Leptospirosis: An Occupational Hazard to Veterinarians

B. F. KINGSCOTE

Agriculture Canada, Animal Diseases Research Institute, P.O. Box 640, Lethbridge, Alberta T1J 3Z4

ABSTRACT

Leptospirosis occurred in two veterinarians in Alberta, following their exposure to leptospires of domestic animal origin. The disease at onset resembled "flu" with fever, muscle and joint pain, and lassitude. It progressed through an extremely debilitating period with mild to severe hepatic and renal dysfunction, icterus and hemorrhage in one case, and cerebral meningitis in the other. Both patients were hospitalized for 11 to 14 days, where they responded to supportive and specific antibiotic and steroid therapy (penicillin G 10^6 IU q.i.d. and steroids, or tetracycline 500 mg q.i.d.). Diagnosis rested in one case on clinical signs and the observation of leptospires in blood and urine. In the other case, a tentative diagnosis of leptospirosis based on history and clinical signs was confirmed by serological test results and by the isolation of *Leptospira interrogans* serovar *pomona* from the patient's blood on day 6. Current occurrences of leptospirosis in man are reviewed. Convenient diagnostic methods, treatment and behavioural sequellae of leptospirosis are discussed.

Key words: Leptospirosis, man, zoonosis, *pomona*, diagnosis, doxycycline, occupational hazard.

RESUME

La leptospirose, un risque professionnel pour les vétérinaires

Deux vétérinaires albertains ont contracté la leptospirose, à la suite d'un contact avec des leptospires d'animaux domestiques. Le début de la maladie ressemblait à la grippe; il se caractérisait par de la fièvre, des douleurs tant musculaires qu'arthritiques et de la fatigue. La condition évolua vers une période extrêmement débilitante qui s'accompagnait d'un mauvais fonctionnement hépatique et rénal plus ou moins marqué, d'ictère et d'hémorragie, dans un cas, ainsi que de méningite cérébrale, dans l'autre. Les deux patients furent hospitalisés pour une période de 11 à 14 jours, au cours de laquelle ils réagirent favorablement à une thérapie de support, ainsi qu'à l'administration de 10^6 U.I. de pénicilline q.i.d. et de stéroïdes, ou de 500 mg de tétracycline, q.i.d. Dans un cas, le diagnostic reposait sur les symptômes et la présence de leptospires dans le sang et l'urine. Dans l'autre, la sérologie et l'isolement de *Leptospira interrogans* sérovar *pomona*, du sang du patient, six jours après le début de la maladie, permirent de confirmer un diagnostic provisoire de leptospirose qui reposait sur l'anamnèse et les symtômes. L'auteur revoit brièvement les façons dont la leptospirose humaine se présente ordinairement; elle en commente aussi les méthodes de diagnostic commodes, le traitement et les séquelles relatives au comportement.

Mots clés : leptospirose, homme, zoonose, *pomona*, diagnostic, doxycycline, risque professionnel.

INTRODUCTION

Leptospirosis is a zoonosis of both tropical and temperate environments all over the world. Leptospires parasitize kidney, eye, brain, gravid, nongravid or male reproductive tracts of mammals. The infection is transmitted by contact with infected tissues, body fluids, urine, or virulent laboratory cultures, or indirectly through contaminated moist environment. Portals of entry include damaged skin, conjunctiva and mucosa. Although most pathogenic leptospires are capable of infecting a wide range of hosts, each serovar is best adapted to one or a few hosts, in which it is maintained and from which it is spread. In Canada, where *pomona* and *hardjo* are widespread in livestock, swine and skunks maintain *pomona* and cattle maintain *hardjo*. Man is an accidental host for both these serovars and intraspecies transmission is rare. Rats (*Rattus* sp) are the natural hosts for *icterohaemorrhagiae*, which causes severe and fatal illness in man. This serovar has been isolated from rats in Canadian port cities (1) and antibodies occur in swine, cattle and horses.

The occupational hazard presented by *hardjo* and *pomona* in temperate regions is gaining recognition as increasing numbers of human cases of leptospirosis are diagnosed and reported (2,3,4). *Hardjo* is associated with dairy farming and *pomona* with exposure to swine on farms and in slaughter plants (5,6,7,8). Human icterohaemorrhagiae infection has tended to be urban (3,9). Recently the prevalence of agglutinins to this serovar has increased in cattle and swine in North America, indicating a wider zoonotic potential.

