CASE REPORT

A mitotic cause of Whipple's triad: non-islet cell tumour hypoglycaemia in incurable low-grade malignancy

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Accepted 14 April 2015

SUMMARY

A 74-year-old man with known metastatic haemangiopericytoma presented with neuroglycopenic symptoms of confusion and light-headedness secondary to recurrent episodes of fasting hypoglycaemia, which resolved with oral carbohydrate intake. Investigations for hypoglycaemia revealed it to be non-insulin mediated, and subsequently due to a rare paraneoplastic phenomenon termed as non-islet cell tumour hypoglycaemia caused by tumoural overproduction of high molecular weight insulin-like growth factor-II. Despite his underlying malignancy being incurable, directed multimodality treatment involving regular oral carbohydrate intake, glucocorticoid therapy and recombinant human growth hormone was effective in relieving symptoms of hypoglycaemia. We discuss the importance of a systematic diagnostic approach to hypoglycaemia fulfilling Whipple's triad, as specific therapies can be invaluable to improving quality of life.

BACKGROUND

While hypoglycaemia is a common complication of therapy in diabetes, occasionally 'spontaneous' hypoglycaemia can occur as a result of other diseases, and a systematic approach to hypoglycaemic disorders is required to determine the underlying cause. Non-islet cell tumour hypoglycaemia (NICTH) is a rare paraneoplastic syndrome characterised by tumoural production of high molecular weight or 'big' insulin-like growth factor-II (IGF-II), which causes hypoglycaemia through stimulation of cellular insulin receptors and increased glucose utilisation. We report a case of incurable metastatic haemangiopericytoma causing NICTH, and describe a multimodal approach to managing the patient's hypoglycaemia.

CASE PRESENTATION

A 74-year-old man with known incurable metastatic low grade haemangiopericytoma presented with recurrent episodes of fasting hypoglycaemia with neuroglycopenic symptoms of confusion and light headedness. Episodes were resolved with the intake of oral carbohydrate. He was first diagnosed with haemangiopericytoma 15 years prior, with the initial solitary meningeal lesion treated with cranial resection. He subsequently developed a series of meningeal recurrences requiring further surgical resection and cranial irradiation, and incurable low-grade lung and liver metastases that had been slow-growing over 7 years (figure 1). He had no history

of diabetes mellitus, and he did not have ready access to hypoglycaemic agents in his home. On physical examination, his vital signs were within normal limits, weight was 89 kg and body mass index 28 kg/m². There were no other significant examination findings. Initial blood tests revealed a normal electrolyte profile, and normal renal and thyroid function. Despite the significant tumour burden involving the liver, he had normal liver enzyme and function tests including a serum albumin and coagulation profile.

INVESTIGATIONS

There was clear documentation of Whipple's triad, as: symptoms, signs, or both, consistent with hypoglycaemia; a low plasma glucose concentration; and resolution of those symptoms or signs after the plasma glucose concentration was raised. The initial targeted investigation of the patient's fasting hypoglycaemia revealed a non-insulin mediated aetiology, as demonstrated by the suppressed serum insulin, pancreatic C-peptide and proinsulin when

Figure 1 CT scan with intravenous contrast (coronal view) showing multiple lung and liver metastatic deposits of haemangiopericytoma.

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To cite: Lee AS, Twigg SM. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-209021

Table 1 Investigations for hypoglycaemia

Investigation	Patient result (abnormal levels are bolded)	Reference range
Serum glucose	2.2 mmol/L	3.5–5.4 mmol/L
Serum insulin	<6 pmol/L	10–96 pmol/L
Serum c-peptide	<33 pmol/L	200–1200 pmol/L
Serum proinsulin	<3.1 pmol/L	<13.3 pmol/L
Serum cortisol (morning)	428 nmol/L	200–600 nmol/L
Sulfonylurea screen	Negative	

serum glucose was 2.2 mmol/L. Adrenal insufficiency was considered unlikely given the cortisol level of 428 nmol/L, and sulfonylurea drug level was undetectable (table 1).

