone. Serum electrolytes (sodium, potassium, chloride, bicarbonate, calcium, magnesium, and phosphate) and albumin were normal. Serum insulin was 39.4 μIU/ml (normal 2.0-19.9 μIU/ml) and insulin to glucose ratio was 1:1. Hyperinsulinism was diagnosed and abdominal ultrasonography was performed with normal result. So an abdominal CT scan and MRI were carried out and a homogeneous mass with a diameter of 1.5-2.0 cm was found at the upper border of the tail of the pancreas (Fig. 2, 3).

Because of the short stature, radiography for bone age was performed; it showed four years old. Serum T4, TSH were normal, but the boy had low morning serum cortisol (0.7 μg/dl). The peak growth hormone levels induced by two growth hormone stimulation tests were 1.6 and 2.6 ng/ml respectively (normal >7 ng/ml). A glucagon stimulation test showed rising serum glucose of more than 30 mg/dl and a peak insulin level of 78.5 μIU/ml.

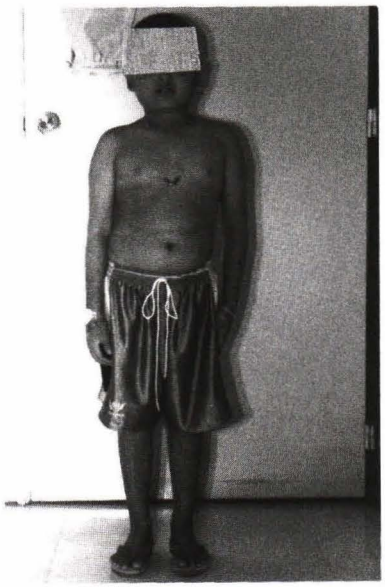

Fig 1. A-9-year old boy with Cushing's appearance.

A firm mass, 1.5 cm in diameter was found during exploratory surgery at the superior aspect of the tail of the pancreas and distal pancreatectomy was considered (Fig. 4, 5). Histopathology of the mass was compatible with islet cell tumor (insulinoma), gyriform pattern with capsular invasion (Fig. 6, 7). Post-operation the patient re-covered well and no convulsions occurred. Plasma insulin levels fell to 9.4 μIU/ml and fasting blood glucose levels rose to 100-120 mg/dl. Prednisolone therapy was tapered off within 3 months with no return of convulsions or lethargy. Six months after the operation the boy was still symptom free, and had grown 3.0 cm in height. Follow-up morning plasma cortisol, calcium, phosphate, growth hormone stimulation tests, and prolactin were all normal. A CT scan of the brain was also normal.

DISCUSSION

Hyperinsulinism from insulinoma is rare in both children and adults. A study from the Mayo Clinic done over 60 years (from 1927-

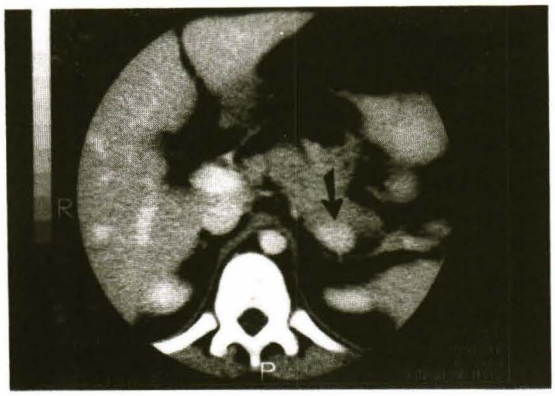

Fig 2. Insulinoma. Axial CT scan with 5 mm thick sections through the pancreas after intravenous contrast enhancement, reveals intense enhancing mass (arrow) at posterior aspect of tail of pancreas.

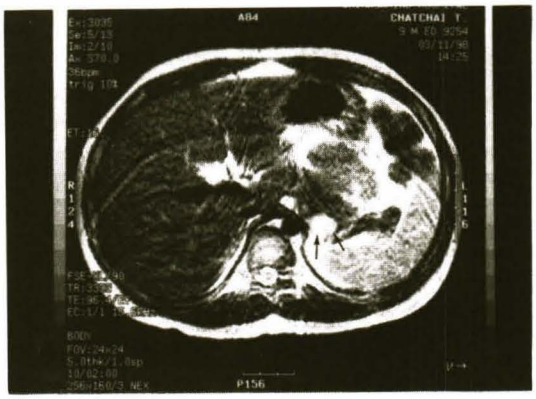

Fig 3. Insulinoma. MRI axial T2 weighted FSE (TR = 3333 msec, TE = 96.4 msec) Reveals a marked hyperintense mass at posterior aspect of pancreas. (small arrows)

Fig 4. A firm mass of 1.5 cm diameter at the superior aspect of the tail of the pancreas.

