The Jarisch–Herxheimer reaction in leptospirosis

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Summary: Three patients with leptospirosis whose condition worsened after initiation of antibiotic therapy are reported. Their clinical deterioration appeared to be due to the development of the Jarisch–Herxheimer reaction rather than to progression of their underlying infection. Relevant aspects of the management of patients with leptospirosis are discussed.

Introduction

The Jarisch–Herxheimer reaction has been reported to occur after the initiation of antibiotic therapy in a variety of spirochetal illnesses including leptospirosis. The benefit of antibiotic therapy in leptospirosis has recently been questioned. We report three patients with leptospirosis who appeared to develop the Jarisch–Herxheimer reaction, in one of whom it may have contributed to his death.

Case report

Case 1

A 15 year old farmer’s son presented with a 1-week history of ‘flu'-like symptoms, severe myalgia and progressive jaundice. On examination, he was pyrexial 101°F, icteric and diffusely tender over all muscle groups.

Investigations on admission revealed a haemoglobin of 10.4 g/dl, platelet count 98 × 10⁹/l and a normal white cell count. Liver function tests demonstrated a hepatic picture with a bilirubin of 87 mmol/l and raised transaminase levels. Creatine kinase was markedly elevated at 100.8 μkat/l (normal 0.4–2.4 μkat/l). He had microscopic haematuria. Chest X-ray on admission was normal.

A clinical diagnosis of leptospirosis was made, and he was commenced on intravenous benzylpenicillin 4 hours after admission. Within the next 4 hours, his condition deteriorated with a further rise in temperature to 102.4°F, a tachycardia of 120 beats/minute, with a blood pressure of 80/60 mmHg (see Figure 1). He was tachypnoeic and his chest X-ray showed diffuse bilateral infiltrates.

He was transferred to the intensive therapy unit, and further treatment included oxygen, intravenous corticosteroids and inotropic support. Over a 12-hour period, he improved and ventilatory support was not required. Chest X-ray changes resolved in 4 days. He was discharged at 7 days, and has remained well. His leptospirosis titres were elevated with a titre rising from 1 in 320 to 1 in 1,280.

Figure 1 Case 1: upper panel shows the blood pressure response and the lower panel the pulse (solid line) and temperature (dashed line) response after intravenous antibiotics (indicated by arrow).

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Case 2

A 20 year old plumber presented with a 6-day history of upper abdominal pain, nausea, vomiting and jaundice associated with general malaise. On examination, he was pyrexial (101°F), tachycardiac (120/minute) and mildly icteric. He had marked generalized myalgia, tenderness in his right upper quadrant and coarse crackles in his left lung base.

Investigations on admission revealed a haemoglobin of 11.8 g/dl, white cell count of 9.6 x 10^9/l, platelets 30 x 10^9/l, and an erythrocyte sedimentation rate of 105 mm/hour. Liver function tests revealed a hepatitic picture. Renal dysfunction was present – a plasma urea 22 mmol/l and a serum creatinine 300 µmol/l (normal 50 – 130 µmol/l). The creatine kinase was grossly elevated at 80 µkat/l. Urine microscopy showed the presence of spirochetes and a diagnosis of leptospirosis was made. The patient was commenced on intravenous benzylpenicillin.

Four hours later, his condition had markedly deteriorated (see Figure 2). Temperature had increased to 103°F, blood pressure fell to 60/0 mmHg and he was markedly hypoaemic. Despite intensive supportive care, his condition deteriorated further and he died 36 hours after admission.

Postmortem examination revealed an interstitial nephritis, with focal tubular destruction. Microscopical examination of the liver demonstrated hepatic necrosis with a mixed inflammatory infiltrate in the portal tracts. The lung was intensely congested and microscopical findings were of an intense haemorrhagic pneumonia. The findings were considered highly suggestive of Weil's disease.

Case 3

A 39 year old housewife presented with a 4-day history of ill-health. She was an epileptic, well controlled on carbamazepine. She complained of cough productive of sputum, headache, anorexia and general malaise.

On examination, she was pyrexial 102°F, had nuchal rigidity and mild conjunctival inflammation but no photophobia. Kernig's sign was negative. Examination of her chest revealed signs consistent with a left basal pneumonia.

