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Severe Hypoglycemia - Putting the Puzzle Together

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A 50-year-old man presented to the emergency department confused and ataxic with slurred speech. He was mildly tremulous, sweating, and mildly tachycardic and hypertensive. Although he appeared drunk, his breath alcohol test was negative. He had no known comorbidities and did not take any regular medications. His capillary blood glucose (finger prick) reading was 34mg/dl.

Is the presentation in keeping with hypoglycemia?

Yes.

He has a combination of autonomic symptoms (e.g., sweating, tachycardia, tremor) and neuroglycopenic symptoms (e.g., confusion, ataxia, dysarthria). Hypoglycemia accounts for over 5% of emergency presentations of an 'altered mental state.'

Dr. NBM tips:

- Hypoglycemia can cause focal neurological signs — don't miss hypoglycemia masquerading as stroke!
- The 'drunk' patient may be hypoglycaemic — even when intoxicated with alcohol.

What is Whipple's triad?

Whipple's triad confirms the diagnosis of clinically significant hypoglycemia.

It consists of:

- the presence of symptoms consistent with hypoglycemia
- a low serum glucose level
- resolution of the symptoms and signs of hypoglycemia with the administration of glucose.

What are the causes of hypoglycemia?

The vast majority of ED hypoglycemia presentations involve patients with diabetes who take insulin or oral hypoglycemic drugs. Hypoglycemia includes missed meals, incorrect medication dosage or administration, intercurrent illnesses, alcohol consumption, increased exercise, and deteriorating renal function.

However, there are other causes of *fasting hypoglycemia* — which my Rosen EM explains.

EXPLAINS H

- **Ex**ogenous drugs — insulin, oral hypoglycemics, quinine, chloroquine, beta-blocker overdose, valproate overdose, salicylate overdose, pentamidine.
- **P**ituitary insufficiency
- **L**iver disease — hepatocellular cancer, hepatitis, and rare genetic defects.
- **Addison's** disease
- **I**slet cell tumors — insulinomas;
- **I**mmune hypoglycemia — e.g., anti-insulin receptor antibodies in Hodgkin's disease or anti-insulin antibodies that release insulin when insulin levels are relatively low;
- **I**nfection — e.g., severe sepsis, malaria
- **N**on-pancreatic neoplasms — fibromas, sarcomas, mesotheliomas, and small cell carcinomas that produce IGF-2; extensive metastases that overwhelm the body's ability to produce glucose;
- **N**esidioblastosis or Noninsulinoma pancreatogenous hypoglycemia (NIPH) syndrome — islet cell hyperplasia, which can be congenital or acquired, e.g., post-gastric surgery
- **S**tarvation and malnutrition
- **H**ypothyroidism (myxoedema coma)

Post-prandial hypoglycemia can also occur due to a rapid surge of insulin ('late dumping') following rapid entry of food into the small intestine. This may occur after gastric

surgery, for instance. Finally, remember to consider pseudohypoglycemia — leukocytosis, thrombocytosis, or erythrocytosis can cause excessive glucose consumption in the collection vial while the sample awaits testing.

What is the emergency treatment of hypoglycemia?

In the awake, cooperative patient, appropriate initial management may be as simple as:

- Oral intake of simple carbohydrates (e.g., a sugary drink, jam, sugar lumps, barley sugars, etc.) followed by a sandwich or biscuits.

In the uncooperative or unconscious patient, parenteral therapy is needed:

- 50 mL 50% glucose (or 5 mL/kg of 10% glucose in small children) — flush with saline as it is hypertonic and can cause phlebitis. Or
- glucagon 1mg IM/SC or IV — Paramedics may administer this at the scene when IV access is difficult. It is inappropriate in settings where liver glycogen stores are depleted (e.g., liver failure or chronic alcoholism).

Full neurological recovery is usually rapid and is expected within about 20 minutes – otherwise, suspect a complication (e.g., stroke) or an alternative coexisting diagnosis.

- Start an octreotide infusion in the case of sulfonylurea poisoning.

What is the role of thiamine in the treatment of hypoglycemia?

