# Extrapancreatic tumour hypoglycaemia

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## DISCUSSION

Extrapancreatic tumour hypoglycaemia (EPTH) has been recognized for over 60 years (Unger, 1966). The hypoglycaemia it causes has frequently been attributed to poor appetite, malnutrition or glucose consumption by the tumour. The problem remains only partly understood (Khan, 1980).

## CASE REPORT

A 64-year-old woman presented with drowsiness and a history of worsening abdominal pain associated with abdominal bloating. Before admission her GP had arranged an ultrasound scan to investigate the abdominal symptoms and the finding of hepatomegaly. However, the development of drowsiness with slurred speech and dizziness prompted her admission. There was no other history of ill health. She was a non-smoker and took alcohol only occasionally.

On examination she was drowsy, restless and had recently vomited. Her Glasgow coma score was 9/15 and her speech was slurred. She was moving all four limbs, plantar reflexes were flexor, pupils equally reactive and fundi appeared normal. She was afebrile, her pulse was 80 beats/minute and regular. Her blood pressure was 170/100 mmHg, and auscultation of heart and lungs was normal. Abdominal examination revealed a football-sized irregular mass in the right upper quadrant.

### Investigations

The immediate capillary blood sugar by meter reading was 0.9 mmol/litre, and laboratory blood sugar was 1.4 mmol/litre. Full blood count, liver function tests, calcium, international normalized ratio, urea, creatinine and electrolytes all normal. Erythrocyte sedimentation rate was 25 mm/hr, electrocardiography showed right bundle–branch block, and the chest X-ray showed multiple nodular shadows. Abdominal ultrasound revealed an 8 cm echogenic mass in the left lobe of the liver and a smaller mass in the right lobe, consistent with metastatic deposits. Barium enema revealed diverticular disease only.

Ultrasound-guided liver biopsy yielded a specimen reported as 'clear cell carcinoma, possibly of adrenal or renal origin'. Computed tomography scanning revealed more widespread disease with numerous pulmonary deposits, a large destructive lesion in the posterior thorax threatening the spinal cord and multiple liver deposits, one extending inferiorly into the abdomen. There were multiple nodules in the left kidney, and no adrenal abnormality was seen.

Insulin level was reported as 25 pmol/litre when blood sugar was 1.5 mmol/litre, i.e. normal plasma insulin levels. C peptide was <75 pmol/litre. Insulin-like growth factors (IGFs) were analysed at: IGF-I = 0.10 u/ml, IGF-II = 1.14 u/ml, IGF-I:IGF-II ratio = 0.09 (normal greater than 0.20). Growth hormone level was 5.4 mu/litre, whereas in the presence of hypoglycaemia it would be expected to be greater than 10 mu/litre.

### Management

Initial treatment was 50% dextrose intravenously culminating in the full return of consciousness. She was able to give a clear history. However, she tended to hypoglycaemia constantly. This was partly controlled by frequent snacks and sugary drinks, but later required continuous dextrose infusion.

Diazoxide, high doses of prednisolone and octreotide injections subcutaneously all failed to alleviate the hypoglycaemia. The patient was given chemotherapy and radiotherapy to the paraspinal deposit. There was no indication of beneficial response and the patient died 5 weeks following admission.

The associated tumours can be of mesodermal, epithelial or haemopoietic origin. They are usually large, slow growing and can be benign or malignant. The presentation of EPTH is typical of insulin-induced hypoglycaemia. However, insulin levels are low in the presence of EPTH (Daughaday et al, 1988; Hyodo et al, 1977; Ron et al, 1989). A non-suppressible insulin-like activity (NSILA) is attributed to the insulin-like growth factors, IGF-I and IGF-II (Rinderknecht and Humbel, 1976). Measurements of the serum levels of IGF-I and IGF-II in patients with EPTH have often been confusing. Generally, patients have been found to have suppressed IGF-I levels and levels of IGF-II within the normal range (Zapf, 1994). Following successful removal of tumour, levels of IGF-I return to the normal range and those of IGF-II remain unchanged.

An explanation for these changes was given by Daughaday and colleagues in 1988. They reported a patient with leiomyosarcoma and EPTH who had an abnormal high molecular weight form of IGF-II constituting 70% of the total IGF-II. Following removal of the tumour, 'big' IGF-II levels dropped to nearly zero. It is now recognized that levels of normal-sized IGF-II are decreased, so accounting for the apparently normal levels of total IGF-II (Zapf, 1994). The tumour content of IGF-II-mRNA is frequently 100 times that of normal human liver or adipose tissue (Zapf et al, 1984).

