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Hyperosmolar diabetic non-ketotic coma, hyperkalaemia and an unusual near death experience

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Generally, cardiac arrest due to pulseless electrical activity has a poor outcome, except when reversible factors such as acute hyperkalaemia are identified and managed early. Hyperosmolar diabetic non-ketotic coma may lead to acute hyperkalaemia. Hyperosmolar diabetic non-ketotic coma is a metabolic emergency usually seen in elderly non-insulin dependent diabetics, characterized by severe hyperglycaemia, volume depletion, altered consciousness, confusion and less frequently neurological deficit. Cerebrovascular accident or transient ischaemic attack may be mistakenly diagnosed, particularly if the patient has no history of diabetes mellitus. Delays in diagnosis and management of glycaemic emergencies presenting as a constellation of neurological abnormalities can be avoided by routine early measurement of blood glucose. Hyperosmolar diabetic non-ketotic coma should be considered in any patient with altered consciousness or neurologic deficit in conjunction with hyperglycaemia. As hyperosmolar diabetic non-ketotic coma results in severe fluid depletion, electrolyte disturbance, profound hyperglycaemia and an altered mental state, the guiding principles of therapy include aggressive rehydration, insulin therapy, correction of electrolyte abnormalities and treatment of any underlying illnesses. Treatment of acute hyperkalaemia includes calcium ions, insulin with dextrose, salbutamol and haemodialysis.

Keywords: hyperosmolar diabetic non-ketotic coma; diabetes mellitus; hyperkalaemia; pulseless electrical activity; cerebrovascular accident; transient ischaemic attack

INTRODUCTION

This case reports a diagnostically complex conjunction of acute hyperkalaemia due to hyperosmolar diabetic non-ketotic coma leading to a pulseless electrical activity (PEA) cardiac arrest. Rapid recognition and treatment of these life-threatening disease processes resulted in the patient's full recovery. This is in contrast to the poor outcome for PEA in general.[1] A review of the management of acute hyperkalaemia and hyperosmolar diabetic non-ketotic coma is presented.

CLINICAL RECORD: AN UNUSUAL NEAR DEATH EXPERIENCE

A 54-year-old woman suffered an unwitnessed PEA cardiac arrest at home. Field paramedics administered intravenous adrenaline (1 mg) and atropine (3 mg) to treat a wide complex bradyarrhythmia with no cardiac output (Fig. 1). This resulted in return of a circulation.

On arrival at the emergency department, her temperature was 36.4°C, respiratory rate 18 breaths/minute and oxygen saturation 97% on 6 l/min of oxygen. She had a wide complex regular tachyarrhythmia of 120 beats/minute with a blood pressure of 100/60 mmHg (Fig. 2).

The patient had a Glasgow Coma Score of 13 (E4 V4 M5) and mid-size equally reactive pupils. She localized to noxious stimuli, but had no movement on her left side. Brisk symmetrical lower limb reflexes and bilateral down going plantar responses were elicited. No neck stiffness, facial weakness, external signs of a head injury or rash was present.

Her blood sugar level (BSL) registered 'high' on the glucometer. Results of arterial blood gases on 40% inspired oxygen include pH 7.27, pCO_2 35 mmHg, pO_2 233 mm, [bicarbonate] 15 mmol/l, base deficit −10.7 mmol/l and [K^+] 6.8 mmol/l.

Intravenous administration of 10 ml 10% calcium chloride resulted in normalization of the QRS duration. No acute ischaemic change was present on her 12 lead ECG (Fig. 3). Treatment with an intravenous insulin infusion and normal saline rehydration led to resolution of her confusional state, hemiplegia and metabolic derangements over 48 hours.

