concentrations, and in practice their measurement may be limited to those patients in whom a particularly high or low result is likely to alter their risk status—that is, those with moderate hypercholesterolaemia. Accordingly we have standardised our criteria for assaying high density lipoprotein cholesterol, and a fortunate result has been the identification of this patient with hyper-α-lipoproteinaemia, a case of hypercholesterolaemia not warranting treatment.

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Grand Rounds—Hammersmith Hospital

Diabetes and rhabdomyolysis

A rare complication of a common disease

Rhabdomyolysis is common in diabetic patients with hyperosmolarity, although it is not always tested for. The most sensitive marker of muscle cell damage is serum creatine kinase concentration, which seems to correlate with the degree of damage incurred.[1] Acute renal failure secondary to rhabdomyolysis is well recognised, but an association with hypersmolarity has been reported in only a few cases. We present the case of a man who developed acute renal failure secondary to rhabdomyolysis with diabetic hyperosmolarity and discuss possible mechanisms that might have caused it.

Case history

A 47 year old Afro-Caribbean man presented to his local hospital with a 10 day history of lethargy, malaise, polyuria, and polydipsia. Twenty four hours before his admission he developed a fluctuating conscious level and had collapsed on a return flight from Jamaica, where he had spent the past month. He had a family history of non-insulin dependent diabetes mellitus. He drank moderate amounts of alcohol, took no regular medication, and had no history of substance abuse. On examination he was unwell but had no fever. He was tachycardic and tachypnoeic with a drop in blood pressure from 100/70 mm Hg when lying to 80/60 mm Hg when sitting. He had impaired consciousness but there was no focal neurological abnormality.

Initial investigations showed hypernatraemia (sodium concentration 150 mmol/l) and renal failure (urea 21 mmol/l, creatinine 567 μmol/l). His blood glucose concentration was greatly raised at 103 mmol/l, giving a serum osmolarity of 430 mmol/kg (normal 280-296 mmol/kg). His serum phosphate concentration was low at 0·23 mmol/l (0·8-1·5 mmol/l) and his creatine kinase concentration was raised at 1500 IU/l (24-195 IU/l). His haemoglobin concentration was 178 g/l, and white cell and platelet counts and a coagulation screen all gave normal results. Arterial blood gas analysis on air showed a partially compensated metabolic acidosis with a pH of 7·30, arterial oxygen tension 19 kPa, arterial carbon dioxide tension 2·7 kPa, and base excess −15. Urine analysis detected glucose and blood cells but no ketones. Urine microscopy showed five white cells and 40 red cells per high power field with occasional granular casts. Electrocardiography showed a sinus tachycardia with a rate of 150 beats per minute and his chest radiograph appeared normal. Renal ultrasonography showed normal sized kidneys with no evidence of obstruction.

He was rehydrated with intravenous fluids and his diabetes was controlled by giving insulin according to a sliding scale. He became oliguric despite good filling pressures and was therefore started on renal dose dopamine (3 μg/kg/min) and frusemide with dextrose-insulin and Calcium Resonium to control his hyperkalaemia. Four days after his admission he was transferred to our hospital because of persistent acidosis, hyperkalaemia, oliguria, and worsening renal failure.

On arrival he had impaired consciousness, had no fever, and was haemodynamically stable. There was no muscle tenderness or swelling. His renal failure had progresed such that his creatinine concentration was 1000 μmol/l with concomitant acidosis and hyperkalaemia. His serum creatine kinase concentration was 100 000 IU/l and he had raised aspartate aminotransferase and uric acid concentrations. His serum phosphate concentration was towards the upper end of the normal range at 1·35 mmol/l and he had myoglobinuria. Other investigations done to test for acute renal failure gave normal results. A toxicological screen and viral serology gave negative results. A muscle biopsy during the acute phase of his illness showed that the overall structure of the muscle was well preserved. There were a few small fibres with basophilic staining and large central nuclei that were regenerative in origin, indicating recent muscle injury (fig 1; top). The fibre type and glycogen content were normal and no lipid accumulation was found (fig 1; bottom).

