Hypercholesterolaemia: not all cases warrant treatment

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Consider hyper- α -lipoproteinaemia before starting lipid lowering drugs in patients with high total serum cholesterol concentrations

Increasing numbers of patients are being treated for hypercholesterolaemia on the basis of total cholesterol concentrations. We describe a 49 year old woman so treated whose high total cholesterol concentration was explained by a high density lipoprotein cholesterol concentration of 3.9 mmol/l and a serum apoprotein AI concentration of 2.75 g/l; this indicated hyper- α -lipoproteinaemia, a condition with no association with cardiovascular disease.

Case report

Following routine health screening by her general practitioner a 49 year old woman was found to have a raised serum total cholesterol concentration of 9.4 mmol/l. She had not smoked for 15 years, was not diabetic, was of normal weight, took regular exercise, and had no family history of ischaemic heart disease. She had no symptoms suggestive of cardiovascular disease and on examination had no corneal arcus and tendinous or cutaneous xanthomas. Her electrocardiogram was normal.

Her medical history included successful renal transplantation at the age of 37 and a total hysterectomy at the age of 45 followed by the start of hormone replacement treatment. One year later she was found to be moderately hypertensive and was started on a cardioselective β blocker (metoprolol). Her other medications were prednisolone (enteric coated) 10 mg twice daily, azathioprine 125 mg/day, and piperazine oestrone 1.5 mg/day.

After the finding of hypercholesterolaemia she was placed on a cholesterol lowering diet and her total cholesterol concentration fell to 8.1 mmol/l over the next two months. No further reduction was achieved, however, and treatment with bezafibrate was started. Eight weeks later her cholesterol concentration remained at 8.2 mmol/l, and simvastatin 10 mg at night was substituted. This reduced her total cholesterol concentration to 7.1 mmol/l, where it fell within the range for triggering low density lipoprotein cholesterol estimation.

Since April 1991 our laboratory computer at St James's University Hospital has been programmed automatically to request high density lipoprotein cholesterol and triglyceride analyses when the total cholesterol concentration is between 6.5 and 7.8 mmol/l. These are then used to calculate low density lipoprotein cholesterol values (by the Friedewald equation¹).

The values obtained were: high density lipoprotein cholesterol 3.9 mmol/l, low density lipoprotein cholesterol 2.8 mmol/l, triglyceride 0.8 mmol/l, and serum apoprotein AI concentration 2.75 g/l. High density lipoprotein cholesterol was measured by the magnesium-phosphotungstate precipitation method and apoprotein AI by rocket immunoelectrophoresis. This concentration of low density lipoprotein cholesterol carries a low risk for cardiovascular disease so the simvastatin was stopped. A subsequent sample, taken several months later, showed: total cholesterol 9.1 mmol/l, low density lipoprotein cholesterol 4.9 mmol/l, high density lipoprotein cholesterol 3.6 mmol/l, triglyceride 1.37 mmol/l, and apoprotein AI 2.85 g/l.

The serum high density lipoprotein cholesterol and apoprotein AI concentrations in the patient's two offspring were normal.

The rise in low density lipoprotein cholesterol from 2.8 mmol/l to 4.9 mmol/l was consistent with the withdrawal of simvastatin therapy. Although the patient's low density lipoprotein cholesterol concentration is now greater than 4.0 mmol/l, the desirable limit of the European Atherosclerosis Society guidelines,² her full lipid profile and medical history indicates a low risk of cardiovascular disease that does not warrant the use of lipid lowering drugs. Nevertheless, the patient should continue to follow advice appropriate to the whole population on diet, weight, and exercise, and further lipid assessment will be required with any change in her drug therapy.

Discussion

This patient illustrates the danger of viewing every patient with hypercholesterolaemia as a high risk candidate for cardiovascular disease. Treatment with such potent long term therapies as the hydroxymethyl glutaryl coenzyme A reductase inhibitors carries risks, including rhabdomyolysis, hepatitis, insomnia, and abdominal pain.³ The guidelines of the European Atherosclerosis Society and the British Hyperlipidaemia Association draw attention to the value of measuring high density lipoprotein cholesterol and low density lipoprotein cholesterol to assess an individual patient's need for medical care.⁴ On screening a general practice population Neil *et al* found that 16% (23% women *v* 9% men) of those with a total cholesterol concentration of 6.5 mmol/l or more and a normal triglyceride concentration had a high density lipoprotein cholesterol of 2.0 mmol/l or more and thus a lower cardiovascular risk than suggested by their total cholesterol concentration alone.⁵

The concentration of high density lipoprotein cholesterol may in fact be very high. Koizumi *et al* described a patient with a concentration of 7.83 mmol/l.⁶ In this and other series the hyper- α -lipoproteinaemia was accompanied by a moderate increase in the total cholesterol concentration with normal low density lipoprotein cholesterol and triglyceride concentrations.^{6,7} This increase in high density lipoprotein cholesterol may be secondary to other conditions such as alcoholism, inhalation of chlorinated hydrocarbon pesticides, and oestrogen administration,⁸⁻¹⁰ or it may be primary. Primary hyper- α -lipoproteinaemia is generally held to be inherited as an autosomal dominant trait associated with longevity.^{7,11} In our patient hormone replacement therapy with an unopposed oestrogen might have caused the hyper- α -lipoproteinaemia.^{7,10}

Identifying patients with hyper- α -lipoproteinaemia is clearly desirable as they may then be spared anxiety and expensive drug therapy. Measurement of high density lipoprotein cholesterol by laboratories in the United Kingdom, however, is often carried out on a random basis with wide differences in requesting patterns.¹² High density lipoprotein cholesterol concentrations are more complex and expensive to measure than total cholesterol or triglyceride

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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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Diabetes and rhabdomyolysis

A rare complication of a common disease

Rhabdomyolysis is common in diabetic patients with hyperosmolality, 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 hypersmolality 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 hyperosmolality 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 μ mol/l). His blood glucose concentration was greatly raised at 103 mmol/l, giving a serum osmolality 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 μ g/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 progressed such that his creatinine concentration was 1000 μ mol/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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