CASE REPORT

A common problem in the elderly with an uncommon cause: hypoglycaemia secondary to the Doege-Potter syndrome

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Accepted 12 January 2015

SUMMARY

Falls due to hypoglycaemia in the elderly is usually a complication of diabetic treatment. In the absence of diabetes, hypoglycaemia may be due to insulin or insulin-like producing tumours. The Doege-Potter syndrome is a rare paraneoplastic syndrome, characterised by non-islet cell tumour hypoglycaemia (NICTH) secondary to a solitary fibrous tumour that secretes insulin-like growth factor (IGF) 2. Definitive treatment of hypoglycaemia due to NICTH is by tumour resection. Our patient was a 78-year-old woman admitted after a fall with a facial injury and a history of significant weight loss. Her blood sugar was persistently low despite intravenous dextrose infusion. CT of the thorax revealed a large heterogeneous mass measuring 11.6×16.3×15.6 cm in the right hemithorax. A biopsy of the mass was reported as a solitary fibrous tumour. Biochemical investigations revealed low insulin, C-peptide, IGF-1 and a high IGF-2:IGF-1 ratio, consistent with NICTH. The patient underwent tumour resection and the hypoglycaemia normalised completely immediately after surgery.

BACKGROUND

Common causes of falls in the elderly are usually related to impaired balance, gait, mobility, sensory impairment, postural hypotension or polypharmacy and medication side effects.¹

Falls in the elderly are costly as they often result in loss of independent function, increased morbidity and mortality, with increased burden on the healthcare system. Thirty-five per cent to 40% of people aged 65 years and above fall annually, and the incidence increases to 50% among those aged 80 years or older, with a higher rate in women.

In patients with diabetes, hypoglycaemia is usually a complication of medication use, and is a common risk factor for falls. Falls from hypoglycaemia in a patient without diabetes is uncommon. We report a case of an elderly woman who suffered a fall from hypoglycaemia caused by non-islet cell tumour hypoglycaemia (NICTH).

CASE PRESENTATION

Our patient is a 78-year-old Chinese woman with no major premorbid illnesses or previous admissions. She does not have a history of diabetes, cardiac or respiratory diseases, and denied taking any medications/supplements. She fell at home, sustained facial contusions and was admitted for investigation. History taken revealed that 1 week before

admission, she experienced non-vertiginous giddiness, weakness and blurred vision after waking up from vivid dreams at night. These symptoms resolved after eating. She also had a significant unintentional weight loss of 4 kg associated with loss of appetite in the past month. She is a non-drinker and a non-smoker. Her initial capillary blood glucose was 1.9 mmol/L. Her family history revealed that her daughter has Graves' disease.

On examination, she was alert, comfortable, thin and did not have features of acromegaly. Her cardiac, abdominal and neurological examinations were normal. She had a moderate-sized soft goitre, distended chest wall and right arm veins, but a negative Pemberton's sign. There were no clubbed fingers or cyanosis. The most significant finding was dullness on lung percussion from the third intercostal space downwards with reduced breath sounds on the right lower half of the chest, without tracheal deviation. There was no lymphadenopathy.

INVESTIGATIONS

Figure 1 is the patient's chest X-ray, which showed a well-demarcated homogeneous space-occupying lesion at the right lower zone with a significantly raised right hemidiaphragm and likely eventration.

Fasting blood tests revealed a significantly low blood glucose, plasma insulin level and C-peptide, with a high IGF-2 (insulin-like growth factor): IGF-1 ratio. Table 1 shows the results and reference ranges of the laboratory tests performed.

The renal and liver functions and thyroid function tests were normal.

Figures 2 and 3 below are the coronal and axial views, respectively, of the CT of the thorax and abdomen, which revealed a large, heterogeneously enhancing mass seen in the right lower hemithorax, measuring 11.6×16.3×15.6 cm, without destruction of the adjacent ribs but with a mass effect on the adjacent lung, superior and inferior vena cava, suggestive of large pleural fibroma.

A CT-guided biopsy and histology of the mass showed a moderately cellular lesion composed of intersecting fascicles of bland spindle cells in a collagenous stroma. Mitotic figures were rare. The spindles were positive for CD34 and bcl-2 and negative for AE 1/3 and S-100. These features were consistent with a solitary fibrous tumour (SFT). Figure 4 (A–D) below shows histological pictures of the biopsy specimen with normal H&E and special stains taken from the pleural mass via a CT-guided biopsy.