We therefore diagnosed acute renal failure secondary to rhabdomyolysis with an associated non-ketotic diabetic state. He was given intravenous insulin and prophylactic heparin and remained dependent on dialysis for three weeks. He was discharged from hospital seven weeks after admission requiring no drugs. His diabetes was controlled by diet alone. Figure 2 shows the changes in serum creatinine and urine output with time. He became polyuric at around day 30, but his urine volumes returned to normal

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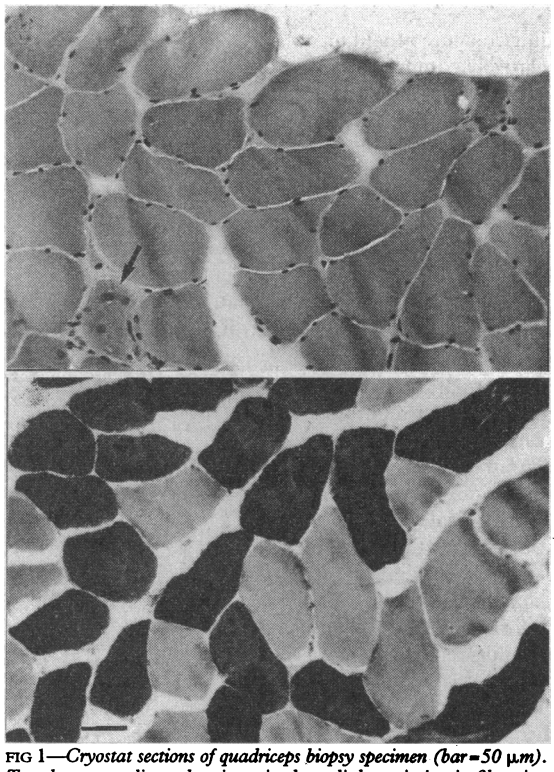

FIG 1—*Cryostat sections of quadriceps biopsy specimen (bar=50 μm). Top: haematoxylin and eosin stain shows little variation in fibre size. One basophilic regenerating fibre is seen (arrow). Bottom: myosin ATPase stain at pH 9-4 shows a normal distribution of type 1 (light) and type 2 (dark) fibres*

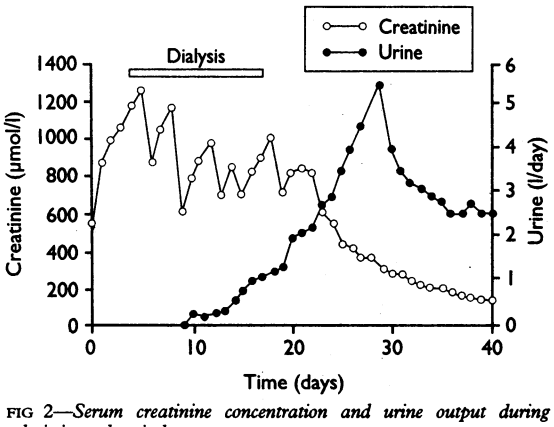

FIG 2—*Serum creatinine concentration and urine output during admission to hospital*

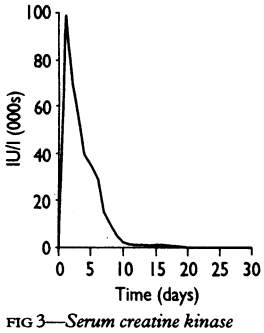

FIG 3—*Serum creatine kinase concentration during admission to hospital*

before discharge. Figure 3 shows the serum creatine kinase concentration over the same time. The rate of fall agrees with a known serum half life of about two days, suggesting there was no rhabdomyolysis after the initial insult.

