*A difficult case***Childhood onset insulin dependent diabetes presenting with severe hyperlipidaemia**

Godfrey Nyamugunduru, Helen Roper

Confronted with a child deteriorating during treatment of diabetic ketoacidosis, Godfrey Nyamugunduru and Helen Roper describe how the child's management was complicated by gross hyperlipidaemia. At the point where the child's condition was deteriorating despite conventional management we invited two experts—Gilbert R Thompson and J I Mann—to suggest a course of action. The original authors then describe how they did manage the case, and our experts comment again.

A mild increase in serum lipid concentrations is a common feature of diabetic ketoacidosis. Severe hyperlipidaemia with milky plasma is rare.¹ It may occur at presentation of diabetes mellitus² or in poorly controlled diabetes.¹ We report a case of a child with newly diagnosed diabetes who presented with severe hyperlipidaemia.

Case report

A 14 year old girl was referred by her general practitioner with a week's history of sore throat, fever, and headache and a two day history of intermittent vomiting. She was taking amoxycillin, which had been prescribed five days earlier. She had no relevant past or family history. She looked well and was afebrile and not dehydrated. Her blood pressure was 115/75 mm Hg. The only abnormality noted was lipaemic retinalis. Blood was taken for measuring glucose concentration, thyroid function, and lipid analysis. The blood appeared creamy pink and biochemical analysis was impossible because the blood was grossly lipaemic even after attempted centrifuge separation. She was admitted for further investigation of hyperlipidaemia.

The next morning she was unwell with frank clinical features of diabetic ketoacidosis. She had acute abdominal pain and was hyperventilating. She had cold cyanosed peripheries, with a small volume pulse at a rate of 180 per minute and a blood pressure of 150/70 mm Hg. Her blood sugar concentration, measured by Boehringer Mannheim (BM) test, was very high (above 28 mmol/l), and a large amount of ketones and glucose was present in the urine. Because of the milky serum it was impossible to measure blood glucose, urea, electrolytes, or amylase values. She was resuscitated with colloid (Haemocel), total volume 1000 ml (20 ml/kg), and was started on insulin (human Actrapid), infused at 0.1 U/kg/h. Pethidine 50 mg (intravenous) was given as analgesia. She was transferred to the intensive care unit.

Blood gases measured on the unit's gas analyser (ABL 510 Radiometer) showed profound metabolic acidosis (pH 7.09, Pco₂ 2.18 kPa, standard bicarbonate 7.8 mmol/l, base excess -23.4 mmol/l). Her blood pressure was 110/70 mm Hg, pulse 180 per minute, central venous pressure (from midaxillary line) 14 cm H₂O, axillary temperature 36.8°C, and peripheral temperature 22.2°C. She was further rehydrated and her central venous pressure was maintained at 16-18 cm H₂O. Her peripheral perfusion gradually improved with the toe-core temperature gap maintained at 1-2°C

and her blood pressure stabilised between 145/90 and 150/90 mm Hg. She was polyuric. She required up to 10 U/h insulin (0.25 U/kg/h) to maintain a blood sugar concentration of 10-15 mmol/l.

Despite adequate rehydration and insulin therapy she continued to deteriorate clinically accompanied by further worsening of the metabolic acidosis. By 15 hours after admission to the intensive care unit her level of consciousness had begun to deteriorate. She was intubated and ventilated. Despite infusions of sodium bicarbonate 8.4%, total 300 ml, the metabolic acidosis persisted.

It was not clear whether the primary disease was hyperlipidaemia complicated by acute pancreatitis producing the metabolic upset or diabetes mellitus presenting as severe hyperlipidaemia. Repeated abdominal ultrasound showed no abnormality of the pancreas. Later analysis of serum after solvent extraction showed an amylase of 64 U/l (normal 80-180). There was thus no evidence for pancreatitis.

The clinical problem was the subsequent management of this 14 year old patient with diabetic ketoacidosis and severe hyperlipidaemia who had a severe and deteriorating metabolic acidosis despite the measures described above.

- 1 Bagdade JD, Porte D, Bierman EL. Diabetic lipaemia: a form of acquired fat induced lipemia. *N Engl J Med* 1967;276:427-33.
- 2 Chance GW, Albutt EC, Edkins SW. Serum lipids and lipoproteins in diabetic children. *Lancet* 1969;i:1126-8.