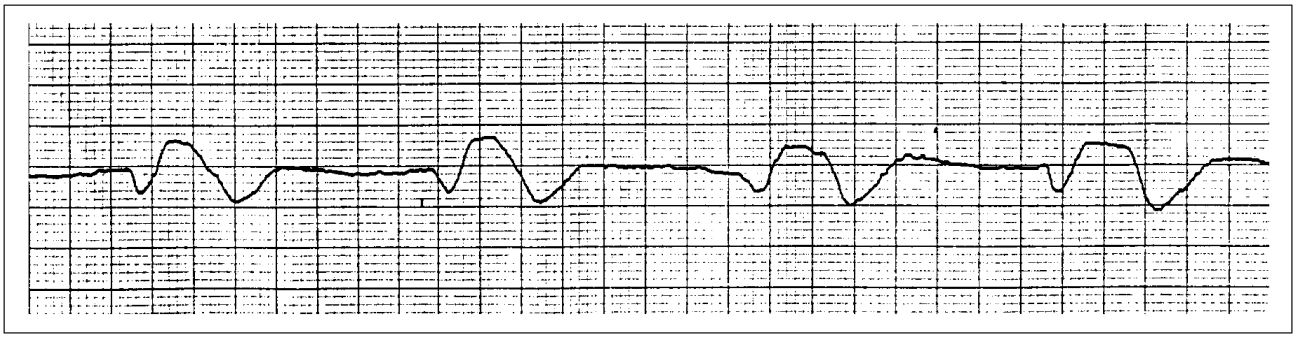

Fig. 1. Paramedic ECG strip showing a wide complex bradyarrhythmia without cardiac output.

A history of poorly controlled non-insulin dependent diabetes mellitus (NIDDM), chronic obstructive pulmonary disease, depression and heavy alcohol intake became available at this stage.

Serum biochemistry at admission revealed [Na^+] 111 (135–145 mmol/l), [K^+] 6.8 (3.2–4.5 mmol/l), [Cl^-] 72 (100–110 mmol/l), [bicarbonate] 12 (22–33 mmol/l), creatinine 0.16 (0.05–0.10 mmol/l), urea 17.1 (3.0–8.0 mmol/l), [glucose] 80 (3.0–7.8 mmol/l), calculated osmolality 312 (270–290 mmol/kg) and measured osmolality 331 (275–295 mmol/kg). The anion gap of 27 was raised for her age (predicted 17 mmol/l). Urinalysis showed 1+ ketones, 2+ glucose and 1+ protein. Her haemoglobin was 118 (115–160 g/l), white cell count 10.2 ($4.0–11.0 \times 10^9$/l) and platelets 196 ($140–400 \times 10^9$/l). A clean catch catheter urine specimen grew *Escherichia coli*.