Comment

Rhabdomyolysis is defined as skeletal muscle injury with release of muscle cell constituents into the plasma. It was first described by Bywaters and Beall in association with crush injuries during the second world war[2] and since then has been recognised as the cause of about 5% of cases of acute renal failure.[3]

Acute renal failure occurs in about 16% of patients with rhabdomyolysis.[4] There are no invariable clinical features, although muscle pain and swelling may be found. The release of muscle contents into the plasma causes hyperkalaemia, raised concentrations of creatinine and muscle enzymes, and hyperphosphataemia. Myoglobin is often not found in the urine because of its short plasma half life of 2-3 hours, but haematuria and proteinuria are common.[1] Treatment is similar to that for other causes of incipient acute tubular necrosis but alkaline diuresis is also done to prevent the dissociation of myoglobin into the toxic ferrihaemate moiety. Dissociation occurs if urinary pH falls below 5·6. It is also important to realise that compartment syndromes may develop, and these require prompt treatment to prevent further muscle damage.

There are many reported causes of rhabdomyolysis, the commonest being alcohol, generalised seizures, and muscle compression. In one large series a multifactorial aetiology was found in over 60% of patients presenting with rhabdomyolysis.[1] Diabetes is known to predispose to rhabdomyolysis in patients with hyperosmolarity. Out of 31 patients in one study, 16 had biochemical evidence of rhabdomyolysis (creatine kinase concentration greater than twice the upper limit of normal) with no clinical or electrocardiographic evidence of cardiac injury.[5] In this group, development of rhabdomyolysis was statistically associated with the severity of the serum hyperosmolarity and the presence of hypernatraemia. There was no statistical difference in potassium or phosphate concentrations between the two groups; although four patients were hypophosphataemic at admission, this was before creatine kinase concentrations peaked.

ACUTE RENAL FAILURE

Acute renal failure is relatively rare in diabetic patients with hyperosmolarity irrespective of the frequency of rhabdomyolysis. Arieff and Carroll found it in only one patient out of 33 studied despite prerenal uraemia being present in over half of the study population.[6] Acute renal failure may be rare in this situation because osmotic diuresis, which is provoked by a high renal glucose load, prevents the development of acute tubular necrosis.

There have been six case reports connecting diabetic hyperosmolar states with acute renal failure secondary to rhabdomyolysis.[7-12] Two patients had a history of diabetes and only one patient had documented myoglobinuria. Two of the patients were hypophosphataemic and subsequently became hyperphosphataemic, presumably because of the rhabdomyolytic process. The four patients who were initially hyperphosphataemic had peak creatine kinase concentrations earlier in the course of their disease, suggesting presentation at a later stage. Two of these patients required temporary dialysis and one died.

ROLE OF PHOSPHATE

Hypophosphataemia seems to be implicated in the aetiology of rhabdomyolysis. In a recent study 46 of 129 of patients with hypophosphataemia due to a variety of primary diseases had biochemical evidence of rhabdomyolysis.[13] Rhabdomyolysis has been reported in chronic alcoholics who are given intravenous fluids without added phosphate. Profound hyperphosphataemia developed within one to two days and rhabdomyolysis two to three days later.[14]

Experimental models suggest that depletion of intracellular adenosine triphosphate concentrations and subsequent failure of electrogenic membrane pumps contributes to rhabdomyolysis in hypophosphataemia.[15] Experiments in animals made hypophosphataemic by dietary deficiency suggest that occurrence of rhabdomyolysis is determined by the rate of fall of serum phosphate concentration and presence of pre-existing muscle cell damage.[16]

However, hypophosphataemia by itself is insufficient to cause rhabdomyolysis. Hypophosphataemia caused by omitting phosphate in total parental nutrition has never been reported to produce rhabdomyolysis.[17] It seems, therefore, that additional factors are required. Studies have shown a significant association between the development of rhabdomyolysis and the presence of serum hyperosmolarity and hypernatraemia.[5,13]

Discussion

CDP: Rhabdomyolysis leading to acute renal failure is a rare complication of this relatively common clinical condition. When this patient came to us it was unclear whether the rhabdomyolysis was directly related to the diabetes, and we were interested in the possibility that muscle compression or ingestion of toxic substances had occurred. However, the most toxic substance he had taken was a large quantity of sugary drinks because he had been very thirsty. I suspect this contributed to his hyperosmolar state. We were left with the conclusion that it was the diabetic hyperosmolar state that had led directly to rhabdomyolysis and acute renal failure.

JS: Do these patients get cardiac dysfunction?

CDP: Yes they do. He was fortunate not to have overt cardiac failure, although this is well reported in severe hypophosphataemia of this nature.

JS: Does rhabdomyolysis occur in the heart?

GML: As far as I am aware this has only been reported twice in conjunction with histological proof from postmortem examination. In our patient there was no clinical or echocardiographic evidence of myocardial damage and the creatine kinase heart isoenzyme accounted for less than 2% of the total enzyme.

MJW: You have implied that his renal failure was due to myoglobin, but his uric acid concentration was 1·2 mmol/l and I wonder if he had urate nephropathy.

CDP: An extremely high uric acid concentration is common in rhabdomyolysis because of its release from muscle cells, but he did have severely impaired renal function before his serum urate concentration became raised. Hyperuricaemia could, however, contribute to the development of renal failure in rhabdomyolysis.

AJR: However, there were no urate crystals in his urine.

CB: Are you sure that there was no evidence of muscle compression or injury on the return flight from Jamaica, associated with a near comatose state?

GML: Yes. Throughout the flight he was fully conscious and he had a rapid passage through customs to the local emergency department.

KAAD: When he first presented he had a relatively modest creatine kinase concentration for a large man, and yet he deteriorated rapidly. Is there any treatment that could have prevented his worsening renal failure?

CDP: An alkaline diuresis is often helpful, provided the patient is not oliguric. There is also some suggestion that rapid correction of hyperosmolarity may cause phosphate to enter cells and worsen hypophosphataemia, so gentle correction of this may be of benefit. At presentation he was probably already in established acute renal failure and management from that point is entirely supportive.

JS: Could he have had some underlying metabolic abnormality such as an inherited enzyme deficiency?

CDP: Clearly the commoner myopathies have been excluded by the investigations presented above.

FMM: There was no lipid accumulation and the overall architecture of the muscle was normal so I think that this is unlikely.

CDP: The other possibility to consider is a latent form of malignant hyperpyrexia. It has been suggested that this syndrome may be responsible for heat stroke or exercise induced rhabdomyolysis. This can be detected only by functional muscle studies. However, there was no family history to suggest an inherited muscle defect.

JS: Why is myoglobin so toxic to the tubules?

CDP: It is not the myoglobin but the ferrihaemate, an iron containing pigment that dissociates from myoglobin in acidic conditions in the tubules. It is a problem not only of protein precipitation but of direct proximal tubular toxicity from the pigment.

JS: Is this due to free radical attack?

CDP: The precise molecular mechanism of the toxicity is unclear.

SRB: This is a classic story of a diabetic patient becoming unwell and drinking large volumes of sugary drinks. Treating the hyperosmolar state more slowly might have been helpful. There have been suggestions that slow treatment may prevent cerebral oedema and other complications, but there is equal evidence that treatment should be prompt to limit the damage that hyperosmolarity may cause.

I thank Dr Caroline Sewry at the neuromuscular unit, Hammersmith Hospital, for preparing and interpreting the histological material.

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Update box for *Oxford Handbook of Clinical Medicine* (3rd ed), p 354

Nasal continuous positive airway pressure ventilation

During nasal continuous positive airway pressure ventilation pressure in the airways of a patient who is breathing spontaneously is kept positive relative to the atmosphere throughout the respiratory cycle. This is achieved by delivering air through a tight fitting nasal mask. Such ventilation increases the functional residual capacity.

Uses

- To splint collapsing airways in the sleep apnoea syndrome (p 362).
- To improve gas exchange—for example, in pulmonary oedema or pneumocystis pneumonia.

M K SRIDHAR

Anyone may submit an update box; all boxes are peer reviewed.