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The bioavailability of the IGFs is controlled by their carrier proteins (IGF binding protein; IGF-BP). Human IGF binds to a 150 kD or a 50 kD binding protein, a small proportion remains unbound. The 150 kD IGF-BP transports 70–80% of the IGF and has a half-life of 12–16 hours. The 50 kD IGF-BP has a half-life of approximately 30 minutes and gives much greater bioavailability of IGF (Zapf et al, 1984; Guler et al, 1989).

Patients with EPTH tend to have lower levels of the 150 kD IGF-BP (production of which is growth hormone dependent, growth hormone levels suppressed). The majority of IGF ('big' IGF-II in EPTH) is carried in the 50 kD IGF-BP, or is unbound. It is now possible to study the behaviour of the IGF-BPs using Western ligand and immunoblotting methods. The enhanced bioavailability of big IGF-II leads to NSILA with subsequent increased glucose uptake by muscle, suppression of hepatic gluconeogenesis and adipose tissue lipolysis, all contributing to hypoglycaemia. This is aggravated by glucose consumption by the tumour and skeletal muscle in the presence of low levels of free fatty acids. There is also upregulation of insulin receptors in the presence of low insulin levels (Stuart et al, 1986), therefore worsening the IGF-II induced hypoglycaemia (*Figure 1*).

EPTH is difficult to manage unless the tumour can be successfully treated. Exogenous growth hormone may be helpful, but the additional gluconeogenic action of high dose steroids may be needed. This patient had a relentlessly rapid growth of malignant tumour and required large quantities of intravenous glucose to allow her to remain conscious. **HM**


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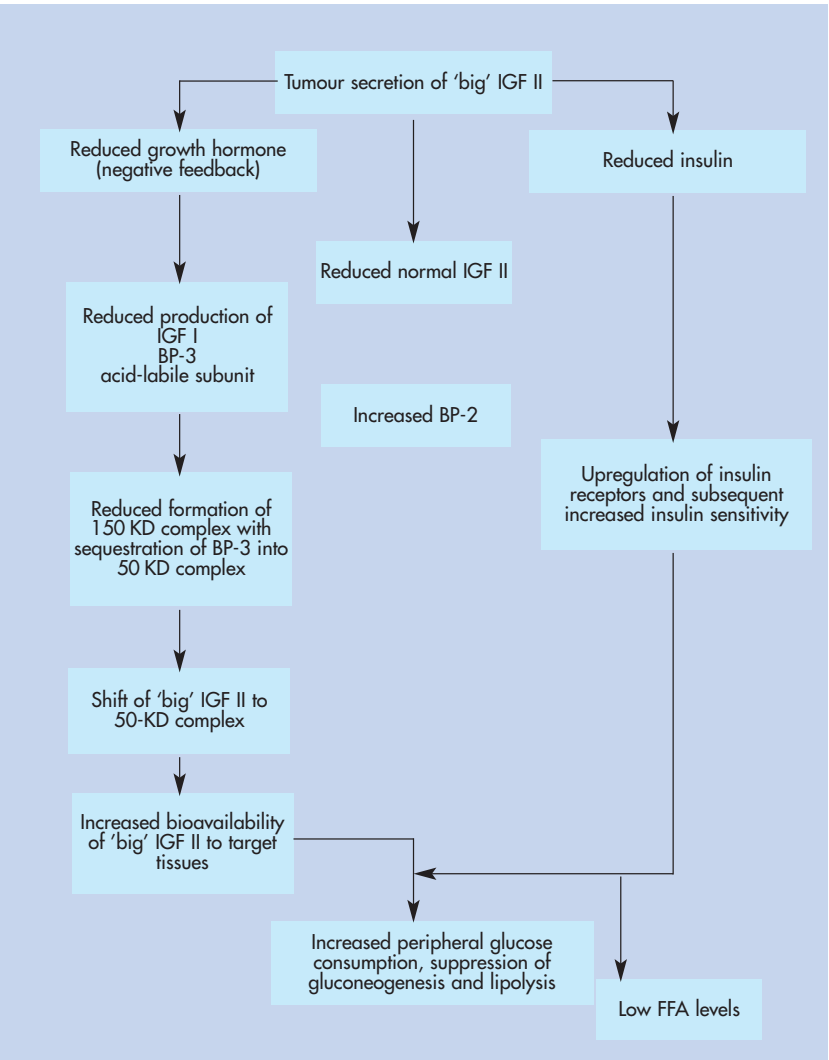


***Figure 1. Proposed mechanism for the development of extrapancreatic tumour hypoglycaemia. The presence of 'big' insulin-like growth factor (IGF) II iniates a cascade of events which results in a hypoglycaemic state. There is suppression of insulin, normal IGF II and growth hormone levels (consequently IGF I levels), along with changes in the IGF binding proteins (BP). There is an increased amount of big IGF I available to insulin receptors, with subsequent glucose uptake in skeletal muscle by insulin and IGF I receptors. Modified from Zapf et al (1992). FFA = free fatty acid.***