Investigations on admission included haemoglobin 7.6 g/dl, white cell count 13 x 10^9/l, platelets 135 x 10^9/l. Chest X-ray revealed minimal shadowing in the left lower zone. Twelve hours after admission, she was commenced on intravenous ampicillin. Five hours later, she was hypotensive with blood pressure 80/60 mmHg. Temperature had increased to 103.2°F (see Figure 3). She was commenced on intravenous fluids and subsequently transfused. Her condition improved over the next 24 hours and she made an unremarkable recovery.

Because of meningism and conjunctival inflammation, leptospiroserology was requested: this was positive at 1 in 160 and rose to 1 in 640.

Discussion

These three cases have a number of features in common: each had a spirochetal illness that was
treated with intravenous bactericidal antibiotic therapy; all had been unwell prior to admission but not critically so; within a few hours of the introduction of antibiotic therapy in each case there was a marked clinical deterioration associated with an increase in tachycardia and hypotension.

The Jarisch–Herxheimer reaction as originally described in 1895 is a distinct clinical entity that follows the first adequate dose of an antimicrobial agent in a variety of infectious diseases. The severity and frequency of the reaction depends, however, on the nature of the underlying infectious process. It is particularly explosive in those with underlying syphilis or louse-borne relapsing fever, a disease in which this reaction has been particularly well studied. Its occurrence has also been described in non-spirochetal illnesses including brucellosis and meningococcal septicaemia. It has been described in leptospirosis but the incidence remains controversial. In a large study in Malaya, the incidence was reported as high as 80%.4

The Jarisch–Herxheimer reaction is characterized by a number of pathophysiological events: by alteration in body temperature, typically an initial rise of 1–2°C sometimes followed by a subsequent fall in temperature. There is associated hyperventilation and vasoconstriction, often followed by a period of intense vasodilatation leading to hypotension. Exacerbation of existing lesions, classically the rash of secondary syphilis is said to occur. The reaction is typically a brisk all-of-nothing event.

The pathogenesis of the reaction has not been fully elucidated. Jarisch postulated the cause of the reaction was a toxin liberated from lysed spirochetes but it was not until 1961 that endotoxin-like activity was implicated. The role of lipopolysaccharide was investigated when its presence was discovered in spirochetes in 1973. More recent work has focused on the part played by cytokines in the pathogenesis of this reaction. Activation of the cytokine cascade during the degeneration of spirochetes may play a fundamental part in its pathogenesis and implicated substances include tumour necrosis factor, interleukin-6 and interleukin-8. These cytokines have been demonstrated to rise in tandem with the associated pathophysiological changes in patients with relapsing fever due to *Borrelia recurrentis* infection, a disease in which the reaction is particularly florid.

Spirochetes are not removed *en masse* from the circulation until a bactericidal agent is administered, and it has been suggested that abnormal forms of the organism are rendered susceptible to phagocytosis by macrophages and that this in part leads to cytokine production. The heterogeneity of the reaction produced by different infectious agents may be related to their individual propensity to activate mediators of inflammation, such as the cytokines, when undergoing lysis.

A number of attempts have been made to limit the severity of the reaction pharmacologically. Corticosteroids have not been shown to be of benefit. The partial opiate agonist meptazinol showed some promise in diminishing the reaction in relapsing fever. Overall results remain disappointing with little currently available to ameliorate this reaction.

A recent prospective randomized controlled clinical trial of intravenous benzylpenicillin in icteric human leptospirosis demonstrated little benefit in clinical outcome between the groups who received antibiotic therapy and those who received placebo. Increasing knowledge of the immunological basis of the inflammatory process and of the development of shock raises serious questions about the old doctrine of organism – antibiotic cure. In other disease processes, in particular septic shock, attempts are being made to control the immunological response to sepsis and its sequelae by the use of monoclonal antibodies directed against endotoxin, tumour necrosis factor and members of the cytokine cascade. The results in patients with Gram-negative septicaemia are encouraging. There are as yet no trials of monoclonal antibody therapy in the Jarisch–Herxheimer reaction.

Larger controlled clinical trials are needed to demonstrate whether antibiotic therapy in patients with leptospirosis is beneficial. Further trials are required to examine methods of modulating possible Jarisch–Herxheimer reactions when they occur. At present, it is our practice to administer intravenous antibiotic therapy to such patients and to anticipate any possible adverse reactions at the earliest possible time so that supportive care can be optimized.