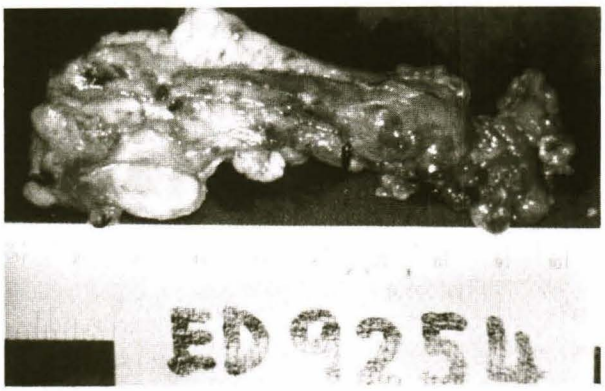

Fig 5. Cut surface of the well circumscribed mass.

1987) showed 13 of 224 patients were under 20 years of age[1]. In our patient, the presenting symptom was chronic convulsions hence the misdiagnosis of epilepsy and then hypoglycemia from insufficient adrenal activity. Though many causes of hypoglycemia in infancy and childhood have been classified, hyperinsulinism should be considered in all age groups. Endogenous hyperinsulinism was suspected because the plasma glucose was below 45 mg/dl and the plasma insulin concentration was greater than 6 mIU/ml[6]. Nesidioblastosis (or functional beta cell disorder) is much more common in infancy while insulinoma is the most common cause of endogenous hyperinsulinism in childhood[7]. Localization of the sites of the tumor is necessary prior to surgery. Several localization techniques have been suggested in the literature such as: abdominal

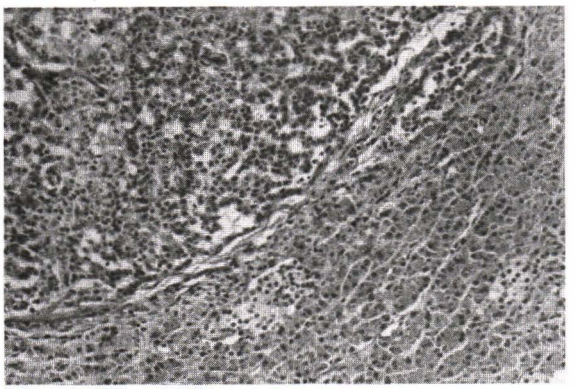

Fig 6. **Photomicrography of the tumor and adjacent normal pancreas. The tumor is composed of small, relatively uniform cuboidal cells with centrally located nuclei. Ribbon and festoons of tumor cells were presented throughout the tumor, separated by delicate vascular stroma. (H&E 200X)**

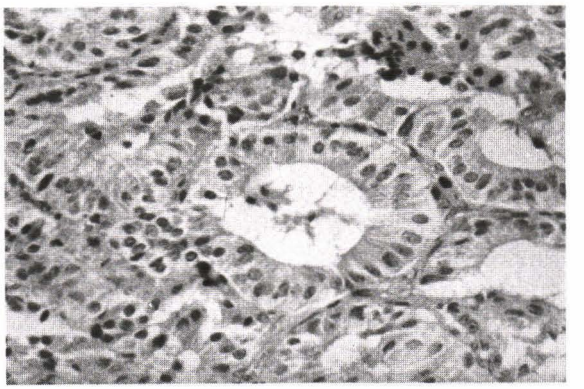

Fig 7. **Photomicrography of the tumor (H&E 400X) showing cuboidal tumor cells with centrally located nuclei.**

ultrasonography, intraoperative ultrasonography, endoscopic ultrasonography, computed tomography, magnetic resonance imaging, selective arteriography, percutaneous transhepatic portal venous sampling, and pancreatic venous sampling (4,5,8-18). The procedure of choice depends on expertise available at each institution. Because of the small size of multicentric tumors, preoperative localization studies were not positive in all patients. Careful palpation with intraoperative ultrasonography gave the best results(3,5,10,17). In our patient, abdominal ultrasonography was negative and required further investigations before the insulinoma was found on a CT scan and MRI.