It is traditionally advocated that thiamine 100mg IV be given before administering a glucose bolus to a patient with altered mental status. This comes from the concern that ***Wernicke's encephalopathy*** may be precipitated or exacerbated by the glucose load in the absence of thiamine administration.

The concern is that an excessive carbohydrate load will build toxic metabolites when these enzymes' activity is reduced because of thiamine deficiency. However, there appear to be no instances of a single glucose bolus precipitating Wernicke's encephalopathy, although prolonged carbohydrate administration (e.g., from total parenteral nutrition) without thiamine supplementation certainly can.

> Never delay the correction of hypoglycemia because of an irrational desire to administer thiamine first.

- By all means, give thiamine (and magnesium, another cofactor, while you're at it) — especially to the alcoholic or malnourished patient — it is safe. It is an effective treatment for Wernicke's encephalopathy.

What investigations are required in the patient presenting with hypoglycemia?

In the otherwise well patient with diabetes who missed a meal, it might be that no further investigations are needed. Investigations should be appropriate to the clinical situation and aim to identify the causes and complications of the hypoglycemic episode.

Useful investigations may include:

- glucose, insulin, beta-hydroxybutyrate, C-peptide
- **High/normal insulin with no excess ketones** is consistent with insulinoma, sulfonylureas, insulin administration, and insulin autoantibodies. C-peptide is absent if exogenous insulin is administered.
- **Low insulin with no excess ketones** is consistent with anti-insulin receptor antibodies and non-pancreatic neoplasms.
- **Low insulin with high ketones** is consistent with ethanol-induced hypoglycemia and pituitary and adrenal failure.

Consider other causes, such as:

- Septic screen, thick and thin films for malaria, or malaria antigen tests.
- LFTs and INR (liver disease)
- UEC, 24h creatinine clearance, renal imaging (renal failure)
- Endocrine tests:
- cortisol (adrenal insufficiency)

- GH response to hypoglycemia stimulation test, synACTHen test (pituitary failure)
- TFTs (hypothyroidism)
- Monitored prolonged fasting for recurrent hypoglycemia (especially if investigations were not obtained on the presenting episode of hypoglycemia)
- Tests for insulinomas — the absence of C-peptide suppression following insulin administration, pancreatic arterial calcium stimulation, and vein sampling.
- autoantibodies — anti-insulin receptor and anti-insulin antibodies
- tumor imaging (e.g., MRI)
- Drug levels if occult drug administration is suspected (e.g., sulfonylureas).
- **Unusual hypoglycemia causes may not be suspected at the initial presentation. If feasible, save 20 mL of blood in serum tubes for later analysis before correcting the hypoglycemia's initial episode (but do not unduly delay treatment!).**

What is the cause of hypoglycemia in this patient?

Following the initial management of his hypoglycemia, the patient became conscious. He said he began to feel unwell after taking some Cialis bought online for his erectile dysfunction.

Does Cialis cause hypoglycemia?

No. Cialis is the trade name for tadalafil. It is a cyclic GMP-phosphodiesterase 5 inhibitor used for erectile dysfunction. Its principal adverse effects include priapism, hypotension, and the exacerbation of symptoms in those predisposed to ischemia. **It does not cause hypoglycemia.**

What is the likely explanation?

The 'Cialis' may have been a counterfeit drug. This can be determined by laboratory analysis of the remaining tablets. Laboratory tests showed that the tablets contained the **sulfonylurea oral hypoglycemic agent glibenclamide.**

According to WHO estimates, up to 1% of drugs in the industrialized world are counterfeit. Globally it is an even bigger problem — up to 10% of drugs worldwide are considered counterfeit. This is a particular hazard for those who purchase medications from overseas using the Internet.

No sulfonylurea drugs were detected when the patient's blood was tested. How can this be explained?

- The glibenclamide may have been undetectable for the following reasons:
- The laboratory test may not have been sensitive enough. Checking with the lab to confirm the sensitivity of drug screens, particularly in forensic cases, is essential.
- The hypoglycemic effects of sulfonylureas may persist after the elimination of the drug from circulation.
- If the possibility of sulphonylurea toxicity was not initially suspected, the test might have been performed during the hypoglycemic episode. The blood sample may have been sent sometime after the initial presentation.

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Further reading:

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