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REVIEW

Diabetic and endocrine emergencies

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Endocrine emergencies constitute only a small percentage of the emergency workload of general doctors, comprising about 1.5% of all hospital admission in England in 2004–5. Most of these are diabetes related with the remaining conditions totalling a few hundred cases at most. Hence any individual doctor might not have sufficient exposure to be confident in their management. This review discusses the management of diabetic ketoacidosis, hyperosmolar hyperglycaemic state, hypoglycaemia, hypercalcaemia, thyroid storm, myxoedema coma, acute adrenal insufficiency, pheochromocytoma hypertensive crisis and pituitary apoplexy in the adult population.

hormones of glucagon, catecholamines, cortisol and growth hormone leading to increased glucose production in the liver and decreased utilisation in peripheral tissues.¹¹ In DKA, the severe deficiency in insulin and increased counter-regulatory hormones lead to increased lipolysis and production of ketone bodies and resulting metabolic acidosis.¹² It is not known why people with HHS do not develop ketoacidosis, but it is postulated to be owing lower level of free fatty acids or higher portal vein insulin.¹³

CLINICAL FEATURES

The presentation of DKA is rapid, usually within <24 h although symptoms may be present for several days before the development of ketoacidosis. For HHS, the history is that of several days to weeks. DKA also tends to occur in younger, leaner patients with type 1 diabetes, whereas HHS is more likely to occur in older, obese patients with type 2 diabetes. The presenting symptoms are often vomiting and abdominal pain (only in DKA), with history of polyuria, polydipsia and weight loss. The mechanisms of abdominal pain are poorly understood, but possible mechanisms include delayed gastric emptying, ileus, oesophagitis with ulceration, subacute pancreatitis, hepatic capsule expansion or bowel ischaemia.^{14–16}

The physical signs include evidence of dehydration with evidence of hypotension, fruity breath from acetone in DKA, increased respiratory rate and Kussmaul breathing. Confusion is an unusual presentation for DKA but is more common in HHS, correlates better with serum osmolality (>340 mmol/l) than with blood glucose and is vital to investigate for alternative causes.^{17–18}

The differential diagnosis for patients presenting with ketoacidosis are reasonably straightforward, as most of them would have a known history of diabetes. Alcoholic ketoacidosis can present with nausea and vomiting, but these patients usually have a long history of chronic alcohol misuse and absence of hyperglycaemia. In starvation ketoacidosis, where patients typically have intake of <500 calories/day, an accumulation of ketone bodies is rare and the serum bicarbonate rarely falls <18 mmol/l. The differential diagnosis for metabolic acidosis with high anion gap is more difficult and includes lactic acidosis and overdose of salicylate, methanol, paraldehyde and ethylene glycol.

LABORATORY FINDINGS

The two principal laboratory findings are hyperglycaemia and hyperosmolality, with substantial

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS; or hyperosmolar non-ketotic hyperglycaemia) are the most common and most serious diabetic emergencies. Most of these occur in patients with known diabetes. It has long been assumed that DKA is pathognomic of type 1 diabetes mellitus, but it is now recognised that DKA can occur in type 2 diabetes, especially in African-American and ethnic minorities.^{1–2} DKA is a triad of hyperglycaemia, ketosis and acidaemia, and the diagnostic criteria, as defined by the American Diabetes Association, are blood glucose >13.8 mmol/l (250 mg/dl), pH <7.30, serum bicarbonate <18 mmol/l, anion gap >10, and ketonaemia.³ HHS is caused by inadequacy of insulin and defined as blood glucose >33.3 mmol/l (600 mg/dl), pH >7.30, bicarbonate >15 mmol/l, serum osmolality >320, and a small amount of ketones may be present.³

With improved care and early detection, DKA or HHS can be entirely prevented. However, this is not reflected in the hospital admissions in England, with just >7700 admissions in 1998–9 and just <8400 admissions in 2004–5 for admissions with DKA and around 2000 admissions for HHS.⁴ The EURODIAB study reported an incidence of DKA in type 1 diabetes of 8.6%.⁵ The mortality from DKA remains low at <5%, but it is the most common cause of death in young people with diabetes and is high in those >65 years of age.^{6–8} For HHS the mortality remains high at around 15% and is even higher in the older population.⁹

World wide the most common precipitating cause of DKA and HHS is infection, being responsible for nearly half the cases.¹⁰ Of course, any stressful conditions such as cardiovascular accident, myocardial infarction, trauma, drugs and non-compliance can also precipitate the crisis.

The pathogenesis of DKA or HHS comprises insulin deficiency with increased counter-regulatory

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depletion in sodium, potassium, magnesium, phosphate and water. In DKA, the blood glucose is rarely >40 mmol/l, which is likely due to the rapid presentation with symptoms and because it occurs in younger patients with reasonable renal function, but in HHS the blood glucose is often >50 mmol/l. DKA can impair lipoprotein lipase activity, resulting in gross elevation of triglyceride causing a pseudohyponatraemia.¹⁹

Although there is a potassium deficit at presentation, the measured serum potassium can be normal or raised due to a shift of potassium from intracellular to extracellular space after the shift in water. There is a deficit in phosphate balance in both conditions, but initially serum levels can be high. With treatments marked hypophosphataemia occurs, but rarely is replacement justified as it has not been shown to improve outcomes and is actually associated with problems relating to hypocalcaemia and hypomagnesaemia.^{20–21}

Amylase level is raised in 21–79% of patients with DKA, but it does not indicate pancreatitis. The mechanism for this is poorly understood but is believed to be multifactorial, owing to salivary amylase and reduced renal clearance.^{22–23}

It is normal for a mild leucocytosis ($10\,000$ – $15\,000$ mm³) to occur in patients with DKA owing to stress, dehydration and demargination of leucocytes without any underlying infections. A leucocyte count $>25\,000$ mm³ is suggestive of an underlying bacterial infection.²⁴

MANAGEMENT

The treatment goals for DKA and HHS are to correct the fluid depletion, decrease the blood glucose level, correct the electrolyte imbalance and treat the precipitating causes. This will require close monitoring of the patient's clinical and metabolic status to ensure that treatments are working and, if not, to recognise in advance the need to increase the level of care required. Headaches and decreased level of consciousness may indicate the development of cerebral oedema and the need for intensive care in patients with DKA. Most DKA are mild to moderate and can be nursed in high-dependency units. No clear advantages have been shown for managing DKA in intensive care units over high-dependency units or even general medical wards.^{25–26} However in those with severe DKA or critical illness that precipitated the event, admission to the intensive care unit is required. Most hospitals will have an agreed local protocol for managing DKA or HHS and it is important to refer to these guidelines.