There was no history of an ingestion of calcium

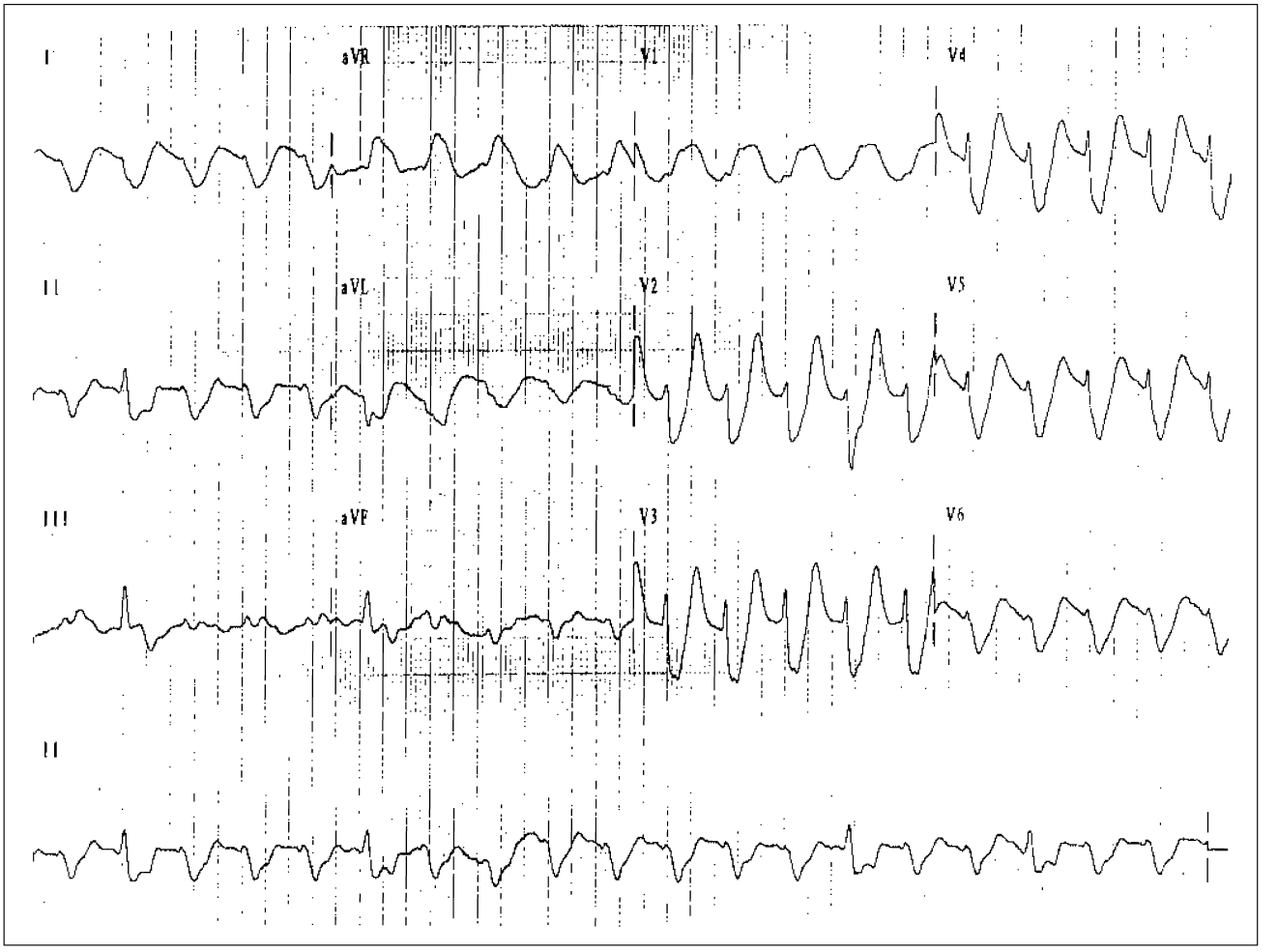

Fig. 2. First ECG in the emergency department demonstrating wide complex tachyarrhythmia.

