Unusual association of diseases/symptoms

Ketoacidosis in type 2 diabetes- is it type 1 and 1/2 diabetes?

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A 64-year-old female with a background of type 2 diabetes became acutely unwell after being transferred from insulin to liraglutide, which is one of the new glucagon like peptide 1 analogues. On assessment in accident and emergency, she was diagnosed with diabetic ketoacidosis and pancreatitis. Glutamic acid decarboxylase antibodies were positive at 45 (0–1 U/ml) and C-peptide was low <94 pmol/l in keeping with the diagnosis of latent autoimmune diabetes of adults (LADA). This type of diabetes is characterised by slow autoimmune destruction of β cells of pancreas and can often be mistaken for type 2 diabetes. Patients suffering from LADA or type 1 and 1/2 diabetes require insulin to prevent ketoacidosis. She recovered with insulin treatment.

BACKGROUND

This case highlights the need to consider the increasingly recognised diagnosis of latent autoimmune diabetes of adults (LADA), also known as type 1 and 1/2 diabetes, in patients who do not fit the typical profile of type 2 or type 1 diabetes. This has become more important recently with the advent of glucagon like peptide 1 (GLP-1) analogues which will not work if there is no endogenous insulin production and may in fact precipitate ketoacidosis.

Type 1 diabetes is usually diagnosed in young people and results because of autoimmune and, less often, non-immune destruction of pancreatic β cells. These patients therefore typically need insulin for survival very early after the diagnosis, although some patients can remain insulin free for longer.

Patients with type 2 diabetes are typically older, overweight and insulin resistant. They may also need insulin for better control of diabetes but typically will not develop ketoacidosis without it. There is, however, a group of people who fall in between the two typical types of diabetes. These patients may be older but have immune mediated slow destruction of β -cells and may need insulin earlier than expected. This metabolic state has been called type 1 and 1/2 diabetes or LADA. Physicians should be aware of this diagnosis to avoid the risk of ketoacidosis.

CASE PRESENTATION

A 64-year-old female with a background of type 2 diabetes diagnosed in 2004 and with a body mass index (BMI) of 30 attended the emergency department with a 3 day history of vomiting and abdominal pain. Diabetic control was poor (HbA_{1c} 11.8%) on lantus 32 units daily (started in 2005), glimepiride 3 mg daily and metformin 500 mg five times daily. However, the patient stated that the insulin had been switched to a newer once daily injectable medication 5 days before this admission by the primary care team. This drug was later discovered to be liraglutide.

On examination, the patient was very unwell with tachycardia (heart rate 140 bpm) and tachypnoea. The abdomen was diffusely tender but not peritonitic, however the chest and cardiac examinations were unremarkable.

INVESTIGATIONS

Arterial blood gases showed a severe metabolic acidosis with a pH of 7.1, pO₂ 16.9, pCO₂ 1.2, HCO₃ 3 5.8, base excess-24.5. Blood glucose was 50.2 mmol/l and urine ketones were strongly positive. Serum amylase was raised at 1443 (30–110) U/l and corrected calcium was only 1.86 (2.10–2.55) mmol/l. An abdominal CT scan did not pick up any obvious cause for the raised amylase.

It was later discovered that glutamic acid decarboxylase (GAD) antibodies were positive at 45 (0–1 U/ml) and C-peptide was low <94 pmol/l.

TREATMENT

She was treated with aggressive intravenous fluid resuscitation and sliding scale insulin, as per the local hospital protocol for diabetic ketoacidosis (DKA).

OUTCOME AND FOLLOW-UP

She was initially transferred to the intensive care unit, but eventually made a good recovery. She was discharged from hospital after 10 days, and subsequent clinic visits showed her glucose control to be much improved with patient education about how to manage autoimmune diabetes.

DISCUSSION

This patient has LADA, a condition first described by Tuomi *et al* in 1993¹. Between six and fifty percent of people with type 2 diabetes in different populations actually have LADA.² Patients present in adulthood with diabetes but often do not fit the typical profile of type 2 diabetes. They may have a normal or mildly elevated BMI (as in our case) and there is an increased prevalence in individuals with a family history of other autoimmune conditions. However, there is some evidence that insulin resistance also plays a role in LADA as it does in type 2 diabetes. A Norwegian study suggested that increasing age, being overweight, and physical inactivity are strong risk factors for LADA as well type 2 diabetes.³

LADA can be recognised by the presence of antibodies to islet-cells, GAD or careful clinical criteria.^{1 4 5} The

presence of anti-GAD antibodies indicates autoimmune diabetes and can identify people who are more likely to require insulin sooner rather than later, some within a matter of months from diagnosis. In one series, the presence of anti-GAD antibodies had a positive predictive value of 50 percent and a negative predictive value of 97 percent for late onset insulin deficiency.⁶

This patient developed DKA as a result of an incorrect diagnosis of type 2 diabetes which led the diabetic nurse to change her insulin to liraglutide, a GLP-1 analogue. These drugs reduce hyperglycaemia secondary to food intake via a number of mechanisms which include delaying gastric emptying, increasing insulin secretion, suppressing glucagon secretion and reducing appetite. There is also evidence in animal studies that they preserve the number of pancreatic β cells. Benefits include reduced risk of hypoglycaemia (because they only act in response to hyperglycaemia), reduced serum triglyceride levels and weight loss.

The main side effects of liraglutide are gastrointestinal, and are mild and short-lived. In phase two and three drug trials, seven patients developed pancreatitis out of the 4257 treated with liraglutide, compared with only one case in the 2381 patients in the control group.⁷ The small numbers make it difficult to draw further conclusions. Doctors and patients should be aware of this possible side effect, and persistent or severe nausea and vomiting should prompt patients to seek medical advice, since this may be early manifestations of pancreatitis. In our case study, the patient was warned about the small risk of pancreatitis but did not seek help immediately because she did not recognise the symptoms until they had become severe. Although serum amylase may be raised in ketoacidosis without pancreatitis in 17% of cases,⁸ the low calcium levels in our case suggest she did have pancreatitis in addition to DKA. The pancreatitis was probably not picked up by the CT scan because it was relatively mild and short-lived; the scan was done a couple of days after admission. Biochemical tests to ascertain whether the amylase was of pancreatic or salivary origin were not carried out.

In 2010 National Institute of Clinical Science approved the use of GLP-1 analogues as adjuncts in adults with type 2 diabetes who

- have a body mass index of over 35 (for European patients), or under 35 if losing weight would significantly

reduce other weight related problems or use of insulin would impact upon work.

- have inadequate control with dual therapy with metformin, plus a sulphonylurea or a thiazolidinedione⁹.

Our patient fulfilled the second criteria, however her BMI was less than 35 and she had no other weight related problems.

Learning points

- Any patient who does not fit the typical profile of type 2 diabetes that is becomes insulin dependent sooner than expected, has an erratic glucose profile for no apparent reason and who does not follow the expected clinical course should be referred to secondary care services for further investigations to exclude LADA.
- GLP-1 analogues should only be used for type 2 diabetes and with warning about potential side effects like pancreatitis.

Competing interests None.

Patient consent Obtained.

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