Fluid depletion is estimated to be between 5 and 8 l for patients with DKA and up to 8–10 l in those with HHS. Most protocols will start with isotonic saline infusion (in the absence of cardiac failure) aiming to restore renal perfusion with 1000–1500 ml within the first hour. Correcting the fluid deficit will lower the plasma osmolality and reduce the blood glucose levels. The rate of fluid infusion depends on the clinical status of the patients, although too rapid fluid infusion is dangerous in the young owing risk of cerebral oedema. In patients with shock there is a need for rapid fluid repletion but, in the absence of cardiovascular compromise, it is sufficient to replace the fluid deficit within 24 h. The optimum time to use 0.45% saline remains uncertain. Most experts would not recommend its use until euvolaemia is achieved and unless serum sodium concentration is >150 mmol/h but the aim is for gradual reduction in serum osmolality by not >3 mmol/kg/h or decrease in sodium concentration by <1 mmol/h.

Insulin treatment will increase glucose utilisation in peripheral tissues and decrease hepatic glucose production, thereby lowering blood glucose concentration. Insulin decreases ketogenesis and inhibits the release of free fatty acids, thereby correcting the acidosis. The use of low-dose intravenous insulin infusion (initially 6 unit/h) is now standard and allows for a

steady fall in blood glucose concentration although other routes of administration have also been shown to be effective.^{27–29} Once the blood glucose level falls to <15 mmol/l, 5% dextrose can be infused at a rate of 1000 ml within 6 h. If further fluids are still required, isotonic saline can be infused along with the dextrose, but at a slower rate. The aim is not to let the blood glucose fall to <10 mmol/l.

To prevent development of hypokalaemia after initiation of treatment for DKA, potassium replacement should be started after the first litre of fluid, aiming to maintain the concentration between 4 and 5 mmol/l. If initially the potassium level is low, then immediate replacement is required to prevent profound hypokalaemia, which may be life threatening. Potassium can be added to the isotonic saline or 5% dextrose and rarely will >20 mmol/500 ml be required.

Bicarbonate replacement in patients with DKA remains controversial as randomised control clinical trials have not been able to show a clear benefit. Most experts would not recommend its use unless the pH is <7 . It can be given as 1.4% sodium bicarbonate 500 ml over 30 min, but worsen the hypokalaemia.^{30–31}

Although phosphate depletion is often found in patients with DKA, replacement is not usually required. No clear benefit has been shown in the routine correction of hypophosphataemia using intravenous phosphate; it may actually be harmful, causing hypocalcaemia and hypomagnesaemia.^{32–34} If replacement is required, it is safer to use oral supplementation. No study has focused on phosphate replacement in patients with HHS.

DKA and HHS predisposes patients to risk of thrombosis, with severe dehydration and haemostatic changes.³⁵ Although prophylactic anticoagulation should be considered, there are no data to support its safety or efficacy. It is known that there is an increased risk of gastrointestinal bleeding in patients with DKA, that about 9% of patients are affected and that this is associated with increased non-bleeding related mortality.³⁶

Fortunately, serious complications related to treatment for DKA or HHS are rare in adults, but includes cerebral oedema and adult respiratory distress syndrome. Cerebral oedema is thought to be caused by the rapid shift in extracellular fluid to intracellular space owing to the rapid lowering of extracellular osmolality. This is contributed by rapid correction of blood glucose level and too rapid fluid replacement.^{37–38} Adult respiratory distress syndrome or non-cardiogenic pulmonary oedema is believed to be related to the adverse osmotic gradients leading to interstitial oedema of the lungs.³⁹ Hyperchloraemic metabolic acidosis is often seen in patients with DKA and is probably because of loss of ketoanions in the urine and excessive chloride in fluid replacement.^{40–41} However, there seems to be no adverse effect and it will be corrected spontaneously.⁴²

The transition from continuous insulin infusion to subcutaneous insulin injections can be difficult and is often mis-handled by junior medical staff. The involvement of the diabetes team would be preferred. Subcutaneous insulin can be initiated once DKA has resolved. The criteria for resolution of DKA as proposed by the American Diabetic Association are glucose level <11 mmol/l (200 mg/dl), venous bicarbonate >18 mmol/l and venous pH >7.30 . Also, insulin infusion should not be stopped until patients are able to eat and drink normally. Patients with known diabetes can then be restarted on the current subcutaneous insulin regimen. In those newly diagnosed, a twice daily regimen using intermediate acting insulin is often used. The dose is split into two thirds given in the morning and one third in the evening. The dose of insulin is approximately 0.5–1.0 U/kg/day or to use the insulin requirement in the past 24 h on insulin infusion as a guide. The

subcutaneous insulin needs to be started at least 1 h before the discontinuation of insulin infusion to avoid rebound hyperglycaemia and even DKA. However, with the new rapid acting human insulin analogues (Aspart, Lispro and Glulisine), it may be possible to stop the insulin sliding scale immediately on starting subcutaneous insulin. Some patients with type 2 diabetes may be discharged on oral antiglycaemic agents.

About 50% of DKA admissions may be prevented and hospital admissions reduced with diabetes educations and follow-up care.

HYPOGLYCAEMIA

Hypoglycaemia is a biochemical diagnosis defined as blood glucose level of <2.5 mmol/l, but is believed by patients, friends and family as a group of symptoms. In 2004–5, in England, there were just around 8000 hospital admissions related to hypoglycaemia, most of which were due to insulin treatment of type 1 or 2 diabetes mellitus, although sulphonylurea drugs can also cause hypoglycaemic episodes.⁴³ However, most hypoglycaemia episodes are managed by patients and by the ambulance services, and account for about 90 000 callouts per year in the UK.⁴⁴ Hypoglycaemic episodes are an inevitable consequence of tight control in the management of diabetes, with the Diabetes Control and Complications Trial showing a 2–6-fold increase in risk of severe hypoglycaemia in the intensively treated type 1 diabetes arm compared with the conventional group.⁴⁵ The fear of hypoglycaemia can result in patients having their blood glucose on the higher side, but the way to reduce its risk is to have close monitoring of their blood glucose level and to take appropriate actions when symptoms develop.