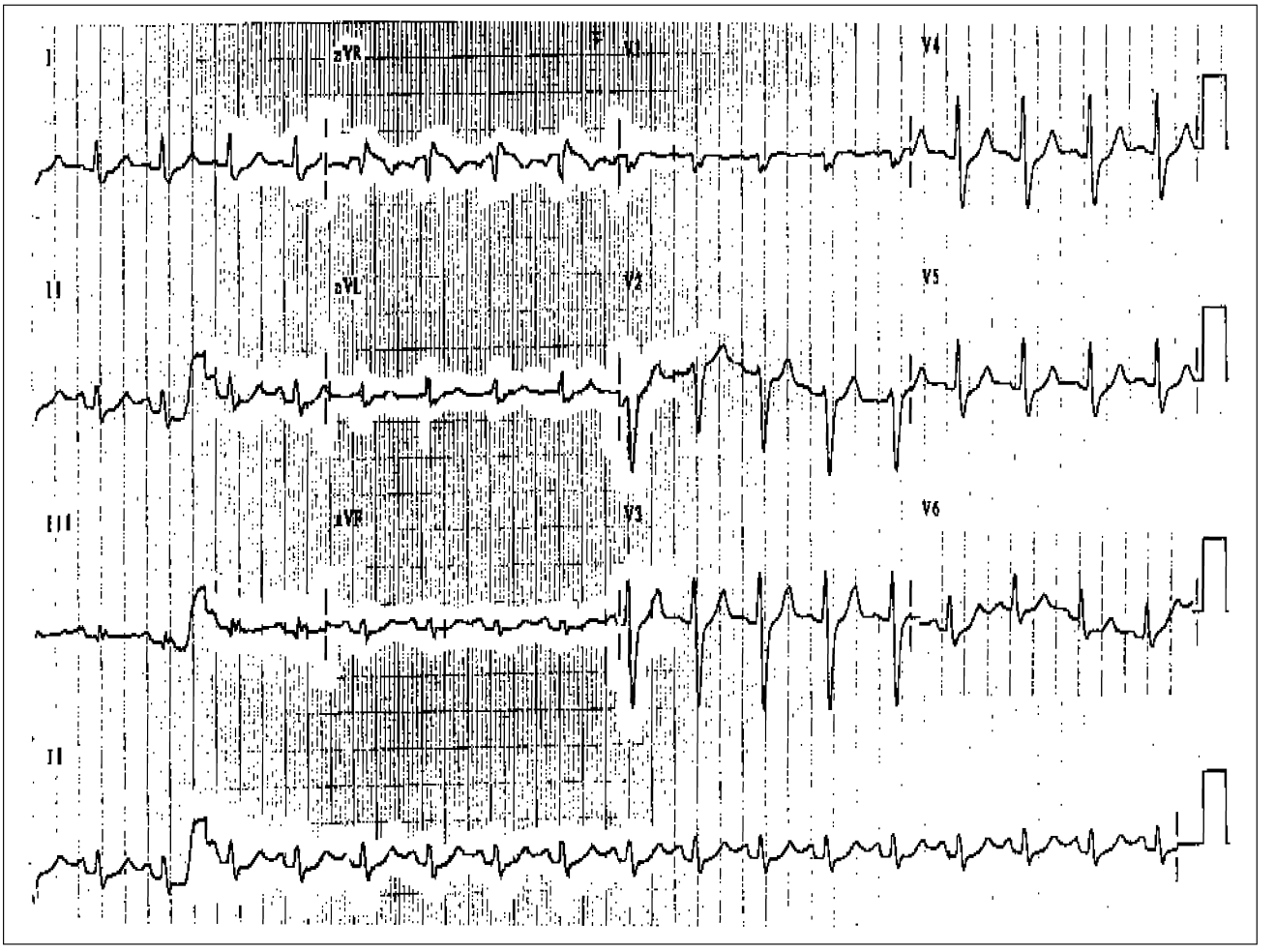

Fig. 3. Normalization of ECG after calcium chloride administration.

channel or beta-blockers, tricyclic antidepressants and digoxin. Screening for paracetamol, salicylate and ethanol was negative. A diagnosis of PEA cardiac arrest from acute hyperkalaemia due to hyperosmolar diabetic non-ketotic coma was made.

DISCUSSION

Pulseless electrical activity

PEA occurs when there is no detectable pulse in the presence of organized electrocardiographic activity. Well-known causes of PEA include myocardial ischaemia, pericardial tamponade, hypovolaemia, pulmonary thromboembolism and tension pneumothorax.[2] PEA is the initial rhythm in 17% of out-of-hospital cardiac arrests and has a poor outcome with only 4.4% of victims surviving to discharge from hospital.[1] Acute hyperkalaemia is a rare precipitant of PEA[3,4] with diabetes mellitus being a comorbid condition in 15% of cases.[5]

Hyperkalaemia

Despite a total body deficit of potassium in hyperosmolar diabetic non-ketotic coma and diabetic ketoacidosis (DKA), hyperkalaemia can be present initially.[6,7] Hyperosmolality due to hyperglycaemia causes osmotic shift of intracellular fluid into the extracellular compartment accompanied by passive potassium efflux out of cells.[4] Insulin deficiency, dehydration with impaired renal perfusion and acidosis also contribute to the development of hyperkalaemia.[4,8]

Hyperkalaemia causes cardiac rhythm disturbances by altering cell membrane resting and threshold potentials. A biphasic response to hyperkalaemia is seen. Initially the resting potential is brought closer to threshold and depolarization is facilitated with an increase in membrane excitability. Worsening hyperkalaemia reduces membrane sodium permeability thereby retarding sodium influx and cell excitability. Typical ECG manifestations of hyperkalaemia include peaked T waves, loss of P waves, prolonged PR interval, intraventricular conduction defect and second-degree atrioventricular block. This may progress to widened QRS complexes and a sine wave pattern that precedes asystole. Ventricular tachyarrhythmias and asystole can occur at any level of hyperkalaemia.

The evolution of these rhythm disturbances is unpredictable and there is no correlation between severity of hyperkalaemia and ECG changes. Acute [K^+] greater than 6 mmol/l requires urgent treatment.[8]

Immediate treatment aims to ameliorate the destabilizing cardiac membrane effects of hyperkalaemia, shift extracellular potassium into cells and bind to potassium within the gastrointestinal tract. Although calcium chloride or gluconate can reverse hyperkalaemia-induced cardiac arrhythmia within minutes, they do not lower potassium levels and are therefore only of temporary benefit.[8] The patient had a hyperkalaemia-induced wide-complex tachyarrhythmia which responded well to calcium chloride.

Measures to lower potassium levels[8] need to be instituted after initial myocardial stabilization with calcium. Insulin reliably shifts potassium into cells within 20 minutes. Both an intravenous bolus of 10 units of soluble insulin with 50 ml 50% dextrose or an insulin infusion at 5–10 units per hour are effective. An infusion is preferred if control of hyperglycaemia is also needed.