This paper is intended to alert veterinary practitioners, meat inspectors and laboratory diagnosticians to the risk of leptospirosis to themselves, their clients and their coworkers. Two cases of leptosirosis in veterinarians, which have been presented elsewhere as brief medical case reports, are described here in detail to emphasize the circumstances and prodromal

Present address of Dr. Kingscote: Reference Laboratory Branch, Alberta Agriculture, 6909 - 116 Street, Edmonton, Alberta T6H 4P2.

signs which should prompt an early consideration of leptospirosis as a tentative diagnosis and to discuss how the diagnosis can be confirmed.

Case 1 — History

A veterinarian working in a diagnostic laboratory isolated *Leptospira* serovar *pomona* from urine of aborting sows and proceeded to inoculate rabbits with the culture. Three days later she developed malaise (day 1), with increasing generalized joint and muscle pain, hyperaesthesia of skin and muscle and weakness by day 2. Vital signs and hematology were normal and no diagnosis was made. Aspirin was prescribed. Symptoms abated until the evening of day 4, when severe chills and sweating occurred, culminating 6 h later in a drenching sweat. The following day, headache developed which was partially controlled by aspirin and codeine. By this time the subject suspected that she had contracted leptospirosis. Sweating, chills, weakness, delirium, and headache persisted through the night of day 5. The patient remained ambulatory and presented a blood sample to a veterinary diagnostician, who observed structures resembling leptospires and inoculated culture medium. The patient was admitted to hospital at noon on day 6 and tetracycline and analgesic treatment was begun in the evening, following a tentative diagnosis of leptospirosis.

Clinical Findings

Temperature fluctuated between 36.2 and 39.0°C on days 6, 7 and 8, thereafter remaining normal. Other clinical signs were normal. Weakness, prostration and severe headache characterized the illness, with headache persisting into day 13. The patient was released from hospital on day 17 and convalesced to normal activity within two months. Episodes of stiff neck, arthralgia and myalgia were responsive to tetracycline therapy and recurred three times within eight months of release. Recurrences of headache, distinctly referrable to two bands of intense subcranial pain experienced during hospitalization, were related to fatigue, over a period of 2.5 years. Agglutinins to *pomona* and *autumnalis* at 1/50 titer were detected during a relapse two years after the first attack. The patient responded to tetracycline therapy.

Treatment

The acute attack was treated with tetracyn (tetracycline, Pfizer) from day 6 to 16, at a dose of 500 mg every 6 h. Vomiting was controlled by Gravol (dimenhydrinate, Horner) suppositories, 100 mg and tablets, 50 mg on day 9 and 10, and pain by Tylenol No. 3 (acetominophen with codeine phosphate 30 mg, McNeil) and Talwin (pentazocine, Winthrop) 30-50 mg i/m throughout days 6 to 13.

Laboratory Methods

Standard procedures were used for culture, hematology and kidney and liver function tests on blood samples. Leptospiral antibodies were detected by the microscopic agglutination (MA) test for 11 serogroups, and by the indirect hemagglutination (IHA) test (10). Brucella agglutinins were measured by a standard procedure. Blood was cultured for leptospires by inoculation of one and a few drops of freshly drawn, untreated blood into a commercial albumin-polysorbate-80 medium, which was incubated at 29°C for two months. The leptospiral isolate was typed by cross- absorption and by restriction endonuclease analysis (11).

Urine was tested for somatic cells and bacteria on days 6 and 7, and for indicators of metabolic and renal function on days 6, 8 and 12. Total daily urinary output was compared with the volume of fluid intake on days 10 through 15.

Serological monitoring for leptospirosis was continued over the next seven months. The field strain of *pomona* which was believed to have caused the infection was added to the MA test antigens.

Laboratory Findings

Levels of blood urea, glutamic oxalacetic transaminase and aspartate transaminase were elevated on day 6, while uric acid level was subnormal by day 12. Other chemical parameters of homeostasis remained within normal limits. The platelet count rose from normal on day 9 to 110% of normal on days 12 and 15. Basophilia concurred with the elevated platelet count.

No brucella agglutinins were found in the serum. Microscopic agglutination titers to *pomona, autumnalis* and *hardjo* and IHA titer were 1/50 on day 6. Agglutinins to *pomona* persisted, reaching a peak MA titer of 1/400 on day 12 and remaining at that level two weeks later. By this time (day 26) the IHA titer had reached 1/800. Thereafter the MA titer dropped to 1/100 by week 7 and became negative seven months after the onset of signs of leptospirosis.

Urine cultures were negative and cytology was normal. Blood cultures performed during hospitalization were negative. The diagnosis of leptospirosis was confirmed two months after onset by the isolation of leptospires from blood culture performed on day 6 at the veterinary diagnostic laboratory. The isolate was serotyped as *Leptospira interrogans* serovar *pomona*, identical to the swine isolate from which infection had probably been acquired. Deoxyribonucleic acid analysis showed these isolates to be serovar *kennewicki*, which is indigenous in cattle and swine in the USA and Canada (11).