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To cite: Tay CKJ, Teoh HL, Su S. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-207995

Figure 1 Anteroposterior sitting chest X-ray showing a well-demarcated homogeneous space-occupying lesion at the right lower zone with a raised right hemidiaphragm.

The Doege-Potter syndrome (DPS) was diagnosed on the basis of the above findings.

TREATMENT

Her hypoglycaemia was treated symptomatically with dextrose 10% drip given throughout the night, which persisted in spite of that. The patient was initially trialled on diazoxide 100 mg twice daily, which was stopped as the hypoglycaemia was non-insulin related. Eventually, her hypoglycaemia was relieved by having small frequent meals, scheduled snacks before sleep and prophylactic sugary drinks at 2:00 and 6:00. Preoperatively, a short course of prednisolone was given to increase her blood sugar level. For definitive treatment, she underwent an uneventful right posterolateral thoracotomy and resection of the pleural tumour. Figure 5 shows the resected pleural mass.

OUTCOME AND FOLLOW-UP

Patient review 1 week postsurgery showed normalisation of the blood glucose level around 5–10 mmol/L and she was discharged in a stable condition 7 days postoperation.

Table 1 Summary of the laboratory tests results

Test	Values	Reference range
Venous blood glucose	2.7 mmol/L	3.0–6.0
Potassium	2.6 mmol/L	3.5–5.1
Plasma insulin level	<1 mU/L	2.6–24.9
C-peptide	23 pmol/L	364–1655
β-hydroxybutyrate	<0.1 mmol/L	<0.6
Growth hormone	0.08 µg/L	<8.00
IGF-1	28 µg/L	59–177
IGF-2	681 ng/mL	288–736
IGF-2:IGF-1 ratio	24:1	~3:1

IGF, insulin-like growth factor.

DISCUSSION

Hypoglycaemia-induced falls are common in the elderly as a complication of diabetes or its treatment. In the absence of diabetes, other causes like severe liver and kidney disease, polypharmacy, prolonged starvation, alcoholism, sepsis and other endocrine problems need to be considered. Very rarely, hypoglycaemia can be a manifestation of malignancy. First, tumours can produce excess insulin, for example, insulinoma. Second, tumours can destroy the liver or adrenal glands from massive infiltration. Third, tumours produce substances that interfere with the glucose metabolism as part of the paraneoplastic syndrome.²

DPS/NICTH

DPS is an uncommon complication of uncommon tumours. It is a paraneoplastic syndrome, first described in 1930 by Doege and Potter; it is characterised by NICTH secondary to a SFT that secretes a pro-hormone form of IGF.^{3–5} It manifests as fasting hypoglycaemia that can be recurrent, refractory or even life-threatening. These tumours mediate their action mostly through the IGF system, via secretion of either mature IGF-2 or partially processed precursors of IGF-2, also known as ‘big-IGF-2’.²

SFT are rare spindle cell neoplasms, first described clinically in 1870 by Wagner with a 12–13% chance of malignancy.⁶ Hypoglycaemia is seen in less than 5% of cases. SFT often derives from the pleura but may occur outside of it.^{7 8} Pleural SFTs (SFTP) distribute equally in sexes as well as peak in the sixth to seventh decades of life.⁷

Figure 2 CT of the thorax (coronal view) showing a large heterogeneously enhancing mass seen in the right hemithorax, measuring 11.6×16.3×15.6 cm.

Figure 3 CT of the thorax (axial view) showing a large heterogeneously enhancing mass seen in the right hemithorax, measuring 11.6×16.3×15.6 cm.

Other associations

Up to 10% of NICTH was reported to be associated with thyroid enlargement, with or without thyrotoxicosis, as seen in our patient.⁹

NICTH was noted to be associated with hypokalaemia by Fukuda *et al*,¹⁰ also noted in our patient, who postulated it to be secondary to IGF-2's insulin-like activity.