First priority is to decrease the severity of hyperchylomicronaemia

Gilbert R Thompson

This girl is acutely ill and in the first instance it is immaterial whether her hyperlipidaemia is primary or secondary. Her main requirement is for treatment which decreases the severity of the hyperchylomicronaemia as rapidly as possible. This is best achieved by plasma exchange using a continuous flow blood cell separator with heparin as the anticoagulant and 4.5% human albumin as the exchange medium.

Heparin has the advantages over citrate that it is not hypocalcaemic and that it releases lipoprotein lipase into the circulation, thereby promoting lipolysis and helping to reduce the concentration of triglyceride-rich chylomicrons in plasma.

Plasma exchange not only reduces the triglyceride concentration within a few hours but also decreases the

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accompanying plasma hyperviscosity. This induces prompt relief of abdominal pain due to acute pancreatitis,¹ as well as rapidly improving the level of consciousness in diabetic coma.² In the presence of severe hypertriglyceridaemia an assay of urinary amylase excretion is a more useful diagnostic test of acute pancreatitis than is a serum amylase measurement.^{2,3}

An alternative treatment to plasma exchange would be total parenteral nutrition via the intravenous route.⁴ Were this approach to be used, however, the need to avoid infusing Intralipid and thus having to rely on glucose as the main caloric source might render control of this patient's diabetes even more problematical.

The high insulin requirement and severity of ketoacidosis make it likely that the hyperlipidaemia was secondary to diabetes rather than vice versa. However, it is important to exclude genetic defects which could have caused the hypertriglyceridaemia and precipitated acute pancreatitis, thereby aggravating the hyperglycaemia. These include type III hyperlipoproteinaemia, which in an adolescent girl would have to be due to one of the very rare dominant mutations of the apolipoprotein E (apoE) gene and deficiency of lipoprotein lipase or its cofactor, apolipoprotein CII (apoCII). The relevant diagnostic tests are lipoprotein electrophoresis and apoE phenotyping for type III, plus assaying postheparin activity in plasma and undertaking isoelectric focusing of delipidated very low density lipoprotein to establish whether apoCII is present.

Type III hyperlipoproteinaemia is very responsive to fibrate therapy, whereas deficiency of lipoprotein lipase or apoCII necessitate adherence to a strict low fat diet. In affected women hypertriglyceridaemia can be greatly aggravated by pregnancy or exogenous oestrogens, both of which need to be excluded, even in a 14 year old. Here again plasma exchange has proved its usefulness as a means of rapidly controlling severe hypertriglyceridaemia complicated by acute pancreatitis.⁵

- 1 Betteridge DJ, Bakowski M, Taylor KG, Reckless JPD, De Silva SR, Galton DJ. Treatment of severe diabetic hypertriglyceridaemia by plasma exchange. *Lancet* 1978;i:1368.
- 2 Gerard A, Schooneman F, Guine JM, Roche G, Canton P, Dureux JB, et al. Treatment by plasma exchange of a patient with hyperlipidemia and diabetic ketoacidosis with lesional pulmonary oedema and acute pancreatitis. *Vox Sang* 1982;43:147-50.
- 3 Lesser PB, Warshaw AL. Diagnosis of pancreatitis masked by hyperlipemia. *Ann Intern Med* 1975;82:795-8.
- 4 Weinberg RB, Sitrin MD, Adkins GM, Lin CC. Treatment of hyperlipidemic pancreatitis in pregnancy with total parenteral nutrition. *Gastroenterology* 1982;83:1300-5.
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Late diagnosis of diabetic ketoacidosis and underlying disease influence response to treatment

P J Manning, W Sutherland, J I Mann

This patient with diabetic ketoacidosis has the chylomicronaemia syndrome with plasma triglyceride concentrations in excess of about 45 mmol/l as judged by the presence of lipaemia retinalis. In addition, cerebral oedema, lactic acidosis, pancreatitis, and sepsis may also be present.

A reduced level of consciousness in a child with diabetic ketoacidosis may indicate the presence of cerebral oedema. The potential consequences of cerebral oedema justify immediate administration of intravenous mannitol followed by computed tomography or magnetic imaging resonance scanning of the brain to confirm or refute this diagnosis. The diabetic ketoacidosis should be managed in the usual manner with particular attention paid to maintaining optimal fluid balance and glucose control.