Although there are no specific symptoms of hypoglycaemia, they can be grouped as either autonomic (ie, sweating, warmth sensation, anxiety, nausea, palpitation and even hunger) or related to neuroglycopenia (ie, tiredness, being uncoordinated, visual disturbances, drowsiness, altered behaviour, confusion, and, if left untreated, coma and seizures). The autonomic symptoms tend to occur first, at a blood glucose level of around 3.3–3.6 mmol/l and neuroglycopenia at <2.6 mmol/l. When the autonomic symptoms are mild, they may not be recognised, especially in patients with good control. Those with autonomic neuropathy may develop unawareness of hypoglycaemia.⁴⁶ Hypoglycaemia unawareness occurs in up to one third of patients with type 1 diabetes, but fortunately with avoidance of hypoglycaemic episodes, the unawareness can be reversed; conversely, some patients have hypoglycaemic symptoms when their blood glucose level is above the target range—that is, >7.0 mmol/l.^{47–48} Studies on both type 1 and 2 diabetes showed that autonomic symptoms can be triggered at higher blood glucose level in patients with chronic hyperglycaemia.⁴⁹

Most mild episodes can be treated by consuming refined carbohydrates, such as 2–6 dextrose tablets, followed by long-acting carbohydrates, such as two digestive biscuits. Often the problem is that the hypoglycaemia is overtreated, leading to hyperglycaemia—for example, drinking a whole bottle of lucozade.

When patients have hypoglycaemia, episodes may be treated with hypostop (30% glucose) gel, applied to the buccal mucosa. In unconscious patients, friends or relatives trained in the use of glucagon can give 1 mg of glucagon intramuscularly or subcutaneously while awaiting medical help. Patients in hospital can be treated initially with 50 ml of 50% dextrose intravenous (irritant to peripheral veins) and glucagon, followed by 10% dextrose infusion. The use of a ‘hypobox’ containing all the preferred agents for treating hypoglycaemia and an algorithm of what to do is being established in hospitals, as knowledge of hypoglycaemia has been found to be poor among junior doctors.^{50–51}

Once a patient has had a severe episode of hypoglycaemia, he or she may have impaired recognition of hypoglycaemia symptoms over the subsequent 24 h and so needs to be extra vigilant.

The most important management of hypoglycaemia is to identify the causes to prevent future episodes with education and support.

HYPERCALCAEMIA

Hypercalcaemia is a relatively common laboratory finding, with a wide range of possible causes. Most cases in primary care are due to hyperparathyroidism, whereas about 65% of cases in hospital are due to malignancy.⁵² The symptoms of hypercalcaemia are fairly non-specific and include fatigue, weakness, anorexia, depression, abdominal pain and constipation.⁵³ It has effects on multiple systems. In the gastrointestinal system, the most common manifestation is constipation, increased gastrin secretion and, in severe cases, acute pancreatitis.^{54–55} In the kidney, hypercalcaemia causes nephrolithiasis, acute and chronic renal failure, nephrogenic diabetes insipidus and renal tubular acidosis.^{56–58} Neuropsychiatric disturbances include anxiety, and depression can occur at a calcium concentration of 3 mmol/l; at a higher concentration of >4 mmol/l, confusion, hallucination and coma can occur.⁵⁹

The management of symptomatic hypercalcaemia (>3 mmol/l) regardless of the cause involves volume expansion with intravenous isotonic saline. Up to 3–6 l in 24 h may be required, as most patients are hypovolaemic due to diuresis and nausea and vomiting.⁶⁰ There is no role for the routine use of loop diuretic, as it may exacerbate the hypovolaemia and cause hypokalaemia. It may be used if there is fluid or salt retention due to heart failure or renal failure, but fluid balance will then require very close monitoring.⁶¹

Once patients are rehydrated, the most effective method of lowering calcium is to use intravenous bisphosphonate. The bisphosphonate most commonly used is pamidronate, at a dose of 60 mg if the calcium concentration is between 3 and 3.4 mmol/l and 90 mg if greater.⁶¹ The concentration of pamidronate should not be >60 mg in 250 ml isotonic saline, which can be given as a slow infusion at a rate of 20 mg/h. The calcium will usually fall by day 3 and is at a trough by day 5, with normocalcaemia maintained for over 3 weeks.⁶² Ibandronic acid (4 mg intravenous) is now also a licence for the treatment of hypercalcaemia due to malignancy. It is equally effective in trials when compared with pamidronate, but can be given over 15 min, and normocalcaemia is maintained for over threefold longer.⁶³

Although most patients may respond to bisphosphonates, some may not. In these cases, salmon calcitonin may help when given as 400 IU intramuscularly every 6 h. Although it is relatively safe, side effects such as flushing and nausea are common and duration is limited to 48 h owing to tachyphylaxis.⁶⁴ In some cases, corticosteroids, such as prednisolone 40 mg may be helpful. In extremely resistant cases of hypercalcaemia, especially associated with renal or heart failure, dialysis can be used as the last resort.

There are potential future treatments with the development of non-calcaemic analogues of calcitriol for cancer-induced hypercalcaemia and the development of calcimimetic for primary hyperthyroidism.⁶⁵ Regardless of the causes of hypercalcaemia, the underlying cause should be treated and preventive measures taken to maintain normocalcaemia.

THYROID STORM

Thyroid storm is an extremely rare condition with only 16 cases reported in England in 2004–5, although the total number of admissions related to thyrotoxicosis is just around 750 cases.¹

Thyroid storm is life threatening and the features are usually those of thyrotoxicosis but more severe, and include fever ($>38.5^{\circ}\text{C}$), tachycardia out of proportion to the fever, confusion, agitation, nausea and vomiting, hypertension, congestive cardiac failure, increased alanine transaminase, alkaline phosphatase and bilirubin, with biochemical evidence of thyrotoxicosis. The formal criterion for thyroid storm using a point system is described by Burch and Wartofsky.⁶⁶

It is unusual for untreated hyperthyroidism to present as thyroid storm, as there are usually precipitating events such as surgery, sepsis, burns injury, DKA, cardiovascular accident, parturition, status epilepticus, I^{131} treatment or iodinated contrast dyes. Thyroxine overdose does not cause thyroid storm, but the pathogenesis remains unclear, with acute discharge of thyroxine (T4) and triiodothyronine (T3) from the thyroid gland and implied inhibition of T4/T3 to binding globulin.^{67, 68}

