Thrombocytopenia in hypothermia: a common but poorly recognised complication

Thrombocytopenia is a poorly recognised complication of accidental hypothermia, although it has been observed during the deep hypothermia used in cardiac surgery.¹ Villalobos *et al* showed that sequestration of platelets in the hepatic and splenic circulation is the main mechanism for the thrombocytopenia and that most of the platelets return to the circulation on rewarming.² The thrombocytopenia may also reflect other disorders including disseminated intravascular coagulation,³ and hypothermia may have a direct effect on the bone marrow.⁴ We report two cases of thrombocytopenia as a complication of hypothermia in the elderly.

Case reports

CASE 1

An 82 year old woman was found collapsed at home. On admission she was unconscious and hypothermic with a rectal temperature of 27°C. Pulse was 60 beats/minute regular and blood pressure 120/90 mm Hg. In the chest there were widespread coarse crackles. Abdominal and neurological examinations were normal. She had a considerable epistaxis and bruised easily after venesection. She was not receiving any drugs.

Investigations showed a haemoglobin concentration of 13.2 g/dl, white cell count $5.8 \times 10^9/l$, and platelet count $33 \times 10^9/l$. Serum potassium concentration was 5.7 mmol(mEq)/l, sodium 145 mmol(mEq)/l, urea 10.4 mmol/l (62 mg/100 ml), creatinine 130 μ mol/l (1.5 mg/100 ml), and blood glucose 5.2 mmol/l (94 mg/100 ml). Arterial blood gas tensions (on air) were: pH 7.18, carbon dioxide tension 6.3 kPa (47 mm Hg), and oxygen tension 8.5 kPa (64 mm Hg). Prothrombin time, kaolin cephalin clotting time, and thrombin time, fibrinogen concentration, results of thyroid function tests, and plasma cortisol concentration were all normal. A chest x ray film showed consolidation of the right middle lobe. An electrocardiogram was normal.

On rewarming the platelet count rose to $230 \times 10^9/l$ by the third day of admission. Her pneumonia resolved after treatment with cefuroxime and metronidazole.

CASE 2

An 83 year old woman was found unconscious in a cold room. On admission she was unrousable and her rectal temperature was 31.9°C. She was in atrial fibrillation with blood pressure 140/95 mm Hg. Examination was otherwise normal. After venesection there was considerable bruising of both forearms. Investigation showed a haemoglobin concentration of 15.9 g/dl, white cell count $4.8 \times 10^9/l$, and platelet count $62 \times 10^9/l$. Electrolyte concentrations were normal and blood glucose 3.7 mmol/l (67 mg/100 ml). Results of coagulation screening and thyroid function tests, serum bilirubin concentration, and alkaline phosphatase activity were normal; but serum aspartate transaminase activity was 98 IU/l.

With gradual rewarming and intravenous fluids her conscious level improved over 12 hours. The platelet count rose to $249 \times 10^9/l$ within one week.

Comment

Although thrombocytopenia is a recognised complication of infection, in case 1 the patient did not have septicaemia and the recovery of the platelet count corresponded more closely with rewarming than with the resolution of the pneumonia. Disseminated intravascular coagulation is reported to occur in accidental hypothermia and may explain the low platelet count, but in neither patient was there any evidence for this. A necropsy study of people who died of hypothermia, however, showed multiple haemorrhagic lesions and visceral infarctions,⁵ suggesting that many of these patients may have had thrombocytopenia associated with disseminated intravascular coagulation, so this condition may be commoner than has been clinically recognised.

Although the thrombocytopenia observed in hypothermia is rarely severe enough to cause a coagulation disturbance, the potential danger of bleeding remains. We suggest that a full clotting screen, including a platelet count and fibrinogen concentration, should be included in the initial management of these patients. The thrombocytopenia generally reverses when the patient is warmed, although in one study it worsened.³ Care is therefore advised in the rewarming process. More studies are needed to elucidate the pathogenetic mechanism for the disseminated intravascular coagulation in hypothermia. On balance it would seem logical to give prophylactic

platelet transfusions to patients with platelet counts below $20 \times 10^9/l$, or below $50 \times 10^9/l$ if there is evidence of bleeding.

We thank Dr P Gower for his helpful comments.

