Non-islet cell tumour induced hypoglycaemia as a cause of delirium

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Non-islet cell tumour induced hypoglycaemia (NICTH) is a rare but potentially reversible cause of recurrent low blood glucose.

Case report

An 84-year-old gentleman presented to the Emergency Department following a fall. He was hypoxic and was diagnosed with a community acquired pneumonia, confirmed on chest radiograph and had an Enterococcus faecalis urinary infection. A Mini Mental State Examination of 15/30 confirmed cognitive impairment. He had treatment resistant prostate cancer with rising prostate specific antigen and metastases of the spine and lung, despite being on third-line antiandrogen therapy. His presentation involved many potential causes of delirium. However, he displayed widely fluctuating behaviour throughout each day with episodes of aggression with which he became diaphoretic, followed by lucid periods. He also intermittently agreed and then refused investigations. Computer tomography (CT) of the brain showed extensive small vessel disease but no cause for this new confusion. As part of the investigations of confusion capillary blood glucose (CBG) monitoring was initiated and hypoglycaemia (1.9 mmol/L) was noted during an episode of aggression with which he became diaphoretic, followed by lucid periods. He also intermittently agreed and then refused investigations. Computer tomography (CT) of the brain showed extensive small vessel disease but no cause for this new confusion. As part of the investigations of confusion capillary blood glucose (CBG) monitoring was initiated and hypoglycaemia (1.9 mmol/L) was noted during an episode of aggression and confusion which improved with correction of hypoglycaemia. He fulfilled Whipples’ Triad,¹ low blood glucose concentration with symptoms of hypoglycaemia, resolving when the blood glucose is raised. A further episode of hypoglycaemia was recorded and confirmed on serum glucose (1.1 mmol/L) soon returned, associated with hypothermia (temp 33.1). High dose growth hormone (4 mg per day) was added to the treatment, which maintained normoglycaemia.

Discussion

Hypoglycaemia is a frequent presentation in hospital and simple investigations should initially look to exclude common causes of hypoglycaemia (Table 1) such as excessive doses of subcutaneous insulin in a patient with diabetes mellitus. The Endocrine Society’s Clinical Guidelines on hypoglycaemia suggest that evaluation and management of hypoglycaemia should only be
commenced in patients who fulfil Whipple’s Triad.1 This should prevent unnecessary investigations of hypoglycaemia which can usually be easily explained. However, if none of the more common causes are found then insulinoma and non-islet cell tumour induced hypoglycaemia (NICTH) should be considered.

NICTH is a rare paraneoplastic phenomenon which is typically seen in patients with solid mesenchymal and epithelial tumours. The tumours are usually large and slow growing. Although most patients with NICTH are known to have a tumour prior to the onset of hypoglycaemia, there have been case reports of patients presenting with low blood glucose and then being found to have a sarcoma or benign mesenchymal tumours.2 Tumours which cause hypoglycaemia via NICTH over-express IGF-II genes and secrete excessive amounts of partially processed precursors of IGF-II, named ‘big’ IGF-II. NICTH is four times less common than insulinoma.3 Prostate cancer represents around 2% of the total incidence.4 NICTH may be diagnosed by suppressed C-peptide, and insulin during a hypoglycaemic episode, with low IGF-I and IGFBP-3 levels. IGF-II can be normal or high, as usual laboratory testing cannot differentiate between the different molecular weights in the serum.4

In its normal form, IGF-II is 10 times less effective in reducing blood glucose than insulin and its true physiological role remains unclear.5,6 Unlike insulin, greater than 90% of IGF-II is usually found bound to IGF binding proteins and appears essentially inactive. However, ‘big’ IGF-II is a higher molecular weight form, found mainly unbound in the serum.6,7 As such, there is greater capillary permeability allowing binding to IGF-I receptors and insulin receptors on insulin-sensitive tissues.4 This causes suppression of hepatic glucose production by inhibition of glycogenolysis and gluconeogenesis. There is also lipolysis in adipose tissue and increasing uptake of glucose in peripheral tissues, particularly skeletal muscles. These mechanisms all lead to hypoglycaemia. ‘Big’ IGF-II also binds to IGF-I receptors in the hypothalamus suppressing the secretion of growth hormone. As IGF-I and IGFBP-3 are growth hormone dependent their levels are reduced in the serum.6 C-peptide and endogenous insulin secretion is suppressed.

In tumours that are amenable to surgery, resection can lead to complete resolution of big IGF-II

Table 1

| Causes of hypoglycaemia in adults (adapted from Evaluation and Management of Adult Hypoglycaemic Disorders: an Endocrine Society Clinical Practice Guideline) |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **Unwell or medicated patients** | **Seemingly well individuals**  |
| Drugs                           | Insulin                         | Exogenous hyperinsulinism       | Insulin                         |
|                                 | Insulin secretagogues†          |                                 | malicious, accidental or         |
|                                 | Alcohol                         |                                 | surreptitious use               |
| Critical illness                | Renal failure                   | Endogenous hyperinsulinism      | Insulinoma                      |
|                                 | Cardiac failure                 |                                 | Insulin secretagogues           |
|                                 | Liver failure                   |                                 | Malicious, accidental or         |
|                                 | Sepsis                          |                                 | surreptitious use               |
|                                 | Malaria                         |                                 |                                 |
| Hormonal                        | Cortisol deficiency             |                                 | Autoimmune hypoglycaemia        |
|                                 | Glucagon deficiency             |                                 | Antibody to insulin             |
| Tumour                          | NICTH                           |                                 | Antibody to insulin receptors   |
|                                 |                                 |                                 | Functional pancreatic beta cell |
|                                 |                                 |                                 | disorders†                      |
|                                 |                                 |                                 |                                 |

NICTH, Non-islet cell tumour induced hypoglycaemia

† Such as Gliclazide

‡ Nesidioblastosis
secretion. In patients who are deemed unfit for surgery either because of co-morbidity or by factors relating to the tumour, medical therapies can suppress hypoglycaemia. Steroids stimulate glycogenogenesis and in some cases suppress ‘big’ IGF-II so are first-line treatment. Second-line therapy is growth hormone which is suspected to act via the stimulation of hepatic gluconeogenesis and glycogenolysis, the same mechanism that leads to impaired glucose tolerance in patients with acromegaly.

This case has demonstrated the importance of monitoring blood glucose in patients with delirium as common causes of hypoglycaemia may be easily treatable such as modification to insulin dosage. If the cause of hypoglycaemia is unclear then the investigations described above should be considered along with endocrine review. We should be aware of possible diagnosis of NICTH in hypoglycaemic patients even in those without a previously diagnosed tumour.

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