The treatment principles are to decrease the production and release of thyroid hormones, to block the effects of circulating T4 and T3, and to deal with the underlying precipitants. To block the thyroid hormone synthesis we prefer to use intravenous methimazole 20 mg every 4–6 h (until we are able to take oral carbimazole 30 mg twice daily), but others may prefer propylthiouracil 200 mg every 4 h (orally or via nasogastric tube) as it will also block T4 to T3 conversion. Both drugs can also be given per rectum. To block the conversion of T4 to T3, Lugol's iodine (0.3 ml diluted to 50 ml every 8 h given orally or via nasogastric tube for 5 days) may be used. Previously sodium iodide was used intravenously, but sterile forms are no longer available. If patients are allergic to iodine, lithium carbonate (300 mg every 6 h, with twice daily lithium levels checked until a therapeutic dose of 1 mmol/l is attained) can be used instead. Intravenous steroid will also block the conversion of T4 to T3 and so dexamethasone 4 mg four times daily intravenous (or hydrocortisone 100 mg four times daily) is recommended. If there are no contraindications to β -blocker, then the choice is propranolol 80 mg three times daily (orally or via nasogastric tube), or 1 mg/min intravenously until the pulse rate is <100 beats/min. If β -blocker is contraindicated, the possible alternatives would include calcium channel blockers or digoxin. Supportive treatments may include vigorous fluid resuscitation if appropriate, external cooling and paracetamol for pyrexia (salicylates should be avoided as they inhibit thyroid hormone binding and can worsen the thyroid storm), and patients should ideally be managed on medical high-dependency unit; intensive care unit should be considered.

MYXOEDEMA COMA

Myxoedema coma is a symptom or sign of severe hypothyroidism with decreased mental status and hypothermia. It is associated with high mortality, but is now rare owing to early diagnosis of hypothyroidism.^{69, 70} In 2004 in England there were just over 500 hospital admissions related to hypothyroidism, of which 11 were due to myxoedema coma.¹

Myxoedema coma can be the first presentation of new hypothyroidism, often precipitated by infection, stroke, myocardial infarction, sedative drugs or exposure to cold. Treatment is initiated on the basis of clinical suspicion, especially in unresponsive patients with a history of hypothyroidism, previous thyroidectomy or previous radioactive iodine treatment, although blood should be taken for thyroid function tests and cortisol first. Initially, the precipitating illness needs to be identified and treated and general supportive treatments instigated. Adrenal insufficiency should also be treated with intravenous hydrocortisone until it is excluded, as there may be adrenocorticotrophic hormone (ACTH) deficiency along with thyroid stimulating hormone deficiency in the pituitary.

Useful websites

- Diabetes UK
<http://www.diabetes.org.uk/home.htm>
- American Diabetes Association
<http://www.diabetes.org/home.jsp>
- International Diabetes Federation
<http://www.idf.org/home/>
- Society for Endocrinology
<http://www.endocrinology.org/default.htm>
- The Pituitary Foundation
<http://www.pituitary.org.uk/>
- Addison's Disease Self Help Group
www.addisonsdisease.org.uk
- British Thyroid Foundation
<http://www.btf-thyroid.org/>

The core temperature must be checked using a low reading thermometer, as the mortality of this condition is related to the severity of the hypothermia. The hypothermia is due to decreased metabolism resulting in reduced heat generation. The management of hypothermia is the same as that of any cause, with resuscitation, gradual re-warming and treatment of arrhythmias.

As it is a rare condition, there are no clinical trials to suggest the best method of replacing thyroid hormone. Some endocrinologists prefer T3 (10–25 μg intravenous every 8 h) as it has greater biological activity and T4 to T3 conversion is impaired in hypothyroidism. However, if excess T3 is given mortality may increase.^{71–73} Alternatively, many prefer T4 at 200–500 μg intravenous or via nasogastric tube as the first dose, followed by 50–100 μg daily, using the smaller dose in the elderly people. Others advocate giving a combination of both T3 and T4.

ACUTE ADRENAL INSUFFICIENCY

Acute adrenal insufficiency is a potentially life-threatening emergency that presents with shock and non-specific clinical features such as anorexia, nausea, vomiting, abdominal pain, fever and general lethargy. Most crises occur in undiagnosed Addison's disease in patients on steroid replacement with intercurrent infection or acute stress with failure to increase the steroid dose. Rare causes include bilateral adrenal infarction/haemorrhages and secondary adrenal failure, which can present with hypoglycaemia.^{74, 75} The initial treatment is to resuscitate the patient with intravenous fluid (2–3 l 0.9% saline), with blood taken for random cortisol and ACTH levels (the sample must be placed on ice and must reach the laboratory within 30 min). Intravenous glucocorticoid (100 mg hydrocortisone six hourly) should be initiated immediately and not delayed, pending short synacthen test. Although the hypotension and electrolyte abnormalities are predominantly due to mineral corticoid deficiency, replacement in acute adrenal is not required as sodium and volume replacement with 0.9% saline is sufficient. The precipitating causes of the adrenal crisis need to be identified and treated.

Diagnostic criteria of diabetic ketoacidosis and hyperosmolar hyperglycaemic state according to the American Diabetes Association

Diabetic ketoacidosis

- Glucose >13.8 mmol/l
- pH <7.30
- Serum bicarbonate <18 mmol/l
- Anion gap >10
- Ketonaemia

Hyperosmolar hyperglycaemic state

- Glucose >33.3 mmol/l
- pH >7.30
- Serum bicarbonate >15 mmol/l
- Serum osmolality >320
- Traces of ketones may be present in urines

Once patients are stable, the diagnosis can be confirmed by performing a short synacthen test. A long synacthen test may be required if ACTH level is equivocal to diagnose secondary adrenal failure. The maintenance dose of glucocorticoid is usually hydrocortisone 10 mg twice a day (taken first thing in the morning and at 17:00) or 10 mg in the morning and 5 mg at 12:00 and 17:00 h.⁷⁶ The mineral corticoid replacement is a titrating dose of fludrocortisone 50–200 µg/day according to the patient's symptoms and postural blood pressure. Plasma rennin activity and U&Es may also be used by some endocrinologists.^{77 78}

A steroid card needs to be carried or a medic-alert bracelet purchased to ensure notification of steroid replacement in case of incapacitation. In minor illnesses such as upper respiratory tract infection, patients need to double the usual steroid dosage until they are well and then to gradually reduce to the normal dose. If patients are not able to take drugs orally, hospital admission for intravenous steroid is required. An emergency hydrocortisone intramuscular injection may be given to patients for self-injection to allow some extra time before admission to the in accident and emergency department. The precise amount of steroid cover required for surgery remains uncertain although the standard regimens used are intravenous 100 mg hydrocortisone at induction and 50 mg thrice daily until the patient is fit to take a normal oral dose.