- 1 Waddell WG, Fairby HB, Bigelow WG. Improved management of clinical hypothermia. *Ann Surg* 1957;146:542-4.
- 2 Villalobos TH, Adelson E, Riley PA, Crosby WH. A cause of the thrombocytopenia and leucopenia that occurs in dogs during deep hypothermia. *J Clin Invest* 1958;37:1-7.
- 3 Mahajan SL, Myers TJ, Baldini MG. Disseminated intravascular coagulation during rewarming following hypothermia. *JAMA* 1981;245:2517-8.
- 4 O'Brien H, Amess JA, Mollin DL. Recurrent thrombocytopenia, erythroid hypoplasia and sideroblastic anaemia associated with hypothermia. *Br J Haematol* 1982;51:451-6.
- 5 Duguid H, Simpson RG, Stowers JM. Accidental hypothermia. *Lancet* 1961;iii:1213.

(Accepted 26 March 1985)

Charing Cross Hospital, London W6

P J EASTERBROOK, BSC, MB, house physician in medicine
H P DAVIS, MRCPATH, lecturer in haematology

Correspondence to: Dr P Easterbrook, Department of Cardiology, John Radcliffe Hospital, Headington, Oxford.

Mixed malarial infection due to *Plasmodium falciparum* and *P vivax*

We report on a man who developed both *Plasmodium falciparum* malaria resistant to chloroquine and *P vivax* malaria that may have been resistant to primaquine.

Case report

A 26 year old man returned to Italy in September 1983 after having stayed for one month in a village in Uttar Pradesh, India. On returning home he had chills, vomiting, headache, muscle pains, and fever (39.5°C). Malaria parasites of unidentified species were found and 1500 mg chloroquine base prescribed over three days. He became afebrile after two days. A week later the fever returned, and, without medical advice, he repeated the previous treatment. The fever resolved, but 20 days later he experienced evening fevers and night sweats.

On presentation he was afebrile, slightly jaundiced, and alert. The spleen was palpable 6 cm below the costal margin. A blood film was positive for *P falciparum*, but the parasitaemia was not high; gametocytes could be seen. Laboratory results showed leucopenia, slightly abnormal liver function, and a modest increase in bilirubin concentration. He was prescribed quinine sulphate 650 mg three times daily for 10 days, pyrimethamine 25 mg twice daily for three days, and sulphadoxine 500 mg twice daily for five days.

He did not travel to the tropics or endemic countries again and was well until March 1984, when during a visit to Atlanta, Georgia, United States, he once again experienced fever and headache. *P vivax* malaria was diagnosed at the Centers for Disease Control. Chloroquine 600 mg base for three days and then primaquine 15 mg base daily for 14 days were prescribed. This primaquine schedule is currently recommended as the usual dosage for radical cure of *P vivax* malaria.^{1,2} The patient, who had always shown good compliance, followed the recommended schedule.

A few days after his return to Italy in November symptoms of malaria recurred. The spleen was enlarged 7 cm below the costal margin, and a blood film was again positive for *P vivax*. Chloroquine 1500 mg base over three days and then primaquine 45 mg base plus chloroquine 300 mg base weekly for eight weeks were prescribed.³ We chose this intermittent high dose regimen to overcome drug resistance and to avoid possible gene linked drug induced haemolysis, although he had normal concentrations of glucose-6-phosphate dehydrogenase.¹ After completing the course in January 1985 without any untoward side effects he remained in good health. Before we can state that this high dosage was effective against relapse, however, 12 months will have to elapse.

Comment

Strains of *P falciparum* resistant to chloroquine are well known in Uttar Pradesh. Strains of *P vivax* requiring a higher dose of primaquine for radical cure have been reported from the south west Pacific.⁴ In Tamil Nadu, India, 1.3% of over 8000 people infected with *P vivax* relapsed after a course of primaquine lasting only five days. On the other hand, in some areas of Thailand 30% of patients relapsed after receiving 15 mg daily for 14 days.⁴ Mixed infections with *P vivax* and *P falciparum* are quite common in India and have been reported

previously. Usually *P vivax* is superimposed on *P falciparum* so that when the patient has apparently recovered *P vivax* malaria recurs.

