Infection with Yersinia enterocolitica in patients with iron overload

Yersinia enterocolitica commonly causes fever and mild gastroenteritis[1] but occasionally causes severe illness, particularly in patients with iron overload in whom its virulence is enhanced.[2] Desferrioxamine used therapeutically may potentiate the growth of yersinia, which uses desferrioxamine as a siderophore to chelate iron.[3] We describe three patients with transfusional haemosiderosis and infection with *Y enterocolitica*.

Case reports

CASE 1

A 25 year old white man with congenital sideroblastic anaemia, which had been diagnosed in 1965 and who had subsequently received regular blood transfusions (450 units) and subcutaneous desferrioxamine (serum ferritin 2460 μg/l), was admitted with symptoms of anaemia, three days of fever (39·5°C), slight diarrhoea, which he initially denied, but no abdominal pain.

He had hepatomegaly (10 cm) and slight abdominal tenderness. His haemoglobin concentration was 53 g/l with normal white cells. The day after admission he started to receive a blood transfusion of three units with 6 g of desferrioxamine. Within eight hours he had severe diarrhoea, after 12 hours severe dyspnoea due to a persistent metabolic acidosis (bicarbonate 13 mmol (mEq)/l), and by 40 hours he had died. Intravenous penicillin, gentamicin, metronidazole, and rehydration were given to no avail.

Necropsy showed an ulcer in the terminal ileum, multiple tiny colonic ulcers, and grossly enlarged purulent mesenteric lymph nodes. Stools and blood culture later grew *Y enterocolitica*.

CASE 2

A 19 year old Greek Cypriot woman with β thalassaemia diagnosed at 3 years and splenectomy at 8 years had received regular blood transfusions (200 units) but refused subcutaneous desferrioxamine. Her serum ferritin concentration was 1720 μg/l and white cell ascorbic acid 7 μg/10^8 cells.[4] She was admitted with 24 hours of fever (38°C), malaise, one loose stool, and tenderness in the right iliac fossa. Her haemoglobin concentration was 78 g/l and white cell count $27·8\times10^9$/l with a neutrophilia of 92%. Blood culture yielded negative results. Penicillin was given. The next day she discharged herself and returned in three days to receive three units of blood with 6 g of desferrioxamine. Two days after transfusion she was readmitted with fever, severe diarrhoea, and pain in the right iliac fossa, where a mass had developed. Yersinia infection was diagnosed.

Intravenous mezlocillin and netilmicin were given, and eight hours later in a dramatic recovery her temperature settled. Desferrioxamine was withheld. A few days later the diarrhoea and mass resolved. *Y enterocolitica* grew profusely from her stool. The *Y enterocolitica* titre in her blood taken at discharge was 1/20 and five months later 1/320.

CASE 3

A 22 year old Greek man with β thalassaemia major received regular blood transfusions in Athens and subcutaneous desferrioxamine (his serum ferritin concentration was 1700 μg/l). He was referred to London because of recurring abscess formation in the right inguinal region for five months. Pus had grown *Y enterocolitica*, and he had received various antibiotics. Desferrioxamine treatment had been withdrawn. The abscess in the inguinal region, which was discharging pus, and several smaller retroperitoneal abscesses, with a sinus extending to the psoas muscle, were surgically drained and debrided. Tetracycline, clindamycin, and penicillin were given together with local irrigation with hydrogen peroxide. He made a good recovery.

Yersinia was not cultured, possibly because of previous antibiotic treatment. The patient's yersinia titre was positive at 1/1280.

Comment

We have described three patients with iron overload, two of whom were treated with subcutaneous desferrioxamine, who developed infection with yersinia and right iliac fossa disease. Two patients (cases 1 and 2) with mild intercurrent infections received routine transfusions with intravenous desferrioxamine 6 g and then became severely ill. One of these patients (case 1), who had previously received daily subcutaneous desferrioxamine, died 40 hours after transfusion, the other (case 2), who had refused regular desferrioxamine treatment but whose iron stores were lower survived. The third patient (case 3) developed chronic multiple abscesses and survived. Desferrioxamine treatment had been withdrawn.

Desferrioxamine may potentiate yersinia infection in patients with iron overload and has been shown to cause systemic yersinia infections in healthy children who received desferrioxamine after iron overdosage.[5] Our observations, although anecdotal, suggest that desferrioxamine treatment should be temporarily withheld in febrile patients with iron overload, especially those with gastrointestinal symptoms, and appropriate antibiotics given at once.