PHAECHROMOCYTOMA OR CATECHOLAMINE CRISIS

Hypertension is an extremely common problem but, fortunately, accelerated or malignant hypertension with acute vascular injuries of the kidneys and eyes is now rare. There is no arbitrary level of blood pressure at which hypertension becomes an emergency, rather than urgency but systolic blood pressure >220 mm Hg and diastolic blood pressure >120 mm Hg are the generally accepted limiting values. Patients with

Resolution of diabetic ketoacidosis and starting subcutaneous insulin regimen

- Glucose <11 mmol/l
- Venous bicarbonate >18 mmol/l
- pH >7.30
- Able to eat and drink

Hypoglycaemia symptoms

Autonomic

- Sweating, sensation of warmth
- Nausea
- Palpitation
- Anxiety
- Hunger

Neuroglycopenia

- Tiredness
- Incoordination
- Visual disturbances
- Drowsiness
- Altered behaviour
- Confusion

phaeochromocytoma crisis may present with clinical features of profound sweating, marked tachycardia, pallor, numbness, tingling and coldness of hands and feet.⁷⁹ Crisis can be precipitated by straining, exercise, pressure on the abdomen, and drugs such as anaesthesia. An episode can last for a few minutes to several hours and may occur as often as several times a day or once a month or less. If phaeochromocytoma is suspected as the underlying cause of the hypertensive crisis, the treatment of choice should be intravenous α -blockers such as phentolamine (1–5 mg repeated every 15 min as required) or phenoxybenzamine (1 mg/kg infused over at least 2 h, with risk of contact sensitivity). A β -blocker may also be used, but it must always be given after the α -blocker to prevent unopposed α -mediated vasoconstriction which may worsen the hypertension. An alternative would be sodium nitroprusside (initial infusion of 0.3 µg/kg/min with dose increased every 5 min titrating to blood pressure response), but it contains the danger of severe hypotension and so its use requires close monitoring. Cyanide toxicity is an extremely rare complication of sodium nitroprusside and may be reduced by infusion of hydroxocobalamin 25 mg/h. Once the blood pressure is controlled, the definitive treatment is surgery, which leads to control of blood pressure in about 75% of cases. The identification of patients with hypertension secondary to phaeochromocytoma is difficult.⁸⁰ However, the classic triad of headache, palpitations and sweating in the presence of hypertension has high specificity (93.8%) and sensitivity (90.9%) for the diagnosis of phaeochromocytoma.⁸¹ Unfortunately, this will not prevent all cases of crisis as not all patients with phaeochromocytoma have symptoms or signs.

PITUITARY APOPLEXY

Acute hypopituitarism is rare and is due to either infarction of the pituitary gland or haemorrhage. Infarction usually occurs after substantial loss of blood during childbirth in Sheehan's syndrome, and is usually suspected if at days or weeks after delivery there is lethargy, anorexia and failure to lactate. Pituitary apoplexy results from haemorrhage into pituitary adenoma. The precise pathophysiology remains uncertain but is associated with trauma, hypertension, cardiac surgery, dynamic pituitary function test and a large number of other conditions.^{82 83} Symptoms may evolve over several hours or days and include headaches, visual field defects, nausea and vomiting, focal neurology and altered conscious level.^{84 85} It is a rare disorder but is reported to occur in between 0.6% and 25% cases of treated adenoma.^{86–88}

Thyroid storm

Clinical features

- Fever >38.5°C
- Tachycardia
- Confusion and agitation
- Nausea and vomiting
- Hypertension
- Congestive cardiac failure
- Abnormal liver function test

Treatments

- Treatment of underlying causes and supportive care
- Intravenous methimazole 20 mg 4–6 hourly or propylthiouracil 200 mg 4 hourly orally or via nasogastric tube
- Lugol's iodine 0.3 ml diluted to 50 ml water 8 hourly; alternative, lithium carbonate
- Dexamethasone 4 mg intravenous 6 hourly
- Propranolol 80 mg 8 hourly orally or via nasogastric tube; alternative, calcium channel blocker or digoxin

A high degree of suspicion is needed to make the clinical diagnosis, although the common differential diagnosis of subarachnoid haemorrhage and bacterial meningitis will require imaging of the brain and should identify a pituitary problem. Although a computed tomography scan of the head is easier to obtain, this is less sensitive in the diagnosis of pituitary lesions. In a retrospective series, a computed tomography scan identified pituitary tumour in 93% and haemorrhage in 21% of cases, whereas magnetic resonance imaging identified 100% and 88%, respectively.⁸⁹

The immediate management is supportive with close observation of vital function, including blood glucose monitoring 1–2 hourly. The cardiovascular collapse is due to cortisol deficiency secondary to ACTH deficiency and the management is as for Addisonian crisis, with hydrocortisone 100 mg intravenous six hourly. Mineral corticoid is not needed because ACTH deficiency does not cause salt wasting, volume contraction and hyperkalaemia as aldosterone secretion is unaffected. It is highly probable for other pituitary hormone deficiencies to be manifested, although pituitary apoplexy can occur in the setting of chronic hypopituitarism from other causes.⁹⁰ If thyroxine is to be given it must be given after administration of glucocorticoid, to avoid exacerbation of the cardiovascular collapse after correction of the metabolic rate.

Controversy exists over whether pituitary apoplexy should be managed conservatively or should undergo early neurosurgical decompression. Most doctors advocate routine early transphenoidal surgery, especially when there is visual acuity or visual field abnormalities, as recovery is greater.⁹¹ Yet some studies have found that, in patients in whom there is no visual deficit or the deficit is resolving spontaneously, early surgical intervention does not offer any improvement in outcomes in terms of final neuro-ophthalmological defect or endocrine deficiencies compared with conservative management.⁹² Once these patients are stable, they will require a full endocrine investigation to assess the requirement of hormone replacement, and life-long follow-up will be required.

In conclusion, most endocrine emergencies encountered by general physicians relate to hyperglycaemia or hypoglycaemia in diabetes and should be managed according to local protocols, to reduce the high mortality and morbidity associated with

these conditions. The remaining endocrine emergencies are extremely rare and therefore optimal management should involve the appropriate specialists at the earliest opportunity, but treatment should never be delayed for confirmatory test. The actual diagnosis can always be confirmed once the patient is stable.