This case of double infection with two relapses (recrudescences)⁵ of *P falciparum* malaria after chemotherapy with chloroquine and a relapse of *P vivax* malaria after the usual dosage of primaquine for radical cure confirms the increasing importance of the problem of drug resistant malaria imported from the tropics into Europe.

- 1 Rollo IM. Drugs used in the chemotherapy of malaria. In: Gilman AG, Goodman LS, Gilman A, eds. *The pharmacological basis of therapeutics*. 6th ed. New York: Macmillan, 1980:1038-69.
- 2 Bruce-Chwatt LJ. *Essential malariology*. 2nd ed. London: Heinemann, 1985: 224-5.
- 3 Alving AS, Johnson CF, Tarlov AR, Brewer GJ, Kellermeyer RW, Carson PE. Mitigation of the haemolytic effect of primaquine and enhancement of its action against exoerythrocytic forms of the Chesson strain of *Plasmodium vivax* by intermittent regimens of drug administration. *Bull WHO* 1960;22:621-31.
- 4 Peters W. Antimalarial drug resistance: an increasing problem. *Br Med Bull* 1982; 38:187-92.
- 5 Bruce-Chwatt LJ. Terminology of relapsing malaria: enigma variations. *Trans R Soc Trop Med Hyg* 1984;78:844-5.

(Accepted 18 March 1985)

Spallanzani Hospital for Infectious Diseases, Unit of Tropical Medicine, USL RM/16, Rome, Italy

LORENZO SAVIOLI, MD, physician in charge of unit
ANNA PAOLA DE FELICI, MD, senior registrar, laboratory
MARIA GRAZIA PAGLIA, BSc, registrar, laboratory
GIUSEPPE VISCO, MD, chief IInd division

Correspondence to: Dr L Savioli, Vicolo del Farinone 24, 00193 Rome, Italy.

Increased serum pancreatic enzymes after treatment with methylprednisolone: possible evidence of subclinical pancreatitis

On the basis of anecdotal clinical evidence and the results of giving steroids to experimental animals it has been claimed that steroids may be associated with acute pancreatic injury. This report provides evidence that the serum concentrations of the three pancreatic enzymes (trypsin, lipase, and amylase) may increase after administration of large intravenous doses of methylprednisolone.

Patients, methods, and results

Ten patients with progressive endocrine exophthalmos (euthyroid and with normal renal function) were included in this study. Seven had previously been thyrotoxic and been treated with carbimazole or radioactive iodine. Two were currently receiving carbimazole 10 mg daily. One was hypothyroid and receiving a replacement dose of thyroxine 0.1 mg daily. Two had not had any thyroid dysfunction. All were treated with 1 g methylprednisolone in 500 ml saline intravenously over two hours on three consecutive days.

Blood samples were collected before the administration of methylprednisolone and daily after treatment for several days. In four patients blood samples were also collected at half hour intervals for three hours after the first methylprednisolone infusion. Serum immunoreactive trypsin concentration was measured by radioimmunoassay using a kit (Hoechst) as described previously.¹ Total and pancreatic amylase and pancreatic lipase concentrations were measured by kits.^{2,3}

In all 10 patients serum immunoreactive trypsin concentrations increased considerably (by 35-109%) after administration of methylprednisolone (table). This was paralleled by similar increases in pancreatic amylase and lipase concentrations. Salivary amylase activity in the serum did not alter. Immunoreactive trypsin concentration peaked on days 5-8 after the infusion, the peak occurring on day 5 in five patients. Peaks in pancreatic amylase and lipase concentrations also occurred on days 5-8. The increase in pancreatic enzymes was still observed on day 10, though the concentrations then were considerably lower than the peak values. There was a highly significant correlation between immunoreactive trypsin and pancreatic lipase; immunoreactive trypsin and amylase; and pancreatic lipase and amylase ($r=1.74$; $p=0.002$). No immediate effect of methylprednisolone on pancreatic enzymes was observed.

None of the patients developed clinical features of pancreatitis or parotitis.