There were also several reports describing the presence of acromegaloid features in patients with NICTH. Skin tags, seborrhoeic keratosis, excessive skin oiliness and rhinophyma were some of those features,^{11 12} but were absent in our patient. These changes were thought to stem from the IGF-2-mediated stimulation of multiple subclasses of insulin-related and IGF-1-related receptors.

In our patient, she also presented with signs of Superior Vena Cava Obstruction (SVCO), such as distended chest wall and arm veins, with symptoms of light-headedness, visual changes, which

Figure 5 Large solitary tumour excised from the right hemithorax. Courtesy of Associate Professor Lim Chong Hee, Senior Consultant, Cardiothoracic Surgery, National Heart Centre, Singapore.

occurred after lying down. Such symptoms overlap with hypoglycaemic symptoms; it is difficult to establish the exact mechanism or its main aetiology. However, there was radiographic evidence of partial SVCO in the CT of the thorax. Case reports of pleural tumours causing SVCO are few,^{13 14} possibly due to the location/earlier manifestations of the tumour. Nevertheless, we postulate that SVCO is a possibility in DPS as the slow growing nature of SFTP with minimal symptoms can result in a large enough tumour impinging on the superior vena cava.

Pathophysiology

Gene expression

NICTH-causing tumours have been found to abundantly express IGF-2 mRNA, which is mainly attributed to either mutations or loss of imprinting in tumour suppression genes.¹⁵

Figure 4 (A) Low-power view of the pleural tumour biopsy displaying spindle cells arranged in a patternless pattern (H&E 100×). (B) High magnification highlighting the bland nature of the spindle tumour cells (H&E ×400). (C) CD34 immunohistochemical stain (×400). (D) BCL2 immunohistochemical stain (×400). All histological slides courtesy of Dr Thomas Choudary Putti, Associate Professor and Senior Consultant at the Department of Pathology, National University of Singapore and National University Hospital.

This over-expression results in overproduction of pro-IGF-2.¹⁶ However, the enzymes in the neoplastic cells involved in the post-translational processing are unable to manage the comparatively higher amounts of pro-IGF-2.¹⁷ This results in formation of more IGF-2 with a 21 amino acid extension of the E domain, which is also known as 'big-IGF-2'.¹⁸

Metabolic effects

Hypoglycaemia

Hypoglycaemia is mediated in DPS via several mechanisms. First, the tumour can consume glucose. However, it does not usually result in hypoglycaemia unless there is upregulation of glucose transporters and hexokinases in the tumour itself.^{19 20}

Second, the tumour secretes large amounts of 'big-IGF-2' as aforementioned. Although the hypoglycaemic effect of IGFs is roughly 10 times less than insulin,²¹ the several-fold increase in mature IGF-2 and 'big-IGF-2' can approximate the effects of insulin.²¹ In addition, 'big-IGF-2' appears to possess characteristics that prohibit the proper formation of the normal ternary 150 kDa complex with IGF binding protein (IGFBP)-3 and acid-labile subunit (ALS), a leucine-rich glycoprotein.²² As such, these 'big-IGF-2' form mostly smaller 40–50 kDa binary complexes with IGFBPs, resulting in a greater fraction staying in the free unbound form.¹⁷ These smaller complexes increase peripheral tissue IGF bioavailability due to their increased capillary permeability, and hence cause hypoglycaemia via action on insulin receptors (IR) and IGF-1 receptors (IGF1R).²³

Furthermore, the increased production of 'big-IGF-2' may also displace free mature IGFs from IGFBPs, leading to the increased serum concentration of free, unbound IGFs.²⁴ Highly elevated levels of free IGF-1 and IGF-2 mean that there will be a heightened insulin-like glucose-lowering effect. This effect may result in the marked suppression of growth hormone (GH) secretion from the anterior pituitary via the negative feedback mechanism as in most NICTH. Reduced GH levels result in decreased liver production of GH-dependent proteins, such as IGF-1, IGFBP-3 and ALS.²⁵ This also contributes to the formation of the binary complex form, causing hypoglycaemia as explained above.

Circulating glucagon is also suppressed due to the dual action of IGF-2 on IGF1R and IR of pancreatic cells. Low levels of glucagon compounded by low levels of GH could possibly further augment the glucose-lowering effect of NICTH by impairing counter-regulatory responses to hypoglycaemia.²⁶

Occasionally, a mixture of other factors unrelated to the IGF system may cause hypoglycaemia. Tumour infiltration causing liver destruction can decrease hepatic glucose production, and could be a vital factor in explaining the onset of hypoglycaemia.