SUMMARY

- Endocrine emergencies are rare
- Use local protocol if available
- Do not delay treatment for investigation results
- Involve the endocrine team early on

SELF ASSESSMENT QUESTIONS (TRUE (T), FALSE (F); ANSWERS AT END OF THE REFERENCES)

- Which of the following statements about DKA are true?
 - DKA only occurs in people with type 1 diabetes
 - The ADA definition of DKA includes a blood glucose of greater than 13.8 mmol/l
 - Ketones may not be present
 - Mortality is greater than 15%
 - The most common precipitant is ischaemia
- The differential diagnosis of a metabolic acidosis with a high anion gap includes:
 - Lactic acidosis
 - Paracetamol overdose
 - Alcohol intoxication
 - Paraquat poisoning
 - Salicylate poisoning
- The management of DKA routinely includes:
 - Intramuscular insulin
 - Phosphate supplementation
 - Use of 0.45% saline iv
 - Bicarbonate therapy
 - Anticoagulation with warfarin
- Which of the following statements are true about hypoglycaemia?
 - Autonomic dysfunction may cause hypoglycaemic unawareness
 - In the conscious patient are best treated with intravenous dextrose
 - Hypostop gel can be administered by a friend or relative
 - Glucagon can be given orally
 - Is commonly precipitated by infection
- Features of thyroid storm include:
 - Depression
 - Nausea and vomiting
 - Agitation and confusion
 - Hyperpyrexia
 - Bradycardia
- Treatment of thyroid storm may include:
 - Lugol's iodine

- B. Intravenous dexamethasone
 - C. α -Blockers
 - D. Salicylates
 - E. Methimazole
7. Acute adrenal insufficiency
- A. May present with abdominal pain
 - B. Is best treated with oral hydrocortisone
 - C. May be precipitated by sudden cessation of long term exogenous steroids
 - D. Can cause hypoglycaemia
 - E. Is never life threatening
8. Pituitary apoplexy
- A. Occurs secondary to infarction or haemorrhage of the pituitary gland
 - B. Is usually associated with a hemiplegia
 - C. Requires surgery in all cases
 - D. Should be treated with hydrocortisone until ACTH reserve is confirmed
 - E. Requires urgent visual field assessment