Late diagnosis of diabetic ketoacidosis probably accounted for the patient being in a state of "shock" (low volume pulse, tachycardia, and poorly perfused peripheries) when appropriate treatment was started. This shocked state may be explained by dehydration alone or in combination with a second pathological process such as sepsis. In this setting poor tissue perfusion is a potent stimulus for lactic acid production. Serum lactate concentrations should be measured. Although bicarbonate therapy for lactic acidosis remains controversial, large quantities may be required to raise arterial pH. In addition, ensuring adequate oxygenation is important. Septic shock should be considered and a source of underlying sepsis sought. The history of prior headache, vomiting, and fever indicate possible central nervous system infection. The possibility of infection is sufficiently likely to warrant the administration of broad spectrum antibiotics after obtaining appropriate cultures.

Pancreatitis, as a result of the chylomicronaemia syndrome, cannot be ruled out as a cause of the abdominal pain and unresolving metabolic acidosis. Apparently normal serum amylase values after solvent extraction to remove interfering triglycerides does not exclude a diagnosis of pancreatitis. Although most patients with pancreatitis due to chylomicronaemia have raised serum amylase concentrations, this is not invariably the case. Also, solvent extraction of serum does not exclude the possibility that a non-triglyceride inhibitor of the amylase assay¹ might lead to falsely low serum amylase values. These should be retested using diluted serum.² Serial ultrasound examinations are not sensitive enough to rule out pancreatitis. It would therefore be appropriate to treat this patient as having acute pancreatitis while excluding other causes of acute abdominal pain.

The most likely cause of this patient's chylomicronaemia is the virtual absence of lipoprotein lipase activity secondary to severe insulin deficiency as a result of diabetes and acute infection. Acute infection may raise levels of stress hormones, which in turn would exacerbate the insulin deficiency and chylomicronaemia. Chylomicronaemia and lipaemia retinalis during diabetic ketoacidosis have been observed previously in a child, in whom plasma lipid values returned to normal when the diabetic ketoacidosis was successfully treated.³ Usually diabetes is accompanied by the chylomicronaemia syndrome only if an independent familial hypertriglyceridaemia is also present. Rarely, chylomicronaemia is due to a genetic deficiency in lipoprotein lipase or in the apolipoprotein CII activator of the enzyme, but genetic lipoprotein lipase deficiency usually manifests itself in early childhood and is seldom associated with diabetes. It is theoretically possible that hyperlipidaemia resulted in pancreatitis, which in turn caused diabetes, but this

seems unlikely. In the unlikely event that pronounced hypertriglyceridaemia persisted after successful treatment of the diabetic ketoacidosis then these genetic disorders would need to be considered.

- 1 Lesser PB, Warshaw AL. Diagnosis of pancreatitis masked by hyperlipidaemia. *Ann Intern Med* 1975;82:795-8.
- 2 Fallat RW, Vester JW, Glueck CJ. Suppression of amylase activity by hypertriglyceridaemia. *JAMA* 1973;225:1331-4.
- 3 Blackett PR, Holcombe JH, Alaupovic P, Fesmire JD. Case report: plasma lipids and apolipoproteins in a 13 year old boy with diabetic ketoacidosis and extreme hyperlipidemia. *Am J Med Sci* 1986;291:342-6.

Actual management: partial separation of excess lipid from plasma

Godfrey Nyamugunduru, Helen Roper

We formulated a hypothesis to explain our patient's progressively worsening metabolic acidosis despite treatment for shock and hyperglycaemia. We proposed that the oxygen carrying capacity of her blood was impaired by the lipid, leading to tissue hypoxia and lactic acidosis. Plasma lactic acid concentrations could not be measured. We hoped our patient would be improved by removal of some of the excess lipid.

We first tried lipid separation by plasmapheresis. This method failed as the grossly lipaemic blood clogged the plasma filter. We next tried a cell separator but this machine failed to distinguish blood cells from the lipaemic sludge and the tubing became clogged and blocked. Eventually separation by centrifuge was successful. A unit of blood (450 ml) was removed from the patient through a femoral venous line and centrifuged, separating the red cells from lipaemic serum. The red cells were made up to 450 ml with albumin and retransfused. A unit of blood after centrifugation and removal of the red cell fraction is shown in figure 1. In all, four units of blood were removed from the patient and treated similarly. After this procedure the metabolic acidosis quickly improved and resolved.