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Acute renal failure associated with acute pyelonephritis and consumption of non-steroidal anti-inflammatory drugs

We report four cases in which urinary infection precipitated acute renal impairment in patients taking non-steroidal anti-inflammatory drugs.

Case reports

Case 1—A 27 year old woman with seronegative arthritis was admitted with a five day history of right loin pain and fever. For three years she had been taking azapropazone 2·4 g daily. She had had a urinary tract infection two years previously. Renal function then had been normal, although intravenous urography had shown pelvicaliceal clubbing. On examination she was feverish with tenderness in the right loin. Plasma creatinine concentration on admission was 199 μmol/l (2·3 mg/100 ml) (calculated creatinine clearance 44 ml/min). Intravenous urography and ultrasound scanning showed an enlarged right kidney with poor excretion. Urine and blood cultures were sterile, but treatment with antibiotics had been started before admission. Intravenous co-trimoxazole improved her condition, and within three days renal function had returned to normal. Although azapropazone was stopped, she developed a further episode of pyelonephritis four weeks later, during which renal function remained normal.

Case 2—A previously fit 61 year old woman presented with a five day history of rigors, vomiting, and right loin pain. Ten days previously she had begun taking ketoprofen 400 mg daily for pain in her right knee. On admission she was feverish and dehydrated with tenderness in the right loin. Plasma creatinine concentration was 244 μmol/l (2·8 mg/100 ml) and *Escherichia coli* was cultured from a midstream specimen of urine. Despite treatment with intravenous fluids and ampicillin plasma creatinine concentration rose to 819 μmol/l (9·3 mg/100 ml) four days later, and peritoneal dialysis was therefore begun. Within five days her renal function had improved and dialysis was stopped. Intravenous urography during convalescence showed a poorly excreting right kidney. Four months after admission plasma creatinine concentration was 126 μmol/l (1·4 mg/100 ml).

Case 3—A 64 year old woman with a long history of rheumatoid arthritis presented with a three week history of nausea, vomiting, dysuria, rigors, and confusion. After a year's treatment with penicillamine she had taken naproxen 750 mg daily for two years. Six months before admission plasma creatinine concentration had been 164 μmol/l (1·9 mg/100 ml). Plasma creatinine concentration on admission was 1285 μmol/l (14·5 mg/100 ml), and *E coli* was grown from the urine. She was treated with peritoneal dialysis and intravenous ampicillin, ceftazidime, and flucloxacillin. Dialysis was stopped after four days, and within three weeks plasma creatinine concentration was 377 μmol/l (4·3 mg/100 ml). Ultrasonography showed bilateral small kidneys, and renal biopsy showed changes of acute on chronic pyelonephritis.

Case 4—A 71 year old woman was admitted with a fractured neck of femur. A left nephrectomy had been performed for tuberculosis 20 years previously, but plasma creatinine concentration one month before admission had been 120 μmol/l (1·4 mg/100 ml). Six days before admission she had started taking ibuprofen 1·2 g daily for backache. On admission she was dehydrated and confused. Plasma creatinine concentration was 177 μmol/l (2·0 mg/100 ml), and *E coli* was grown from the urine. Despite rehydration and administration of

intravenous cefuroxime plasma creatinine concentration rose to 383 μmol/l (4·3 mg/100 ml) (calculated creatinine clearance 14·5 ml/min) after three days. Ibuprofen was stopped, and within 10 days plasma creatinine concentration was 135 μmol/l (1·5 mg/100 ml).

Comment

Acute renal impairment in acute pyelonephritis is rare; patients are normally predisposed to it if they have underlying renal disease such as chronic pyelonephritis, papillary necrosis, or obstructive uropathy.[1] Three of our patients had evidence of underlying renal disease, but the fact that all four patients were taking non-steroidal anti-inflammatory drugs raises the possibility that in patients with either underlying renal impairment or urinary infections these drugs may predispose to both acute pyelonephritis and acute renal impairment. Other renal side effects are well documented.[2] The mechanism for what we have described might be an abnormality of immune function or of autoregulation of renal blood flow secondary to impaired synthesis of prostaglandin.[3]

We suggest that non-steroidal anti-inflammatory drugs should be prescribed with caution in patients with renal impairment, chronic pyelonephritis, or recurrent urinary infection.

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Increased capillary fragility at high altitude

Since the observation by Frayser *et al* of retinal haemorrhages in people at high altitude[1] there has been debate about their cause as well as the effect of altitude induced hypoxia on other body tissues. Most theories propose that vessel wall weakness and increased intraluminal pressure rather than platelet dysfunction are responsible for high altitude retinal haemorrhage. Other haemorrhagic phenomena reported at high altitude include microscopic haematuria, subungual splinter haemorrhage, buccal mucosal haemorrhage,[2] and widespread cerebral capillary haemorrhage.[3] We used the method of mucosal petechiometry to examine the relation between capillary fragility and increasing altitude.