Comment

In all cases but one the increase in pancreatic enzyme concentrations occurred more than two days after infusion and the peak occurred on days 5-8. The absence of an immediate increase after

Effect of intravenous methylprednisolone on serum pancreatic enzyme concentrations

Case No	Time of measurement	Immunoreactive trypsin (µg/l)	Lipase (U/l)	Amylase (U/l)		
				Total	Pancreatic	Salivary
1	Basal	412	253	102	96	6
	Peak (day 5)	857	298	192	174	18
	Day 10	627	229	150	132	18
2	Basal	344	72	168	78	90
	Peak (day 8)	699	200	300	156	144
	Day 10	499	180	200	160	140
3	Basal	323	147	138	102	36
	Peak (day 8)	730	286	252	222	30
	Day 10	499	249	240	216	24
4	Basal	217	89	90	66	24
	Peak (day 3)	930	350	330	306	24
	Day 10	360	141	162	120	42
5	Basal	223	81	282	126	156
	Peak (day 5)	342	99	228	168	60
	Day 10	214	74	222	144	78
6	Basal	239	82	65		
	Peak (day 5)	436	288	50		
	Day 10	420	235	55		
7	Basal	340				
	Peak (day 7)	510				
	Day 10	410				
8	Basal	320				
	Peak (day 5)	580				
	Day 10	425				
9	Basal	275				
	Peak (day 6)	600				
	Day 10	433				
10	Basal	410				
	Peak (day 5)	810				
	Day 10	700				
Normal ranges		140-400	50-200	40-150	30-160	

methylprednisolone and the delay before peak pancreatic enzyme concentrations were reached suggest that this effect was due to the cumulative effects of the steroid and not merely an alteration in the secretory pattern of these enzymes.

Increased serum pancreatic enzyme concentrations have previously been found in association with acute damage of the pancreas, as in acute pancreatitis, and with chronic pancreatic damage, as in cystic fibrosis³ and β thalassaemia with iron overload; and in elderly asymptomatic subjects.⁴ As serum concentrations of immunoreactive trypsin and other pancreatic enzymes do not increase greatly after a meal or the injection of pancreozymin (in contrast with the changes in intraduodenal pancreatic enzyme concentrations), their delayed and persistent increase after methylprednisolone probably reflects an injury of the pancreatic acinar cell or the acinar basement membrane, or both. This increase in immunoreactive trypsin concentration after methylprednisolone contrasts with the inhibition of exocrine pancreatic secretion into the duodenum after much smaller doses of hydrocortisone and adrenocorticotrophic hormone.⁵

We conclude that an increase in serum pancreatic enzyme concentration after a large dose of steroids may indicate subclinical damage of the pancreatic acinar cell. Persistence of such a stimulus, or its presence in combination with another pancreatic toxin like ethanol or with biliary disease, may predispose to clinical pancreatitis. Our data do not clarify the pathogenesis of pancreatitis induced by steroids, but they show a consistent injurious effect of large doses of these drugs on the exocrine pancreas.

- 1 Dandona P, Elias E, Beckett AG. Serum trypsin in diabetes mellitus. *Br Med J* 1978;ii:1125.
- 2 Foo Y, Rosalki SB, Ramdial L, Mikhailidis DP, Dandona P. Low pancreatic amylase in diabetes mellitus. *J Clin Pathol* 1980;33:1102-5.
- 3 Junglee D, Katrak A, Penketh A, Hodson M, Batten JC, Dandona P. Serum pancreatic lipase in cystic fibrosis. *Br Med J* 1983;286:1693-5.
- 4 Mohiuddin J, Katrak A, Junglee D, Green M, Dandona P. Serum pancreatic enzymes in the elderly. *Ann Clin Biochem* 1984;21:102-4.
- 5 Dreiling DA, Janowitz HD, Rolbin H. Effect of ACTH and adrenocortical steroids on external pancreatic secretion in man. *N Engl J Med* 1958;258:603-5.

(Accepted 11 April 1985)

Departments of Chemical Pathology and Human Metabolism and Endocrinology, Royal Free Hospital and School of Medicine, London NW3

P DANDONA, DPHIL, MRCP, senior lecturer and director, metabolic unit
D JUNGLEE, MSc, medical laboratory scientific officer
A KATRAK, BSc, medical laboratory scientific officer
V FONSECA, MD, MRCP, research fellow
C W H HAVARD, DM, MRCP, consultant physician and endocrinologist

Correspondence to: Dr P Dandona, Metabolic Unit, Department of Clinical Pathology and Human Metabolism, Royal Free Hospital, London NW3 2QG.