The patient was extubated on day 4 after admission and discharged home on day 12 completely well with no neurological problems. She was discharged on insulin (Humulin M3) 10 U twice daily. She was prescribed a diet with moderate fat restriction and a carbohydrate intake of 210-240 g/day. Her hyperlipidaemia gradually improved and by six weeks after discharge had completely resolved (table 1). Her lipid restriction was then discontinued. A year later she remains well and her diabetes is well controlled on Humulin M3, 30 U in the morning and 20 U in the evening (1 U/kg/day).

Thyroid function was normal: thyroid stimulating hormone 1.2 mU/l (normal 0.3-3.8) and free thyroxine 17.3 pmol/l (normal 11.0-24.0). Her mother's and father's lipid profiles were normal. Since her hyperlipidaemia had completely resolved with insulin therapy it was clear the hyperlipidaemia was secondary to diabetes mellitus and there was no coexisting primary lipid disorder.

Comment

A study in 1969 of 135 children aged 10 months to 13.5 years with newly diagnosed diabetes mellitus showed that up to 64% had total serum lipid values raised above the normal range before treatment.²

Fig 1 A unit of patient's blood after separation and removal of red blood cells

Three of the children had creamy serum at the time of diagnosis. In all, the hyperlipidaemia returned to normal with insulin therapy. There have been other reports of children with severe hyperlipidaemia at presentation with diabetes mellitus. Ponder *et al* described a 6 year old girl with new onset diabetes mellitus and ketoacidosis with severe hyperlipidaemia and creamy pink blood (triglycerides 168 mmol/l, cholesterol 26 mmol/l).³ Blackett *et al* reported a similar case of a 13 year old boy (triglycerides 163 mmol/l, cholesterol 29 mmol/l).⁴ In both cases the ketoacidosis resolved with insulin therapy and normal serum lipid values were achieved in two months.

Our patient presented with signs of hyperlipidaemia and the diagnosis of diabetes mellitus was delayed. Simple tests of urine and blood sugar were not done on admission and the lipaemic serum interfered with formal glucose analysis. If diabetes mellitus had been diagnosed earlier the management problems described might not have occurred. We believe our patient is the first case of severe diabetic hyperlipidaemia reported where partial lipid separation was performed in order to reverse intractable metabolic acidosis.

The cause of hyperlipidaemia in insulin dependent diabetes mellitus is poorly understood. The most popular view is that insulin deficiency results in subnormal lipoprotein lipase activity in adipose tissue, leading to reduced removal of lipid from plasma.^{1 2 4 5} The degree of hyperlipidaemia is not related to age, sex, blood sugar concentration, or severity of ketoacidosis.² It is not understood why a few diabetic children present with severe hyperlipidaemia. Those presenting in this way may be biologically different from the rest of the diabetic population, perhaps in the regulation of function of their lipoprotein lipase.

Table 1 Lipid profile from admission to 10 weeks later

	Normal	Day 1-3 admission	Day 4	Day 5	2 weeks	6 weeks	10 weeks
Cholesterol (mmol/l)	3.6-6.5	Too turbid	17.0	12.5	11.3	4.5	3.9
Triglycerides (mmol/l)	<2.0	Too turbid	43.3	10.1	7.6	2.1	0.9
HbA _{1c} (%)	<5	Too turbid	13.8	—	7.6	—	6.0

- 1 Bagdade JD, Porte D, Bierman EL. Diabetic lipaemia: A form of acquired fat induced lipemia. *N Engl J Med* 1967;276:427-33.
- 2 Chance GW, Albutt EC, Edkins SW. Serum lipids and lipoproteins in diabetic children. *Lancet* 1969;i:1126-8.
- 3 Ponder SW, Elerian L, Travis LB. Extreme hyperlipidemia in type 1 diabetes mellitus: case presentation. *Clin Pediatr* 1993;32:375-6.
- 4 Blackett PR, Holcombe JH, Alaupovic P, Fesmire JD. Plasma lipids and apolipoproteins in a 13 year old boy with diabetic ketoacidosis and extreme hyperlipidemia: case presentation. *Am J Med Sci* 1986;291:342-6.
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Traitement héroïque?