Further investigation of the patient's non-insulin mediated hypoglycaemia showed a high molar ratio of serum IGF-II (80 nmol/L, RR 47–94 nmol/L) to IGF-I (3.6 nmol/L, RR 8.3–24.4 nmol/L) of 22:1, consistent with NICTH mediated by IGF-II (table 2) arising from his large tumour burden.

TREATMENT

The patient's hypoglycaemia was initially treated with intravenous dextrose infusion, and subsequently with ongoing regular oral carbohydrate intake and dexamethasone 1 mg orally twice daily. Over the next 3 months, he developed increasingly frequent hypoglycaemic episodes, especially overnight, occurring up to every 1–2 days, while on oral dexamethasone 1 mg twice daily. Home capillary glucose recordings were as low as 2.6 mmol/L. Neuroglycopenic symptoms occurred below a threshold of 3 mmol/L glucose, and were resolved with oral intake of fast-acting carbohydrate. His dexamethasone was increased to 2 mg twice daily to prevent recurrent hypoglycaemia, and he underwent palliative chemotherapy with doxorubicin. On attempts to wean the dexamethasone due to glucocorticoid side-effects, hypoglycaemia recurred, and he was started on concurrent recombinant human growth hormone therapy (rhGH), to help reduce bioavailable IGF-II. A favourable biochemical response to rhGH was seen with an increase in serum insulin-like growth factor (IGF-I) and IGF-BP3 secondary to increased liver synthesis in response to the GH therapy (table 3).

OUTCOME AND FOLLOW-UP

Subsequently, the combination of low dose dexamethasone 1 mg twice daily, rhGH 0.45 IU/day, and consumption of regular carbohydrate-containing meals was found to improve the patient's quality of life ongoing across many months after his course of palliative chemotherapy. He had resolution of his hypoglycaemia, and this enabled him to be managed in ambulatory care, living at home.

Table 2 Investigations for non-insulin mediated hypoglycaemia

Investigation	Patient result (abnormal levels are bolded)	Reference range
Plasma IGF-I	3.6 nmol/L	8.3–24.4 nmol/L
Plasma IGF-II	80 nmol/L	47–94 nmol/L
Plasma IGF-BP3	2.3 mg/L	2.8–5.7 mg/L
Plasma GH	0.2 mU/L	<2.6 mU/L

GH, growth hormone; IGF-I, insulin-like growth factor; IGF-II, insulin-like growth factor-II.

DISCUSSION

Evaluation of hypoglycaemia

Hypoglycaemia is an uncommon clinical event in people who are not on glucose-lowering treatment for diabetes mellitus. Documentation of Whipple's triad (symptoms, signs, or both, consistent with hypoglycaemia, a low plasma glucose concentration and resolution of those symptoms or signs after the plasma glucose concentration is raised) establishes that a hypoglycaemic disorder exists.¹ A systematic approach to patient history including medication usage, physical examination and review of laboratory data will guide further evaluation of the hypoglycaemia. Malignancies can cause hypoglycaemia via several different mechanisms: by producing excess insulin such as in the case of pancreatic insulinomas, through destruction of the liver and adrenal glands by massive tumour invasion, and, finally, by tumour production of substances that cause hypoglycaemia, such as insulin-receptor antibodies, cytokines, catecholamines, IGF-I and high molecular weight IGF-II.²

Non-islet cell tumour hypoglycaemia

NICTH is a rare but serious paraneoplastic phenomenon, where the underlying mechanism of hypoglycaemia is overproduction of IGF-II by the tumour, which includes mature IGF-II in addition to incompletely processed forms of IGF-II referred to as 'big' IGF-II.³ Hypoglycaemia occurs due to activation of insulin-related receptors by IGF-II, which results in glucose utilisation by skeletal muscle, suppression of free fatty acid release by adipocytes, and inhibition of glycogenolysis, gluconeogenesis and ketogenesis in the liver. Furthermore IGF-II causes suppression of the counter-regulatory hormones glucagon and growth hormone (GH).³

This case displayed the typical laboratory findings of NICTH, including low glucose with simultaneous low insulin, low C-peptide, low proinsulin and low GH. The normal molar ratio of IGF-II to IGF-I in plasma is 3:1. Although our patient had a total IGF-II within the normal range, the high ratio of IGF-II to IGF-I of 22:1 supports the diagnosis of NICTH, as ratios of >10:1 have been reported to be virtually diagnostic of IGF-II mediated hypoglycaemia.³ The tumoural overproduction of high molecular weight IGF-II suppresses GH biosynthesis. Low GH leads to reduced synthesis of the 140 kDa ternary complex containing IGF, IGF binding protein (IGFBP)-3 and acid-labile subunit (ALS), and as a consequence, most of the IGF-II in NICTH is found in binary complexes of 50–60 kDa with IGFBP-3.⁴ The ratio of binary:ternary complexes is typically reversed to 4:1 in NICTH.⁵ This results in an increased bioavailability of IGFs to target tissues to cause hypoglycaemia through an insulin-like effect via insulin receptors.^{4,6}

Treatment options for NICTH

Initial treatment of hypoglycaemia is achieved with oral or intravenous glucose administration. Complete surgical removal of the IGF-II producing tumour will cause resolution of the hypoglycaemia.⁷ Our patient had incurable malignancy given the large tumour burden and widely metastatic disease. Chemotherapy was given with palliative intent to control tumour burden. Combination therapy with glucocorticoid and rhGH has been found to be more effective than high-dose monotherapy with either drug in re-establishing the IGF system in non-resectable disease.^{6,8} High-dose glucocorticoid therapy stimulates gluconeogenesis, increases IGF-I and partially suppresses 'big' IGF-II tumour secretion, while rhGH acts to decrease the bioavailability of IGF-II by increasing production

Table 3 Biochemical response to recombinant human growth hormone therapy

Investigation	Patient result prior to rhGH (abnormal levels are bolded)	Patient result one month after rhGH (abnormal levels are bolded)	Reference range
Plasma IGF-I	3.6 nmol/L	7.0 nmol/L	8.3–24.4 nmol/L
Plasma IGF-II	80 nmol/L	Not available	47–94 nmol/L
Plasma IGF-BP3	2.3 mg/L	2.7 mg/L	2.8–5.7 mg/L

IGF-I, insulin-like growth factor; IGF-II, insulin-like growth factor-II; rhGH, recombinant human growth hormone therapy.

of IGF-I, IGFBP-3 and ALS to restore the normal ternary-complexed IGF-II.⁶ Other therapies that have been trialled but have been found to be generally unsuccessful in NICTH include diazoxide and octreotide.⁵ Parenteral glucagon can treat acute hypoglycaemia due to NICTH, but generally has a short-lived effect.

CONCLUSIONS

NICTH is a rare paraneoplastic syndrome causing hypoinsulinaemic hypoglycaemia, and multiple treatment modalities may need to be employed to achieve satisfactory quality of life in patients with incurable malignancy. Nutritional approaches are generally insufficient, and antitumour therapies such as chemo-

therapy or localised therapies can be trialled. A multimodal approach combining glucocorticoid therapy and rhGH may be successful, while reducing the side-effects associated with high dose monotherapy.

Contributors AL wrote the detailed case report original manuscript draft and updated subsequent manuscript changes; SMT generated the case report concept, and helped in planning of the case report structure, he then corrected/edited the serial manuscript versions.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- Once Whipple's triad is confirmed, a systematic diagnostic approach to determine the cause of hypoglycaemia will allow subsequent disease-specific treatment to be implemented.
- Even after a long duration of indolent malignancy, new episodic hypoglycaemia due to non-islet cell tumour hypoglycaemia (NICTH) can occur, which may cause morbidity and mortality.
- The diagnosis of NICTH is supported by an increased molar insulin-like growth factor-II:insulin-like growth factor-I ratio.
- A multimodal approach combining nutritional therapy, antitumour chemotherapy, glucocorticoid therapy and recombinant human growth hormone therapy may be successful in treating hypoglycaemia in incurable disease.

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