Intravenous salbutamol can immediately lower potassium levels and a nadir is seen at 90–120 minutes, whereas the effects of nebulized salbutamol has a delayed onset and peak. However, a third of patients with hyperkalaemia fail to respond with this therapy. As there is mounting evidence that bicarbonate is unreliable therapy for hyperkalaemia, it should only be administered to treat a coexistent profound acidosis.[8]

Even though haemodialysis is the most rapid and effective way to lower serum potassium, it is reserved for patients who fail to respond to pharmacologic therapy or require dialysis for another indication such as uraemia, acidosis and fluid overload due to renal failure. Access to the central circulation is required and it takes time and expertise to set up and run. There is a risk of rebound hyperkalaemia after dialysis is completed. Orally or rectally administered exchange resins which bind to enteric potassium are effective in reducing gastrointestinal absorption but are delayed in onset.[8]

Hyperosmolar diabetic non-ketotic coma

In 1886, Dreschfeld[9] described a metabolic disorder characterized by 'drowsiness, soon passing into coma … confined to older diabetics who are still stout and well nourished at the time of the attack'. Hyperosmolar diabetic non-ketotic coma was first described as a clinical entity by Schwartz in 1957.[10] It is a life-threatening endocrine emergency, comprising 10–20% of diabetic comas, with other forms being DKA and hypoglycaemic coma.[11,12]

Diagnostic criteria include extreme hyperglycaemia with serum [glucose] $>$ 33 mmol/l, increased serum osmolality $>$ 320 mmol/kg, mild ketoacidosis with $<$ 3 + urinary ketones and serum [ketone] $<$ 5 mmol/l. The arterial pH is $>$ 7.2 and [bicarbonate] remains $>$ 15 mmol/l, unlike in DKA where significant metabolic acidosis is a prominent feature.[10,13–15]

Typically hyperosmolar diabetic non-ketotic coma occurs in an elderly (mean age 55–75 years) dehydrated patient presenting with confusion and reduced consciousness level. Even though it is most commonly associated with known NIDDM, a third of cases occur in newly diagnosed diabetics.[11,13,16] To complicate matters further, hyperosmolar diabetic non-ketotic coma can occur in younger insulin-dependent diabetics with previous episodes of DKA. Progressive hyperglycaemia with polyuria occurs with poor oral fluid intake, leading to severe dehydration.[11,15]

Hyperosmolar diabetic non-ketotic coma constitutes part of a spectrum of severe metabolic disturbance in diabetes mellitus ranging from pure hyperglycaemic hyperosmolarity with non-significant ketoacidosis to DKA, with overlapping features in a third of patients.[12,15] A relative deficiency of insulin leads to hyperglycaemia. Unlike in DKA, there is no significant ketogenesis due to the presence of low levels of endogenous insulin sufficient to inhibit lipolysis but not gluconeogenesis. Lesser amounts of free fatty acid is diverted into ketogenic pathways.[6,11,12,15] Precipitants are varied and include cerebrovascular accidents (CVA), infection (most common precipitant, seen in 60% of cases), intercurrent illness, non-compliance with diabetic treatment, alcohol abuse, myocardial ischaemia, acute gastrointestinal illness and surgically induced stress.[7,15] A symptomatic *E. coli* urinary tract infection precipitating glycaemic decompensation may have contributed to our subject's acute presentation.

Hyperosmolar diabetic non-ketotic coma results in severe fluid depletion, electrolyte disturbance, profound hyperglycaemia and an altered mental state.[6,7] The guiding principles of therapy include aggressive rehydration, correction of electrolyte abnormalities, insulin therapy and treatment of any underlying illnesses.[17]

Hypoperfusion and hypotension requires aggressive fluid resuscitation until haemodynamic stability is achieved. Colloids and vasopressors are required if there is an inadequate response to fluid therapy.[12] Low cardiac output states due to myocardial dysfunction and arrhythmias require early identification

and treatment. Even if there is no haemodynamic disturbance, fluid depletion is severe. Deficits in the order of 100–200 ml/kg (mean 9–12 litres) result from the insidious evolution of hyperglycaemic decompensation over days to weeks[10,12,14,18] with failure to respond to thirst due to altered conscious state[12] and compromised access to fluids.[15]

The majority of authors[6,10,12,15,19] advocate initial expansion of circulating volume with normal (0.9%) saline in most cases of hyperosmolar diabetic non-ketotic coma as marked total body sodium deficit exists despite high or normal serum [Na^+] and it is maintained within the intravascular space for a longer period than hypotonic fluids.[6,7,12] In addition to replacement of sodium deficit, a more gradual lowering of serum tonicity is possible compared with dextrose-only solutions, reducing the risk of cerebral oedema especially in children aged less than 5 years who are more prone to this complication.[12,17] However, use of normal saline can lead to hypernatraemic hyperchloraemic acidosis.[12,19]

Vigilant assessment of haemodynamic and metabolic response to resuscitation remains the keystone in fluid therapy.[6] 500–1000 ml/h of normal saline will be required until haemodynamic stability is attained (usually achieved in the first 2 hours). Thereafter 250–750 ml/h of half (0.45%) normal saline is administered in the next 4 hours according to acuity and severity of fluid deficit.[6,12,15,20] 5% dextrose is added to the fluid regimen when serum [glucose] declines to 15 mmol/l to prevent hypoglycaemia.[6,7,15] Half the fluid and electrolyte deficit is replaced in the first 12–24 hours,[7,10] aiming for a serum osmolarity of 320 mOsm/kg and serum [glucose] of 15 mmol/l,[12] with a slower rate of correction taking place over the next 48 hours.[15,17] Cautious volume replacement with central venous pressure monitoring is warranted if there is limited cardiorespiratory reserve or renal impairment, with strict attention to fluid balance and close monitoring of urine output.[6,7]

Berger[7] and Small[11] advocate specific fluid regimens that are appropriate to the level of hypernatraemia. Normal saline is used if serum [Na^+] is less than 145 mmol/l. More severe hypernatraemia requires relatively more rapid reduction of hyperosmolarity with lesser concentrations of sodium chloride containing intravenous fluids. For instance, half normal saline is used when serum [Na^+] is 145–165 mmol/l, with 2.5% glucose proposed if serum [Na^+] is greater than 165 mmol/l. Matz[12] recommends hypotonic fluids if serum osmolarity is greater than 320 mOsm/l and isotonic fluids if serum osmolarity is less than 320 mOsm/l. However, serum osmolarity will not be immediately available to determine the type of fluid best suited to the patient.

In this patient, serum [Na^+] has been artefactually lowered to 111 mmol/l by severe elevation in serum [glucose], which causes free fluid to shift from the intracellular to extracellular compartment, therefore diluting serum [Na^+]. Every 3.47 mmol/l of serum [glucose] will lower serum [Na^+] by 1 mmol/l when severe hyperglycaemia is present, reflecting pseudohyponatraemia.[21] The corrected serum [Na^+] in this patient would have been approximately 134 mmol/l (normal 140 mmol/l), with the remaining 6 mmol/l of dilution being attributable to increased water retention due to inappropriately excessive anti-diuretic hormone secretion in an attempt to preserve extracellular volume[18,22] and insulin's antinatriuretic effect on the kidney.[12]

After a intravenous loading dose of 0.1 u/kg of soluble insulin, a low dose infusion of 0.1 u/kg/h (5–10 u/h) is employed to gradually lower serum [glucose].[6,14,15,19] The aim is to reduce serum [glucose] by 5 mmol/l every hour. More rapid attempts to achieve euglycaemia using higher doses of insulin (50–100 u every hour intra-muscularly[18]) is associated with a 25% risk of acute hypokalaemia and hypoglycaemia and are no longer used.[15] Furthermore, there is no evidence that high dose insulin interrupts ketogenesis and corrects metabolic derangements more effectively than a low dose infusion.[6,15,19] Aggressive correction of hyperglycaemia without repletion of fluid deficit may lead to vascular collapse from rapid reduction in serum [glucose] and acute shift of free water from the intravascular to intracellular space.[12,15] In the severely dehydrated state, hyperosmolar plasma helps to preserve circulating volume.[14] High-dose insulin causes relative serum hypotonicity with free fluid shifting into neurons rapidly leading to cerebral oedema in children.[17] This rarely occurs in adults.[6] As such, insulin infusion rate should be slowed down to 0.05 u/kg/h or 2 u/h once BSL reaches 15 mmol/l[12] and titrated according to hourly serum [glucose] measurements.[6,15] Ellis[17] recommends maintaining serum [glucose] at 10–15 mmol/l for the first 24 hours prior to further reduction to reduce risks of cerebral oedema. On the other hand, hyperglycaemia that is resistant to low dose insulin despite volume correction requires increased insulin infusion.[15]