Gilbert R Thompson

The authors' proposal that the oxygen carrying capacity of the blood was impaired by the severity of the hyperlipidaemia is probably correct, inasmuch as it reflects hypoperfusion due to the accompanying hyperviscosity. The initial failure of plasmapheresis was presumably due to their using a hollow fibre plasma separator, which is prone to blockage by chylomicrons. It is not clear what type of cell separator they tried next, but had it been an old fashioned Aminco Celltrifuge, which separates by online centrifugation, they might

have been more successful than they were. The method they eventually used, manual plasmapheresis, was first described by de Gennes *et al* in 1967 as "traitement héroïque."¹

- 1 de Gennes JL, Touraine R, Maunand B, Truffert J, Laudat P. Formes homozygotes cutaneo-tendineuses de xanthomatose hypercholestérolémique dans une observation familiale exemplaire. Essai de plasmaphérèse à titre de traitement héroïque. *Bull Mem Soc Hop Paris* 1967;118:1377-402.

Hyperchylomicronaemia might have resolved anyway

P J Manning, W Sutherland, J I Mann

The authors describe resolution of the metabolic acidosis and improvement in the clinical condition in parallel with plasma exchange. They provide a strong case for a trial of this procedure in this very uncommon clinical situation. Nevertheless, severe hyperchylomicronaemia associated with diabetic ketoacidosis usually resolves with conventional therapy, including meticulous attention to fluid and electrolyte balance. Despite the impressive temporal association between plasma exchange and clinical improvement, it is conceivable that even in this situation the hypertriglyceridaemia would have cleared as the metabolic disturbances were brought under control. We also believe that a deteriorating level of consciousness in a child with diabetic ketoacidosis should be treated as cerebral oedema until proved otherwise.

A PAPER THAT CHANGED MY PRACTICE

Making sense

During my medical house job the only people with hypertension whom I saw were those who were admitted with the consequences of cardiovascular disease. I was therefore desperately worried that my father who was hypertensive was about to have a stroke or a myocardial infarction. Fortunately, my next job was a trainee in general practice, where I daily saw people with hypertension who were living fairly normal lives, which helped to get things back in perspective.

That latter post, and one in accident and emergency, followed by three years out of medicine, helped me to put the acute and chronic pathology I had seen and read about into a population based context. This made me uncomfortable, however, when I went back into hospital based specialties. I was expected to admit patients whom I felt could be managed out of hospital; to investigate them to exclude rare conditions; and recall them for repeated follow up rather than discharge them.

I then read the paper by White and his colleagues describing patient reported illness.¹ One thousand adults were asked to record illness episodes and their outcomes, in terms of contact with health services, over a one month period. Seven hundred and fifty of them had one or more illnesses or injuries but only 250 of these, that is one third of those who had symptoms, consulted a doctor. Only nine of these were admitted to hospital, and only one was referred to a tertiary centre.

This paper raised serious questions about the nature of the clinical experiences of most junior doctors and students of the health professions, particularly in teaching hospitals, and possibly that of some of their teachers and consultants and those who write medical text books. It confirmed to me that I was a misfit in hospital.

I then went into community practice in the days before it was popular and when an important part of the work was well baby clinics, and where by definition all the patients even those in residential placements were in a community rather than a hospital setting. Here I found an environment where children were normal; where the majority of their illnesses and upsets were managed by their parents; and where for the most part the children got better in the end without antibiotics or admission to hospital, which was fortunate since I did not have a prescription pad.

White and his colleagues verbalised in their paper what I felt was the reality for the families I saw; community paediatrics was the nearest I could get to that reality as a doctor. It helped me to make sense of my experience both inside and outside medicine.

Since then I remind myself and my students that we see a very unrepresentative sample of children; that there are an awful lot of illnesses, both numerically and in their variety, that we never see; that the children we do see are not necessarily the sickest; and that we do not necessarily have to investigate and treat every child we see.

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- 1 White KL, Williams TF, Greenberg BG. The ecology of medical care. *NEJM* 1961;265:885-92.

We welcome filler articles of up to 600 words on topics such as *A memorable patient*, *A patient that changed my practice*, *My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk.