An unusual adrenal cause of hypoglycaemia

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History

A 69-year-old gentleman lost consciousness with a glucose of 2.4mmol/L, having experienced recurrent daytime hypoglycaemic symptoms for at least five years, and latterly overnight. He suffered from hypertension, benign prostatic hypertrophy and hypogonadotrophic hypogonadism. There was no personal or family history of diabetes or endocrinopathy. He had never worked in healthcare.

Investigations

Hypoglycaemia (glucose 1.8 mmol/L) was confirmed during a supervised fast. Insulin and c-peptide were inappropriately detectable, consistent with endogenous hyperinsulinaemic hypoglycaemia (Figure 1A).

Cross-sectional imaging (Figure 1B) revealed a large left supra-renal mass invading the left renal vein and inferior vena cava and an enlarged coeliac trunk lymph node. These findings were unexpected and prompted further investigation.

Urine normetadrenaline was elevated. Chromogranin A and B were elevated; the remaining gut peptides were unremarkable. Adrenal androgens were normal and urine cortisol metabolites were consistent with physiological stress. Both the supra-renal mass and lymph node were 18FDG-avid. Additionally, there was diffuse abnormal FDG-uptake throughout the pancreas without an anatomical correlate. The supra-renal mass was MIBG-avid (Figure 1D).

These results are consistent with a tumour of neuroendocrine origin. Given the diffuse pancreatic FDG-avidity, we postulated that tumoural production of a secretagogue was stimulating pancreatic insulin release. Analysis of incretin hormones during hypoglycaemia revealed a markedly and inappropriately elevated GLP-1 (Figure 1C). Neurotensin (co-secreted with GLP-1 from the gut) was undetectable, suggesting that GLP-1 production was ectopic. Genetic testing for a phaeochromocytoma-predisposing mutation was negative.

Management and progress

Hypoglycaemia responded to somatostatin analogue therapy. Doxazosin was added for blood pressure control. Surgery was scheduled but rapid disease progression occurred and chemotherapy was initiated. Disease stability was initially achieved following four cycles of cisplatin/carboplatin and etoposide, however three months later abdominal pain returned and imaging confirmed disease progression. Temozolamide was commenced and a partial response was observed after six cycles. One year following diagnosis he remains independent with few symptoms.

Discussion

Hypoglycaemia is an uncommon but important cause of transient loss of consciousness in non-diabetic patients. Diagnosis requires assessment of blood glucose, insulin and c-peptide during
symptomatic hypoglycaemia in order to determine aetiology. Inappropriately detectable insulin and c-peptide, as here, suggests endogenous hyperinsulinaemic hypoglycaemia, most commonly due to a pancreatic insulinoma.

Imaging findings in this case were unexpected and demonstrated a malignant, locally invasive adrenal lesion with associated lymphadenopathy. Biochemistry and functional imaging were supportive of the diagnosis of phaeochromocytoma.

Phaeochromocytomas are rare but life-threatening neuroendocrine tumours (NETs) of the adrenal medulla. They frequently cause hyperglycaemia due to a combination of increased hepatic glucose production and inhibition of glucose uptake and insulin release. Hypoglycaemia occurring immediately following resection has been widely observed (Chen et al. 2014) but preoperative hypoglycaemia is rare and is often mediated by IGF-2 and not insulin (Gorden et al. 1981).

Two phaeochromocytomas with insulin-mediated hypoglycaemia that fulfil Whipple's triad have been reported. In one (Uysal et al. 2007), tumour immunohistochemistry was positive for insulin, suggesting direct insulin secretion. In the other (Frankton et al. 2009), it was negative and massive insulin release due to pancreatic haemorrhage was the postulated mechanism.

In our case, diffuse pancreatic FDG-uptake prompted assessment of the incretin hormones. GLP-1 was inappropriately elevated at the time of hypoglycaemia, to a magnitude similar to that seen during hypoglycaemia following gastric bypass surgery. An undetectable neurotensin confirmed ectopic GLP-1 secretion. GLP-1 mediated hypoglycaemia has previously been reported in association with ovarian (Todd et al. 2003) and pancreatic (Roberts et al. 2012) NETs. In both these cases, unlike ours, concurrent hyperglycaemia was also present due to secretion of somatostatin and glucagon respectively.

This is the first report to our knowledge of hypoglycaemia due to a GLP-1 secreting phaeochromocytoma.

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Learning Point for Clinicians’

The accurate diagnosis of spontaneous hypoglycaemia requires a combination of clinical awareness and careful biochemical evaluation to determine aetiology. Further investigation and considerations are necessary if imaging findings are inconsistent with the most frequent responsible pathology.

Figure Legend

A – Glucose (black) and insulin (green) concentrations during a fast. The red line represents hypoglycaemia (plasma glucose 2.2 mmol/L).

B – T2-weighted axial abdominal MRI showing the large left adrenal mass (yellow arrow) and the enlarged coeliac trunk lymph node (red arrow).

C – Glucose (black) and GLP-1 (blue) concentrations during a fast. The red line represents hypoglycaemia as in figure A.

D – I-123 MIBG scintigraphy demonstrating avidity in the left adrenal mass.
References