Substantial total body potassium depletion occurring in hyperosmolar diabetic non-ketotic coma is the consequence of brisk osmotic kaliuresis. The degree of total body potassium depletion is often underestimated because of initially elevated or normal [$K+$],[12] which masks total body K^+ deficit. This is maintained by intravascular volume contraction in excess of K^+ losses, insulin deficiency and acidosis-induced transcellular shift of K^+ from the intracellular into

extracellular compartment.[6,7,15] A low serum [K^+] therefore suggests severe potassium depletion[15] and therefore requires aggressive K^+ replacement at 40 mmol/h.[6,7] If initial hyperkalaemia is present, K^+ replacement can be safely administered once serum [K^+] falls below 5.5 mmol/l, at a rate of 20 mmol/h.[6,7,12,14] Replenishment is started provided there is an adequate urine output, with 70% of K^+ administered being lost in the urine in the first 24 hours.[6,7] Complex shifts in serum [K^+] during the acute phase of treatment mandates close hourly measurement of serum [K^+].[12] If there is concurrent hypophosphataemia, potassium phosphate is preferred over potassium chloride, with the latter exacerbating hyperchloraemia.[12]

Although phosphate replacement makes physiologic sense, there is no controlled data to show that it alters outcome in uncontrolled diabetes unless [phosphate] is less than 0.5 mmol/l or the patient is symptomatic.[7,15] Routine phosphate replacement is therefore not indicated[14,15] because levels return to normal with rehydration and insulin therapy.[14] Phosphate ions can be administered at 10–15 mmol/h.[6] Routine administration of magnesium in hyperosmolar diabetic non-ketotic coma is safe and physiologically appropriate if levels fall below 0.6 mmol/l.[7]

There is no evidence to support the use of bicarbonate in hyperosmolar diabetic non-ketotic coma when arterial pH is greater than 7.1. Adverse effects of bicarbonate adminstration include hyperosmolar load and paradoxical intracellular acidosis within the central nervous system.[7,15,18] It is recommended that 44 mmol of bicarbonate and 15 mmol of K^+ be given every 2 hours until pH is greater than 7.[15] Empiric broad-spectrum antibiotics (covering Gram negative organisms) pending culture results may be beneficial if the patient is febrile or critically ill.[6] The risk of thromboembolic events due to hyperviscosity in hyperosmolar diabetic non-ketotic coma is reduced with prophylactic doses of subcutaneous heparin. Full anticoagulation carries a high risk of gastrointestinal bleeding.[6,7] Most patients need to be managed in an intensive care unit.[10,20]

Early detection and treatment of underlying precipitants (present in 50%) of hyperosmolar diabetic non-ketotic coma such as acute myocardial infarction, CVA and sepsis is crucial if the patient is to have an improved outcome. Addressing patient non-compliance with diabetic therapy is important in preventing further episodes of glycaemic decompensation.[6,7]

The main causes of death are sepsis, metabolic and cardiovascular decompensation,[6] thromboembolic complications and renal failure.[11,13] Mortality rates for hyperosmolar diabetic non-ketotic coma is three-fold higher than for DKA, ranging from 10% to 70%,[10,12,16] reflecting severe metabolic disturbances in elderly patients with prior comorbidities.[10] Delayed diagnosis is contributory and as a third of patients have no history of diabetes mellitus, a high index of suspicion needs to be maintained.[12,13,15,16] Inadequate treatment and specifically under-resuscitation[19] also plays a part in high mortality rates that have not changed despite advances in diabetic care.[17]

CVA can precipitate or become a complication of hyperosmolar diabetic non-ketotic coma, with diabetes mellitus being a well-recognized risk factor for thrombotic CVA.[23] Thirty per cent of patients with hyperosmolar diabetic non-ketotic coma have reversible neurological deficits that may mimic CVA.[12,20] A quarter of patients are unconscious on presentation.[12,15] On the other hand, prolonged hypoglycaemia will result in neurological damage. Therefore all patients presenting with neurological deficit, altered consciousness or confusion should have an early BSL measurement to detect and treat any glucose abnormality. Hyperosmolar diabetic non-ketotic coma needs to be considered when hyperglycaemia occurs in this situation.

This case illustrates an unusual complication of hyperosmolar diabetic non-ketotic coma, that of pulseless electrical activity cardiac arrest due to hyperkalaemia-related arrhythmia. Haemodynamic, metabolic and neurological recovery was achieved by early recognition and treatment of these life-threatening processes.

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