Case 2 — History

A veterinarian in large animal practice was stricken suddenly with severe lassitide and somnolence, which persisted on day 2 with a temperature of 39°C. A family physician suspected "flu", and recommended rest. Initial symptoms intensified and anuria, profuse diarrhea, severe chilling and joint and muscle pain developed, accompanied inability to focus the eyes, loss of temporal awareness and lucid but irrational speech. At the time of hospitalization, the patient had become icteric and was considered to be in critical condition.

Clinical Findings

Oral temperature remained at 39°C until day 7, when it returned to normal 24 h following institution of penicillin G therapy. Abnormal signs included icteric conjunctiva, pulse 85 per min, hyperaesthesia of the skin and muscles and liver palpable two fingers below the costal border. Ultrasound scan showed no remarkable hepatic nor splenic abnormalities. Hemorrhage occurred between the toes and subcutaneously on the dorsum of a foot.

A 13% weight loss occurred during hospitalization. The patient was released on day 17. Despite persistent fatigue, a normal routine of large animal practice and exercise was reestablished over the following 6 wk. Sequellae 15 months after onset included occasional slight loss of balance and failure to regain normal weight.

Treatment

Initial treatment in hospital included intravenous fluids and ampicillin 1 g q.i.d., which failed to halt the progress of disease. After hemorrhage was observed and leptospirosis was diagnosed by laboratory test, antibiotic therapy was changed to penicillin G, 10^6 IU, q.i.d., also Solucortef (hydrocortisone sodium succinate, Upjohn) 100 mg t.i.d. was administered and platelets were transfused. The patient responded promptly with a return of normal temperature and a rising platelet count.

Laboratory Methods

Blood and urine profiles were obtained for cellular and biochemical analysis at intervals from the day of admission to hospital until discharge. Determinations focused on indicators of blood cell destruction, blood loss and renal and hepatic function. Bone marrow cytology included iron staining of reticuloendothelial cells. Serological assays for cold agglutinins, hepatitis B surface antigen, fluorescent antinuclear antibody, and rheumatoid factor, were performed. After leptospiremia was observed, leptospiral agglutinins were assayed by the IHA and MA tests, as in case 1. Blood was cultured for bacteria by standard hospital laboratory methods, not including the use of leptospiral media, and blood and urine were examined by direct dark field microscopy.

Laboratory Findings

Major abnormalities were seen in the blood chemistry, indicative of severe hepatic and renal failure. Serum levels of enzymes, creatinine, urea, uric acid and total bilirubin were markedly elevated during the first three days of hospitalization. During the next week, levels fell gradually to normal except for alkaline phosphatase, which continued to rise, reaching 435 units/L 12 days after admission. Blood cell counts and protein levels remained within normal limits, but platelet counts fell from 45,000 on admission (day 3) through 22,000 and 15,000 to 10,000 in periodic checks during the next two days. Following steroid and bone marrow therapy, the platelet count rose to 44,000, 140,000 and 279,000 by days 8, 10 and 13, respectively. Peripheral blood smear during thrombocytopenia showed a shift to the left with large platelets, suggesting diffuse intravascular coagulation (DIC), although erythrocytes did not show characteristic morphological changes of DIC. Bone marrow cytology was normal except for a moderate increase in megakaryocytes and increased iron stored in reticuloendothelial cells.

Initial serological assays were negative. Leptospires were seen in blood and urine by dark field microscopy on day 6, three days after admission to hospital. No antibody response was detected by MA test on an acute sample, nor by IHA and MA tests six weeks after onset.

DISCUSSION

Torten (12) in his discussion of human leptospirosis throughout the world, emphasizes the lack of a pathognomonic syndrome and the misconceptions that hinder diagnosis. Gutman *et al* (13) illustrate this in their detailed clinical account of a severe case of *icterohaemorrhagiae* infection which was signalled by ocular pathology. The diagnoses in the cases reported here were delayed because neither patient was conscious of having been exposed to infection and their physicians did not suspect leptospirosis initially. This is consistent with the earlier observations of Heath *et al* (3) in the U.S.A. and with the contemporary data of Swart in Australia (14). The cases currently cited by Hart in England (15) and Avery in New Zealand (16) describe the consequences of unrecognized leptospirosis. Faine (17) concludes that leptospirosis should be considered as a diagnosis in all cases of fever or influenza-like syndrome in patients who have had direct or indirect contact with livestock. This would include swimmers exposed to recreational waters frequented by domestic animals (18). The dramatic increase in confirmed cases in Great Britain in 1983 (120 cases) over 1982 (61 cases) (2) is more likely to be the product of medical enlightenment than to be a reflection of real increase in prevalence.