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REFERENCES

- 1 Umpierrez GE, Woo W, Hagopian WA, *et al*. Immunogenetic analysis suggests different pathogenesis for obese and lean African-Americans with diabetic ketoacidosis. *Diabetes Care* 1999;**22**:1517–23.
- 2 Balasubramanyam A, Zern JW, Hymn DJ, *et al*. New profiles of diabetic ketoacidosis: type 1 vs type 2 diabetes and the effect of ethnicity. *Arch Intern Med* 1999;**159**:2317–22.
- 3 Kitabchi AE, Umpierrez GE, Murphy MB, *et al*. Hyperglycemic crises in diabetes. *Diabetes Care* 2004;**27**(Suppl 1):S94–102.
- 4 NHS Health and Social Care Information Centre. <http://www.hesonline.nhs.uk/Ease> (accessed 25 Oct 2006).
- 5 The EURODIAB IDDM Complications Study. Microvascular and acute complications in IDDM patients. *Diabetologia* 1994;**37**:278–85.
- 6 National Centre for Health Statistics. Detailed diagnosis and procedures: National Discharge Survey, 1995. *Vital Health Stat* 1997;**13**:130.
- 7 Basu A, Close CF, Jenkins D, *et al*. Persisting mortality in diabetic ketoacidosis. *Diabet Med* 1993;**10**:282–4.
- 8 Malone ML, Gennis V, Goodwin JS. Characteristics of diabetic ketoacidosis in older versus younger adults. *J Am Geriatr Soc* 1992;**40**:1100–4.
- 9 Matz R. Hyperosmolar nonacidotic diabetes (HNAD). In: Porte D Jr, Sherwin RS, eds. *Diabetes mellitus: theory and practice*. Amsterdam: Elsevier, 1997:845–60.
- 10 Ellemann K, Soerensen JN, Pedersen L, *et al*. Epidemiology and treatment of diabetic ketoacidosis in a community population. *Diabetes Care* 1984;**7**:528–32.
- 11 Polonsky WH, Anderson BJ, Lohrer PA, *et al*. Insulin omission in women with IDDM. *Diabetes Care* 1994;**17**:1178–85.
- 12 Felig P, Sherwin RS, Soman V, *et al*. Hormonal interactions in the regulation of blood glucose. *Recent Prog Horm Res* 1979;**35**:501–32.
- 13 Chiasson JL, Aris-Jilwan N, Belanger R, *et al*. Diagnosis and treatment of diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *CMAJ* 2003;**168**:859–66.
- 14 Campbell IW, Duncan LJ, Innes JA, *et al*. Abdominal pain in diabetic metabolic decompensation. Clinical significance. *JAMA* 1975;**233**:166–8.
- 15 Fraser RJ, Horowitz M, Maddox AF, *et al*. Hyperglycaemia slows gastric emptying in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 1990;**33**:675–80.
- 16 De Boer SY, Masclée AA, Lam WF, *et al*. Effect of hyperglycaemia on gallbladder motility in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 1994;**37**:75–81.
- 17 Umpierrez GE, Kelly JP, Navarrete JE, *et al*. Hyperglycemic crises in urban blacks. *Arch Intern Med* 1997;**157**:669–75.
- 18 Kitabchi AE, Wall BM. Diabetic ketoacidosis. *Med Clin North Am* 1995;**79**:9–37.
- 19 Kaminska ES, Pourmotabbed G. Spurious laboratory values in diabetic ketoacidosis and hyperlipidemia. *Am J Emerg Med* 1993;**11**:77–80.
- 20 Fisher JN, Kitabchi AE. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. *J Clin Endocrinol Metab* 1983;**57**:177–80.
- 21 Carroll P, Matz R. Uncontrolled diabetes mellitus in adults: experience in treating diabetic ketoacidosis and hyperosmolar nonketotic coma with low-dose insulin and a uniform treatment regimen. *Diabetes Care* 1983;**6**:579–85.
- 22 Vinicor F, Lehrner LM, Karn RC, *et al*. Hyperamylasemia in diabetic ketoacidosis: sources and significance. *Ann Intern Med* 1979;**91**:200–4.
- 23 Yadav D, Nair S, Norkus EP, *et al*. Nonspecific hyperamylasemia and hyperlipasemia in diabetic ketoacidosis: incidence and correlation with biochemical abnormalities. *Am J Gastroenterol* 2000;**95**:3123–8.
- 24 Slovis CM, Mork VG, Slovis RJ, *et al*. Diabetic ketoacidosis and infection: leukocyte count and differential as early predictors of serious infection. *Am J Emerg Med* 1987;**5**:1–5.
- 25 Moss JM. Diabetic ketoacidosis: effective low-cost treatment in a community hospital. *South Med J* 1987;**80**:875–81.
- 26 May ME, Young C, King J. Resource utilization in treatment of diabetic ketoacidosis in adults. *Am J Med Sci* 1993;**306**:287–94.
- 27 Alberti KG, Hockaday TD, Turner RC. Small doses of intramuscular insulin in the treatment of diabetic "coma". *Lancet* 1973;**2**:515–22.
- 28 Sacks HS, Shahshahani M, Kitabchi AE, *et al*. Similar responsiveness of diabetic ketoacidosis to low-dose insulin by intramuscular injection and albumin-free infusion. *Ann Intern Med* 1979;**90**:36–42.
- 29 Fisher JN, Shahshahani MN, Kitabchi AE. Diabetic ketoacidosis: low-dose insulin therapy by various routes. *N Engl J Med* 1977;**297**:238–41.
- 30 Morris LR, Murphy MB, Kitabchi AE. Bicarbonate therapy in severe diabetic ketoacidosis. *Ann Intern Med* 1986;**105**:836–40.
- 31 Lever E, Jaspán JB. Sodium bicarbonate therapy in severe diabetic ketoacidosis. *Am J Med* 1983;**75**:263–8.
- 32 Fisher JN, Kitabchi AE. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. *J Clin Endocrinol Metab* 1983;**57**:177–80.
- 33 Wilson HK, Keuer SP, Lea AS, *et al*. Phosphate therapy in diabetic ketoacidosis. *Arch Intern Med* 1982;**142**:517–20.
- 34 Winter RJ, Harris CJ, Phillips LS, *et al*. Diabetic ketoacidosis. Induction of hypocalcemia and hypomagnesemia by phosphate therapy. *Am J Med* 1979;**67**:897–900.
- 35 Hamblin PS, Topliss DJ, Chosich N, *et al*. Deaths associated with diabetic ketoacidosis and hyperosmolar coma. 1973–1988. *Med J Aust* 1989;**151**:1439, 441–2, 444.
- 36 Faigel DO, Metz DC. Prevalence, etiology, and prognostic significance of upper gastrointestinal hemorrhage in diabetic ketoacidosis. *Dig Dis Sci* 1996;**41**:1–8.
- 37 Bello FA, Sotos JF. Cerebral oedema in diabetic ketoacidosis in children. *Lancet* 1990;**336**:64.
- 38 Rosenbloom AL. Intracerebral crises during treatment of diabetic ketoacidosis. *Diabetes Care* 1990;**13**:22–33.
- 39 Lorber D. Nonketotic hypertonicity in diabetes mellitus. *Med Clin North Am* 1995;**79**:39–52.
- 40 Oh MS, Carroll HJ, Uribarri J. Mechanism of normochloremic and hyperchloremic acidosis in diabetic ketoacidosis. *Nephron* 1990;**54**:1–6.
- 41 Madias NE, Homer SM, Johns CA, *et al*. Hypochloremia as a consequence of anion gap metabolic acidosis. *J Lab Clin Med* 1984;**104**:15–23.
- 42 Oh MS, Banerji MA, Carroll HJ. The mechanism of hyperchloremic acidosis during the recovery phase of diabetic ketoacidosis. *Diabetes* 1981;**30**:310–13.
- 43 Shorr RI, Ray WA, Daugherty JR, *et al*. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. *Arch Intern Med* 1997;**157**:1681–6.
- 44 Sampson MJ, Mortley S, Aldridge VJ. The East Anglian Ambulance Trust diabetes emergencies audit—numbers and demographics. *Diabet Med* 2006;**23**:P101.
- 45 The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;**329**:977–86.
- 46 Stephenson JM, Kempler P, Perin PC, *et al*. Is autonomic neuropathy a risk factor for severe hypoglycaemia? The EURODIAB IDDM Complications Study. *Diabetologia* 1996;**39**:1372–6.
- 47 Fanelli CG, Epifano L, Rambotti AM, *et al*. Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. *Diabetes* 1997;**42**:1683–9.
- 48 Lingenfelser T, Buettner U, Martin J, *et al*. Improvement of impaired counterregulatory hormone response and symptom perception by short-term avoidance of hypoglycemia in IDDM. *Diabetes Care* 1995;**18**:321–5.
- 49 Boyle PJ, Schwartz NS, Shah SD, *et al*. Plasma glucose concentrations at the onset of hypoglycemic symptoms in patients with poorly controlled diabetes and in nondiabetics. *N Engl J Med* 1988;**318**:1487–92.
- 50 Baker H, Horton A, Low P, *et al*. 'HYPOBOX' a practical aid in the management of hypoglycaemia in hospital. *Diabet Med* 2006;**23**:P186.
- 51 Forrest LV, Obuobie KO. Audit of hypoglycaemia management amongst junior doctors. *Diabet Med* 2006;**23**:P187.
- 52 Walls J, Ratcliffe WA, Howell A, *et al*. Parathyroid hormone and parathyroid hormone-related protein in the investigation of hypercalcaemia in two hospital populations. *Clin Endocrinol (Oxford)* 1994;**41**:407–13.
- 53 Mallette LE, Bilezikian JP, Heath DA, *et al*. Primary hyperparathyroidism: clinical and biochemical features. *Medicine (Baltimore)* 1974;**53**:127–46.
- 54 Norton JA, Cornelius MJ, Doppman JL, *et al*. Effect of parathyroidectomy in patients with hyperparathyroidism, Zollinger-Ellison syndrome, and multiple endocrine neoplasia type I: a prospective study. *Surgery* 1987;**102**:958–66.