Other non-hypoglycaemic effects

IGF-2 inhibits lipolysis but increases esterification in the adipocytes by acting on IR. This results in lower circulating free fatty acid levels.²⁷

Diagnosis

NICTH suppresses insulin secretion by β cells, lipolysis and ketogenesis, leading to low C-peptide, and inappropriately low GH and β -hydroxybutyrate serum concentrations.

IGF-2 assay levels are frequently normal in NICTH. As 'big-IGF-2' assays are not commercially available, the IGF-2:IGF-1 molar ratio is considered to be a surrogate marker of 'big-IGF-2' concentration.² In NICTH, IGF-2 provides a central negative feedback of GH, with a subsequent reduction of IGF-1 production. This contributes to an increase in the IGF-2:IGF-1

ratio; a ratio of 3:1 is considered normal, and a ratio greater than 10:1 is virtually pathognomonic for NICTH.²⁸

Treatment/management

Therapeutic strategies in DPS can be divided into therapies that directly reduce the tumour burden (surgery, chemotherapy, etc) and therapies that mitigate hypoglycaemia without treating the underlying tumour.^{29 30}

Complete surgical resection is the only way to cure both benign and malignant SFTP. Resectability is the single most important indicator of clinical outcome. Benign pedunculated SFTP has the highest cure rate of up to 98%. A 6% local recurrence rate was observed in benign sessile SFTP, which is usually curable after re-excision. Malignant SFTP, especially the sessile type, has a 63% recurrence rate even after complete resection. Half of the patients with recurrent disease die of the tumour within 24 months. The overall long-term cure rate after complete resection for all patients is 80–92%.²⁹

Overnight hypoglycaemia can be managed with different strategies. Scheduled snacks and glucose drinks, nocturnal or continuous dextrose infusion, and enteral tube feeding reliably prevent hypoglycaemia. Other strategies such as corticosteroid administration and continuous glucagon infusion have a risk of side effects.

In actuality, non-surgical intervention is difficult to execute. Our patient had scheduled night feeding at home while awaiting surgery. However, it is difficult to expect patients to be compliant with waking up to eat. Moreover, she may be severely hypoglycaemic or comatose before the scheduled snack time.

We also trialled diazoxide in our patient; however, as it was stopped after 2 days, we cannot reliably state that it was ineffective. Perhaps for patients discharged from hospital while awaiting surgery, it would be safer and more reliable to give anti-hypoglycaemic medications. Diazoxide and corticosteroids could be trialled, as the benefits will most likely outweigh the costs in short-term use.

Learning points

- ▶ The Doege-Potter syndrome is an uncommon paraneoplastic syndrome associated with a solitary fibrous tumour and characterised by hypoinsulinaemic hypoglycaemia and fasting hypoglycaemia.
- ▶ The tumour mediates its effect through the IGF system by producing either IGF-2 or its precursor protein 'Big-IGF-2'.
- ▶ Low levels of insulin, C-peptide, IGF-1 and a high IGF-2:IGF-1 ratio indicate non-insulin-mediated hypoglycaemia.
- ▶ Total resection of the tumour gives the best possible chance of recovery from refractory hypoglycaemia, and is potentially curative.
- ▶ Non-surgical management will include scheduled glucose intake and medications such as corticosteroids and diazoxide.

Acknowledgements The authors would like to thank the following doctors: Dr Terence Tang Eng Yeow, Dr Ng Chong Jin, Dr Brenda Lim and Dr Phua Eng Joo for the co-management of our patient. They would also like to thank Dr Thomas Choudary Putti and Dr Lim Chong Hee for providing the relevant figures/pictures attached in this manuscript.

Contributors CKJT contributed to the literature review, acquisition and interpretation of the data and drafting of the manuscript. HLT contributed to the management of the patient, acquisition and interpretation of the data and drafting

of the manuscript. SS contributed to the patient management, liaison with other specialties in the co-management of the patient, drafting of the manuscript and final approval of the version published.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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