Considering the relative simplicity of diagnostic techniques now available, their routine inclusion is recommended in the examination of all febrile patients at risk of leptospirosis. Direct microscopic examination of blood is facilitated by the lysis of erythrocytes in a leptospira-protective solution [1% bovine albumin fraction V in 0.005 M phosphate buffer (19) containing 2% Grobax (Roche Diagnostic, Hoffmann-LaRoche Ltd.)] Acridine orange staining of blood smears also demonstrates leptospires brilliantly under ultraviolet incident lighting (20). The IHA test (10) using stable, safe, antigen as opposed to living MA test antigens detects antibodies to the genus *Leptospira* early in the course of human infection. Enzyme-linked immunosorbent assay and other rapid tests are likely to supersede conventional serological tests in the future (17).

Blood culture with the new, commercially available albumin-polysorbate-80 medium now can be highly successful (14,17), permitting confirmation of diagnosis and identification of the infecting serovar.

Specific etiology in case 2 could not be proven, but it was deduced from a consideration of indigenous serovars and clinical and laboratory findings. The icterus and blood-vascular changes resembled the pathology recorded by both Thiermann (9) and Gutman (13) in severe or fatal *icterohaemorrhagiae* infections. A DIC-like syndrome was produced experimentally with the same serovar in guinea pigs (21).

The course of human leptospirosis usually follows a sequence of leptospiremia with development of hemagglutinating and complement fixing antibodies, followed by nonspecific and later by specific agglutinins. Variation in this pattern occurred in both cases reported here as well as in Thiermann's cases (9) and in an

unpublished case history of *pomona* infection in a man whose agglutinin levels fluctuated between 1/400 and 1/6400 for over ten years. Leptospiremia can persist for several months in the absence of antibody response. Reexposure must always be considered in case of recurrence of symptoms accompanied by a strong antibody response, although there is a growing awareness of recurrences of the original infection (22).

The value of antibiotic therapy is controversial, but there is agreement that it must be begun soon after onset to have any influence over the course of the disease (14,17,23,24). Early diagnosis is essential to the commencement of supportive therapy to limit or compensate for renal damage, which can be severe. Case 1 appeared to respond to tetracycline therapy instituted on day 6, in that minimal hepatic and renal dysfunction developed. Also the agglutinin titer fell rapidly, denoting prompt clearance of antigen from the body, compared to reported leptospiral titers exceeding 1/1000 after seven months (14) and persisting for 17 years (8). Controlled trials of doxycycline therapy in US military personnel strongly endorse the use of this antibiotic (24). Two major advantages of doxycycline are that it penetrates into the cerebrospinal fluid and anterior chamber of the eye, and that it has a long half-life in the body (16 h).

Behavioural changes are being recognized as long-term sequellae to leptospirosis in New Zealand as the improved diagnosis of the acute disease in man provides a basis for correlation. Confusion, schizophrenic psychosis and change in control of aggression have been reported by Avery (16) and Marshall (25). In China, Cheng (26) reports that leptospiral arteritis is one of the major causes of Moyamoya syndrome, a cerebrovascular disease of considerable importance.

The potential exists for exposure of several occupational groups of Canadians in most provinces to *Leptospira* serovars *hardjo, pomona* and *icterohaemorrhagiae* and probably to other serovars as yet not isolated. The attendant risk of debilitating infection with serious sequellae merits the concern of public health authorities to obtain appropriate survey data. Responsibility accrues to the veterinary profession to caution clients and coworkers and to promote action to curtail the sources of infection for human beings. The ultimate responsibility rests with the medical profession to recognize leptospirosis as a zoonosis indigenous to Canada.

ACKNOWLEDGMENTS

The author thanks Drs. S. MacLean, J. Fenton, B. Stillwell and S. Kornell for supplying case data, and Mrs. C. Sulzer, C.D.C., Atlanta, Georgia and Dr. A. Thiermann, N.A.D.C. Ames, Iowa for serotyping and DNA-typing the leptospiral isolates; and Mrs. Ann Crichlow at the Western College of Veterinary Medicine, for culture confirmation of case 1.