Because pancreatic islet cell tumors are one of the manifestations of multiple endocrine neoplasia type 1 (MEN 1), screening for two other diseases: 1) pituitary adenoma and 2) hyperparathyroidism, should be done. The tests include the ionized serum calcium, serum prolactin, serum gastrin, imaging of pituitary and genetic testing (19). MEN 1 has an autosomal dominant pattern of inheritance and is caused by an inherited mutation of the tumor suppressor gene, menin, on the long arm of chromosome 11. Somatic loss of the normal allele results in clonal transformation (20-23). In our patient, we also performed the tests for MEN 1, but could not find the association. Screening for MEN 1 should be done every 3 to 5 years in patients aged more than 15 years (19). Prolonged use of prednisolone caused low serum cortisol and low peak growth hormone levels in our patient. The patient, however, grew normally after six months post operation.

Surgery is the treatment of choice for insulinoma. Most (94%) patients had benign solitary insulinoma. The preferred operation was enucleation, especially for tumors of the head of the pancreas(24,25). Malignancy was observed in 6 per cent of insulinoma and wide resection was recommended(26). For multiple insulinomas in MEN 1, left (distal) pancreatectomy or subtotal pancreatectomy (80% or more of the pancreas) was recommended: the same was recommended for individuals with inadequate diagnostic information to localize multiple tumors(27).

Kusin et al(8) reported postoperative 7.7 per cent mortality associated with insulinomas, and 43.6 per cent postoperative complications (due to pancreatitis, peritonitis, pancreatic fistulae, abscess and intestinal obstruction). The risk of recurrence was greater among patients with MEN 1 (21% at 10 and 20 years) than in those without MEN 1

(5% at 10 years and 7% at 20 years)[1]. Long-term survival (10 years after treatment) for patients with malignant insulinoma was 29 per cent compared to 91 per cent survival observed for patients with benign insulinoma[1].

Medical therapy is indicated in patients with malignant insulinoma who cannot undergo surgery. Diazoxide and somatostatin analogue are effective treatments for hypoglycemia in some patients[28,29]. Streptozotocin, fluorouracil has been tried in these patients[30]. When the malignancy has metastasized to the liver, chemo-embolization is widely used, and should be combined with somatostatin analogues[31]. Overall survival is from 2 to more than 60 months[20].

In our patient, the tumor was confined to the tail of the pancreas, so distal pancreatectomy was performed without complications. Histology of the tumor showed early metastasis from capsular invasion. Long-term follow-up to prevent recurrence or metastasis should be considered.

SUMMARY

Insulinoma is very rare in children, but it should be considered in all patients who have hypoglycemic convulsions with hyperinsulinism. Localization of the small and multicentric tumors pre- or intra-operatively is very important for a proper surgical strategy. Association of this condition with MEN 1 should be followed-up in all patients, especially those in the older age category. Surgery is the treatment of choice but medical therapy is also available for metastatic tumors.

ACKNOWLEDGEMENT

The authors wish to thank Mr. Bryan Roderick Hamman for checking our English and Mrs. Somsong Paetkij for preparing the manuscript.

(Received for publication on October 5, 1999)

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รายงานผู้ป่วยเด็กชายไทยอายุ 9 ปี มีปัญหาเรื่องชัก และตรวจพบระดับน้ำตาลในเลือดต่ำ ผู้ป่วยได้รับการวินิจฉัยว่าเป็นลมบ้าหมู และขาดฮอร์โมนจากต่อมหมวกไต เป็นระยะเวลา 4 ปี ได้รับการรักษาด้วยยากันชัก และเพรดนิโซโลน ผู้ป่วยยังมีชักตลอดเวลา การตรวจทางห้องปฏิบัติการพบว่าผู้ป่วยมีระดับอินสุลินสูงมากในขณะที่มีน้ำตาลในเลือดต่ำ และตรวจพบก้อนเนื้องอกที่ส่วนหางของตับอ่อน จึงได้ทำการผ่าตัดและพบว่าเป็นเนื้องอกของกลุ่มเซลล์ islet ซึ่งเริ่มมีการแพร่กระจายไปนอกก้อน ในผู้ป่วยรายนี้ควรได้รับการติดตามระยะยาวในเรื่องของการกลับเป็นซ้ำ การแพร่กระจายไปตามอวัยวะต่าง ๆ รวมทั้งการตรวจค้นหาโรค multiple endocrine neoplasia ชนิดที่ 1 ด้วย

คำสำคัญ : ก้อนเนื้องอกอินสุลินโนมา, ก้อนเนื้องอกของกลุ่มเซลล์ไอซ์เลท, ภาวะน้ำตาลในเลือดต่ำ, เนื้องอกของตับอ่อน, ภาวะอินสุลินสูงในเลือด

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