- 55 **Paloyan D**, Simonowitz D, Paloyan E, *et al*. Pancreatitis associated with primary hyperparathyroidism. *Am Surg* 1982;**48**:366–8.
- 56 **Benabe JE**, Martinez-Maldonado M. Hypercalcemic nephropathy. *Arch Intern Med* 1978;**138**:777–9.
- 57 **Goldfarb S**, Agus ZS. Mechanism of the polyuria of hypercalcemia. *Am J Nephrol* 1984;**4**:69–76.
- 58 **Manz F**, Jaschke W, van Kaick G, *et al*. Nephrocalcinosis in radiographs, computed tomography, sonography and histology. *Pediatr Radiol* 1980;**9**:19–26.
- 59 **Gatewood JW**, Organ CH Jr, Mead BT. Mental changes associated with hyperparathyroidism. *Am J Psychiatry* 1975;**132**:129–32.
- 60 **Hosking DJ**, Cowley A, Bucknall CA. Rehydration in the treatment of severe hypercalcaemia. *QJM* 1981;**50**:473–81.
- 61 **Bilezikian JP**. Clinical review 51: management of hypercalcemia. *J Clin Endocrinol Metab* 1993;**77**:1445–9.
- 62 **Body JJ**, Borkowski A, Cleeren A, *et al*. Treatment of malignancy-associated hypercalcemia with intravenous aminohydroxypropylidene diphosphonate. *J Clin Oncol* 1986;**4**:1177–83.
- 63 **Body JJ**, Baril R, Burckhardt P, *et al*. Current use of bisphosphonates in oncology. International Bone and Cancer Study Group. *J Clin Oncol* 1998;**16**:3890–9.
- 64 **Ljunghall S**. Use of clodronate and calcitonin in hypercalcemia due to malignancy. *Recent Results Cancer Res* 1989;**116**:40–5.
- 65 **Yu J**, Papavasiliou V, Rhim J, *et al*. Vitamin D analogs: new therapeutic agents for the treatment of squamous cancer and its associated hypercalcemia. *Anticancer Drugs* 1995;**6**:101–8.
- 66 **Burch HB**, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. *Endocrinol Metab Clin North Am* 1993;**22**:263–77.
- 67 **Colebunders R**, Bourdoux P, Bekaert J, *et al*. Determination of free thyroid hormones and their binding proteins in a patient with severe hyperthyroidism (thyroid storm?) and thyroid encephalopathy. *J Endocrinol Invest* 1984;**7**:379–81.
- 68 **Brooks MH**, Waldstein SS. Free thyroxine concentrations in thyroid storm. *Ann Intern Med* 1980;**93**:694–7.
- 69 **Yamamoto T**, Fukuyama J, Fujiyoshi A. Factors associated with mortality of myxedema coma: report of eight cases and literature survey. *Thyroid* 1999;**9**:1167–74.
- 70 **Hylander B**, Rosenqvist U. Treatment of myxoedema coma—factors associated with fatal outcome. *Acta Endocrinol (Copenhagen)* 1985;**108**:65–71.
- 71 **Hylander B**, Rosenqvist U. Treatment of myxoedema coma—factors associated with fatal outcome. *Acta Endocrinol (Copenhagen)* 1985;**108**:65–71.
- 72 **Rodriguez I**, Fluiters E, Perez-Mendez LF, *et al*. Factors associated with mortality of patients with myxoedema coma: prospective study in 11 cases treated in a single institution. *J Endocrinol* 2004;**180**:347–50.
- 73 **Holvey JN**, Goodner CJ, Nicoloff JT, *et al*. Treatment of myxedema coma with intravenous thyroxine. *Arch Intern Med* 1964;**113**:89–96.
- 74 **Burke CW**. Adrenocortical insufficiency. *Clin Endocrinol Metab* 1985;**14**:947–76.
- 75 **Stacpoole PW**, Interlandi JW, Nicholson WE, *et al*. Isolated ACTH deficiency: a heterogeneous disorder. Critical review and report of four new cases. *Medicine (Baltimore)* 1982;**61**:13–24.
- 76 **Howlett TA**. An assessment of optimal hydrocortisone replacement therapy. *Clin Endocrinol (Oxford)* 1997;**46**:263–8.
- 77 **Oelkers W**, L'age M. Control of mineralocorticoid substitution in Addison's disease by plasma renin measurement. *Klin Wochenschr* 1976;**54**:607–12.
- 78 **Smith SJ**, MacGregor GA, Markandu ND, *et al*. Evidence that patients with Addison's disease are undertreated with fludrocortisone. *Lancet* 1984;**1**:11–4.
- 79 **Ram CV**. Pheochromocytoma. *Cardiol Clin* 1988;**6**:517–35.
- 80 **Cryer PE**. Diseases of the sympathochromaffin system. In: Felig P, Frohman LA, eds. *Endocrinology and metabolism*. New York: McGraw-Hill, 2001:525–51.
- 81 **Bravo EL**, Gifford RW Jr. Current concepts. Pheochromocytoma: diagnosis, localization and management. *N Engl J Med* 1984;**311**:1298–303.
- 82 **Okuda O**, Umezawa H, Miyaoka M. Pituitary apoplexy caused by endocrine stimulation tests: a case report. *Surg Neurol* 1994;**42**:19–22.
- 83 **Abbott J**, Kirkby GR. Acute visual loss and pituitary apoplexy after surgery. *BMJ* 2004;**329**:218–19.
- 84 **Ayuk J**, McGregor EJ, Mitchell RD, *et al*. Acute management of pituitary apoplexy—surgery or conservative management? *Clin Endocrinol (Oxford)* 2004;**61**:747–52.
- 85 **Randeve HS**, Schoebel J, Byrne J, *et al*. Classical pituitary apoplexy: clinical features, management and outcome. *Clin Endocrinol (Oxford)* 1999;**51**:181–8.
- 86 **Mohr G**, Hardy J. Hemorrhage, necrosis, and apoplexy in pituitary adenomas. *Surg Neurol* 1982;**18**:181–9.
- 87 **Bills DC**, Meyer FB, Laws ER Jr, *et al*. A retrospective analysis of pituitary apoplexy. *Neurosurgery* 1993;**33**:602–8.
- 88 **Nielsen EH**, Lindholm J, Bjerre P, *et al*. Frequent occurrence of pituitary apoplexy in patients with non-functioning pituitary adenoma. *Clin Endocrinol (Oxford)* 2006;**64**:319–22.
- 89 **Randeve HS**, Schoebel J, Byrne J, *et al*. Classical pituitary apoplexy: clinical features, management and outcome. *Clin Endocrinol (Oxford)* 1999;**51**:181–8.
- 90 **Kaufmann P**, Lax SF, Radner H, *et al*. Severe hypotension and coma secondary to unrecognized chronic anterior hypophysitis. *Intensive Care Med* 1995;**21**:847–9.
- 91 **Arafah BM**, Harrington JF, Madhoun ZT, *et al*. Improvement of pituitary function after surgical decompression for pituitary tumor apoplexy. *J Clin Endocrinol Metab* 1990;**71**:323–8.
- 92 **Maccagnan P**, Macedo CL, Kayath MJ, *et al*. Conservative management of pituitary apoplexy: a prospective study. *J Clin Endocrinol Metab* 1995;**80**:2190–7.

ANSWERS (T, TRUE; F, FALSE)

1. F, T, F, F, F
2. T, F, F, F, T
3. F, F, F, F, F
4. T, F, T, F, F
5. F, T, T, T, F
6. T, T, F, F, T
7. T, F, T, T, F
8. T, F, F, T, T

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