REFERENCES

1. McKIEL JA, COUSINEAU JA, HALL RR. Leptospirosis in wild animals in Eastern Canada with particular attention to the disease in rats. Can J Comp Med 1961; 25: 15-18.
2. Leptospira Reference Unit and Communicable Disease Surveillance Centre (Public Health Laboratory Service). Leptospirosis in man, British Isles, 1983. Br Med J 1984; 288: 1984-1985.
3. HEATH CW, ALEXANDER AD, GALTON MM. Leptospirosis in the United States: Analysis of 483 cases in man, 1949-1961. N Engl J Med 1965; 273: 857-864.
4. SANFORD JP. Leptospirosis - time for a booster. N Engl J Med 1984; 310: 524-525.
5. WHITE FH, SUTHERLAND GE, RAYNOR LE, COTTRELL CR, SULZER CR. *Leptospira interrogans* serovars *hardjo* and *pomona*: causes of infections in dairy cows and humans in Florida. US Publ Health Rep 1981; 96: 250-254.
6. BRAUN JL, McCULLOCH WF, TOP FH. Further observations on the epidemiology of leptospirosis in Iowa. 1. Cases occurring among abattoir employees. Zoon Res 1964; 3: 39-46.
7. MACKINTOSH CG, SCHOLLUM LM, BLACKMORE DK, MARSHALL RB. Epidemiology of dairy farm workers in the Manawotoc. II. A case-control study of high and low risk farms. NZ Vet J 1982; 30: 73-76.
8. SCHOLLUM LM, BLACKMORE DK. Leptospirosis of pig farmers: the results of a serological survey. NZ Med J 1982; 95: 299-301.
9. THIERMANN AB, FRANK RR. Human leptospirosis in Detroit and the role of rats as chronic carriers. Int J Zoonoses 1980; 7: 62-72.
10. SULZER CR, GLOSSER JW, ROGERS F, JONES WL, FRIX M. Evaluation of an indirect hemagglutination test for the diagnosis of human leptospirosis. J Clin Microbiol 1975; 2: 218-221.
11. THIERMANN AB, HANDSAKER AL, MOSELEY SL, KINGSCOTE B. New method for classification of leptospiral isolates belonging to serogroup *pomona* by restriction endonuclease analysis: serovar *kennewicki*. J Clin Invest 1985; 21: 585-587.
12. TORTEN M. Leptospirosis: In: CRC Handbook Series in Zoonoses, Vol 1, Steele JH, ed. Boca Raton, Florida: CRC Press Inc., 1979: 363-421.
13. GUTMAN I, WALSH JB, KNAPP AB. Cotton-wool spots as a sign in leptospirosis. Ophthalmologica, Basel 1983; 187: 133-136.
14. SWART KS, WILKS CR, JACKSON KB, HAYMAN JA. Human leptospirosis in Victoria. Med J Aust 1983; 1: 460-463.
15. HART RJC, GALLAGHER J, WAITKINS S. An outbreak of leptospirosis in cattle and man. Br Med J 1984; 288: 1983-1984.
16. AVERY TL. Leptospirosis and mental illness (Letter). NZ Med J 1983; 96: 701.
17. FAINE S. Leptospirosis- here, now. Pathology 1981; 13: 1-5.
18. CRAWFORD RP, HEINEMANN JM, McCULLOCH WF, DIESCH SL. Human infections associated with waterborne leptospires, and survival studies on serotype *pomona*. J Am Vet Med Assoc 1971; 159: 1477-1484.
19. ELLINGHAUSEN HC. Growth, survival, antigenic stability and virulence of *Leptospira interrogans* serotype *canicola*. J Med Microbiol 1976; 9: 29-37.
20. LAUER BA, RELLER LB, MIRRETT S. Comparison of acridine orange and gram stains for detection of microorganisms in cerebrospinal fluid and other clinical specimens. J Clin Microbiol 1981; 14: 201-205.
21. HIGGINS R, COUSINEAU A. The pathogensis of leptospirosis I. Hemorrhages in experimental leptospirosis in guinea-pigs. Can J Comp Med 1977; 41: 174-181.
22. NICOLESCU M, ANDREESCU N. May human leptospirosis develop as a chronic infection? Zentralbl Bakteriol A 1984; 257: 531-534.
23. ROBERTSON MH. Leptospirosis. Practitioner 1982; 226: 1552, 1555-1557.
24. McCLAIN JBL, BALLOU WR, HARRISON SM, STEINWEG DL. Doxycycline therapy for leptospirosis. Ann Intern Med 1984; 100: 696-698.
25. MARSHALL RB, SCRIMGEOUR G. Schizophreniform psychosis associated with leptospirosis (Letter). NZ Med J 1978; 88: 212-213.
26. CHENG M-K. A review of cerebrovascular surgery in The People's Republic of China. Stroke 1982; 13: 249-255.