

# Tumour-induced hypoglycaemia

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## Introduction

Non islet cell tumour induced hypoglycaemia (NICTH) is a rare para-neoplastic syndrome caused by a large variety of both endocrine and non-endocrine neoplasms. It tends to present late in the course of the disease and the hypoglycaemic attacks can be severe with devastating consequences.

We present the reports of two patients under the care of the palliative care team who presented with hypoglycaemia.

### Case report 1

A 46-year-old man was diagnosed with a malignant nerve sheath tumour of the small bowel in 1994 and underwent tumour resection and radiotherapy. Subsequent hepatic recurrence necessitated partial hepatectomy and further radiotherapy. Three years later, extensive intra-abdominal spread was discovered. A trial of chemotherapy was commenced but abandoned due to disease progression.

He presented to his local district general hospital in 2000 with seizures and episodic abnormal behaviour. Imaging of his brain was reported as normal. A therapeutic trial of anti-convulsants failed to control his seizures and it was subsequently discovered that they were precipitated by hypoglycaemia. Twice daily glucagon was initiated and the patient transferred to our unit. Severe early morning hypoglycaemia persisted with ward capillary glucose readings between 1.2 and 2.8, associated with altered behaviour, confusion and seizures. He was unaware of any prodromal symptoms.

Fasting blood tests revealed:

- 1) Glucose 1.1 mmol/l
- 2) Insulin <1.0 mu/l (3–35)
- 3) IGF I 46 ng/ml (101–303)
- 4) IGFII 705 ng/ml (633–973)
- 5) IGFBP3 1.93 mg/l (2.0–4.3)

Dexamethasone 4 mg daily was commenced and titrated upwards to a final dose of 6 mg daily to maintain

a fasting blood glucose of greater than 2.8. He remains well 4 months later on dexamethasone.

### Case report 2

A 72-year-old woman was diagnosed with T4 N2 transitional cell carcinoma of the bladder in 1996 and underwent cystectomy and formation of ileal conduit followed by radical radiotherapy. Investigation for back pain in 1998 revealed retroperitoneal spread and following six cycles of MVAC chemotherapy, she developed large bowel obstruction secondary to intra-abdominal metastases. A transverse loop colostomy was fashioned and she was referred to our unit for symptom control.

In July 2000, she was found unconscious at home and following admission to our unit had a Glasgow coma score (GCS) of 4 and a right hemiparesis. A ward capillary glucose test was 1.2 (laboratory samples not obtained) and she was given 50 ml of 50% dextrose intravenously and 1 mg glucagon intramuscularly. After 20 min, her GCS was 13 and within 2 h, all neurological signs had resolved. In the morning, her capillary blood glucose levels were consistently below 2.8 and hence she was commenced on dexamethasone 4 mg daily. Two months later, she has had no further neurological episodes.

## Discussion

NICTH is a well-recognized, although rare, complication of a large variety of tumours.

Classically described in mesenchymal tumours,<sup>1</sup> the list of tumours in which hypoglycaemia has now been documented is extensive<sup>2</sup> and includes carcinomas<sup>3</sup> and haematological malignancies,<sup>4</sup> although prevalence is unknown.

The hypoglycaemia has been falsely attributed to excess glucose uptake and utilization by the tumour, impaired hepatic gluconeogenesis and poor oral intake,<sup>4</sup> but we now understand that tumour production of pro IGF II is probably responsible.

In health, IGF II is produced by the liver and is able to bind to, and activate insulin receptors. However, due to extensive protein binding, it has low bioavailability and hence low insulin like activity.<sup>5</sup>

When tumours produce high levels of pro IGF II<sup>5</sup> (a larger, incompletely processed IGF II),<sup>1</sup> normal protein

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binding to insulin like growth factor binding protein 3 (IGFBP 3) and acid labile subunit (ALS) is prevented, resulting in increased free IGF II and pro IGF II and hence increased insulin like activity.<sup>6</sup> Pro IGF II also suppresses growth hormone secretion exacerbating the hypoglycaemia.<sup>2</sup> This typically presents with signs of neuroglycopenia without autonomic features.

The diagnosis of hypoglycaemia is confirmed by a laboratory blood glucose measurement less than 2.8 (ward capillary blood glucose readings are not accurate enough, although in practice, venous blood may be difficult to obtain during hypoglycaemia in a hospice setting), in conjunction with features of neuroglycopenia, which are reversed by restoration of normoglycaemia.<sup>2</sup> Insulinoma, exogenous sulphonylurea/insulin administration, can be excluded by concurrent low insulin levels. Total IGF II will often be normal,<sup>5</sup> but since IGF I is suppressed, the IGF I/IGF II ratio will be less than 0.2 (normal >0.2),<sup>7</sup> as demonstrated in case 1. Pro IGF II measurement is not routinely available.

Treatment options include therapies aimed at the tumour bulk, and agents to manipulate the imbalance in chemical messengers (glucocorticoids, growth hormone and somatostatin analogues).

Surgical excision of the tumour is the definitive treatment, but debulking surgery, radiotherapy<sup>8</sup> or chemotherapy<sup>9</sup> may be equally effective – decreasing tumour bulk decreases pro IGF II levels.

Use of glucocorticoids has been extensively investigated. Steroids directly suppress tumour production of pro IGF II<sup>7</sup> and hence restore the normal physiological balance between the insulin like growth factors and their binding proteins. Since tumour growth may depend, in part, on autocrine stimulation by tumour IGF II,<sup>10</sup> use of glucocorticoids may directly inhibit tumour growth.<sup>1</sup>

The required dose of steroid remains uncertain (ranging between 1 and 12 mg dexamethasone per day).<sup>7</sup>

Growth hormone (GH) has also been used to manage NICTH. It may act by stimulating the liver to produce insulin like growth factor binding proteins and hence reduce bioavailability of tumour IGF II.<sup>11</sup> As it does not directly suppress tumour production of pro IGF II, it is less effective than glucocorticoids.

Additionally, symptoms of acromegaly have been reported, due to the supra-physiological doses used (4–12 IU per day) and there is a theoretical risk that exogenous growth hormone may directly stimulate tumour growth.

Anecdotally, glucagon infusion and somatostatin analogues have been prescribed with some success, but there are little data to support their continued use.

NICTH is therefore a manageable para-neoplastic manifestation of advanced benign and malignant tumours. Definitive treatment with surgery, radiotherapy or chemotherapy should always be considered after restoring euglycaemia with glucose; otherwise, treatment with steroids would appear to be the treatment of choice, adjusting the dose to the individual patient.

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