Subjects, methods, and results

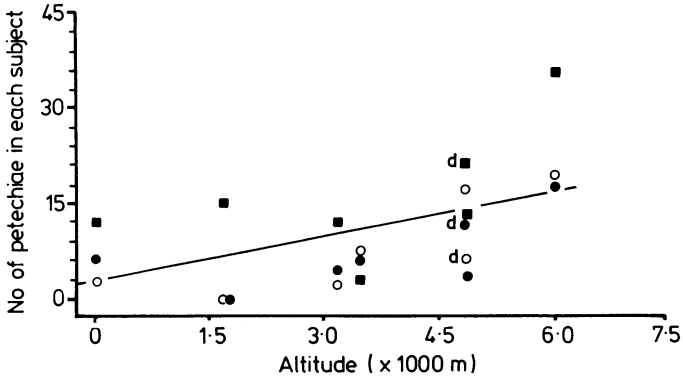
The subjects of this experiment were three healthy white men on a climb of the Indian Himalayan peak Jogin 1, 6465 m (21 210 ft). Capillary fragility was measured using the method described by Stirrups *et al*.[4] This entailed placing a 1 cm plastic bell on the mucous membrane on the inner aspect of the lower lip. A negative pressure of 200 mm Hg was applied for one minute, sucking the mucosa up into the bell. The petechiae so produced were counted by two observers and the results averaged. We tested two sites on each occasion and summed the results. With the exception of the sea level controls all observations were made within 24 hours of arrival at a specified altitude. We also used a positive pressure test—the tourniquet (Hess) test. Funduscopy was performed at base camp, 4750 m (15 580 ft), before and after the climb. Least squares regression analysis was used to test the association between altitude and number of petechiae.

The figure plots against altitude the total number of petechiae in the three subjects at each altitude. The equation of the least squares regression line was $y = 2{\cdot}20 + 2{\cdot}44\,x$, and the associated correlation coefficient was 0·54. The slope of this line was statistically significant at $p < 0{\cdot}02$ in a two tailed test.

Tourniquet test—A maximum of eight petechiae were seen in any one test (up to 10 may be normal) and there was no correlation with altitude. This is consistent with the observation in haematological practice that the tourniquet test is, at best, a poor predictor even of major degrees of capillary fragility.[5]

Funduscopy—At base camp before the climb fundal examination showed dilated and tortuous vessels in all three climbers. On return 11 days later appearances were unchanged in two subjects. The third (subject 1) had two retinal haemorrhages in his right eye and three in his left. All fundi were normal 10 days later.

Acute mountain sickness—Two subjects experienced only the normal dyspnoea of high altitude. Subject 1 experienced moderate acute mountain sickness on ascent, complaining of dyspnoea on exertion, headache, anorexia, and lethargy.



Change in petechiae count with altitude in subjects 1 (■), 2 (●), and 3 (○). d = Observations made on descent.

Comment

These results show that there is an increase in capillary fragility with altitude. The technique used is important for two reasons. Firstly, it detects increased capillary fragility in subjects in whom spontaneous capillary rupture is not observable. This is evidence that increased capillary fragility is a widespread effect of high altitude on the microvasculature. This phenomenon may contribute to the pathogenesis of acute mountain sickness and its life threatening variants, high altitude pulmonary oedema and high altitude cerebral oedema. Secondly, the method might be used to try to determine which components of the high altitude environment affect capillary fragility. Pressure chamber experiments could examine the relation between hypoxia, hypobarism, drug prophylaxis, and capillary fragility.

Of the three subjects studied, the one with consistently more fragile capillaries (subject 1) was the only one to suffer both retinal haemorrhage and acute mountain sickness. It is interesting to speculate that an intrinsically high capillary fragility may predispose a person to capillary leakage or rupture and thus acute mountain sickness. If this were so, then capillary fragility at sea level may be a predictor of performance at altitude.

Given the small number of subjects in this experiment, however, the results should be interpreted with caution. More data are needed before a complete understanding of the relation between capillary fragility and altitude will be possible. We should expect the important factor of acclimatisation to modify this relation.

We hope that this pilot study will prompt further work in this area. If confirmed in a larger series petechiometry may prove a useful tool in the continuing search for an understanding of the pathogenesis of acute mountain sickness and other hypoxic disease.

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