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BIOLOGICAL AGENTS
Rocky Mountain Spotted Fever[1]

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AETIOLOGY

ROCKY MOUNTAIN SPOTTED FEVER (RMSF) is caused by the rickettsial pathogen Rickettsia rickettsii, an obligate, intracellular parasite. These microorganisms are very small (0.3m-0.5m).

Extracellular R. rickettsii ceases metabolic activity and leak cellular components, losing infectivity within a short time.

The organism possesses several virulence factors, including surface proteins, a lipopolysaccharide (LPS) cell wall, and (probably) a slime layer which appears to increase in size with virulence[1,2].

EPIDEMIOLOGY

RMSF is transmitted from wild rodents or dogs to humans by the bite of a tick. The disease is widespread in the United States, Canada, and South America. It is most prevalent in summer months (coincidental with maximum tick activity).

Transmission via aerosols is unlikely although laboratory-acquired illnesses have occurred in this way.

Infected ticks maintain the microorganism efficiently, and usually are not adversely affected by it. Transmission to other ticks is primarily transovarial (i.e.: by producing rickettsial-infected eggs), although immature ticks can acquire R. rickettsii from the blood of rickettsaemic animals (not dogs)[13].

PATHOLOGY

Between 24 and 48 hours after the tick has started feeding on its host, R. rickettsii changes from a dormant form to a highly virulent one. A further period of time is required for the microorganism to be released from the salivary glands of the tick [1]. After inoculation into the skin, rickettsia multiply and enter the lymphatic system and bloodstream. Dissemination to all parts of the body (especially the brain, heart, lung. skeletal muscles liver, kidney, gastrointestinal tract, spleen, pancreas and skin).

Rickettsia primarily infect endothelial cells. After attachment to the plasma membrane, the microorganism induces phagocytosis by the host cell. Pathogens then multiply in the cytoplasm of endothelial cells, which eventually swell and lyse, releasing the parasite. The microorganism may then spread to adjacent endothelial cells or cells deeper in the blood vessel wall. If the latter occurs, vascular smooth muscle tissue may become infected. Organisms proliferate in the endothelium of small blood vessels, causing inflammatory vasculitis. Increased vascular permeability may cause oedema of the surrounding tissues, hypovolaemia, and hypoproteinemia [1].

It is suspected that host defence factors contribute significantly to the physiological manifestations of RMSF'. Infection activates platelets, coagulation and fibrinolytic pathways[4]. No exotoxin or other important immunopathological component has been associated with the pathogen [1].

CLINICAL MANIFESTATIONS

RMSF is usually an acute self-limiting disease but may be life-threatening if treatment is not prompt. Most patients experience a mild to severe illness. Asymptomatic infection is uncommon.

The average incubation period is six to seven days but can be from one to ten days.

Initial symptoms are nondescript. The disease is often characterized by the sudden onset of headache, myalgia, weakness, and high fever. Muscle pain, anorexia, nausea, photophobia, vomiting, and abdominal pain may also be evident[6,7].

A rash usually appears three days later and consists of small (1mm-5mm diameter) lesions with a surrounding pink colour. If the pressure is applied to the spot, blanching will occur[1] Later, the lesions may develop a pin-point haemorrhage in the centre, with no blanching occurring with pressure. Approximately half of untreated RMSF cases will reach his stage, which has a mortality of approximately twenty per cent if untreated[8]. The rash is evidence of direct rickettsial damage to local tissue[1].

The rash usually begins on the extremities (palm, soles, forearms), and spreads within 48 hours to the trunk and buttocks[8].

If a rash does not appear (in approximately ten per cent of cases), a poor prognosis is indicated [6.9] as the absence of rash is often associated with a fatal outcome.

Several factors appear to be related to a life threatening illness, including absence or late appearance of rash, no history of the tick bite, host features (male, over 50 years old, black American), wrong antibiotic regimen, and atypical presentation[5].

Pulmonary involvement may cause oedema into interstitial tissues and airspaces. Symptoms may include cough, dyspnoea, and chest infiltrates and may result in respiratory failure. Mechanical ventilation may be necessary, although a 90 per cent mortality is associated with patients who reach this stage[7].

CNS manifestations may occur if the blood vessels in the brain become infected, causing a rickettsial encephalitis. As many as 28 per cent of RMSF cases show some CNS involvement'. This indicates a poor prognosis[6.7]. Symptoms may include confusion, stupor, delirium, ataxia, seizures, and coma.

Renal failure may occur as a result of hypovolaemia due to leakage of blood vessels. Renal dialysis may be necessary if urea and creatinine levels are high. Severe involvement may induce hypotensive shock and necrosis of renal tubular cells [1].

Gastrointestinal problems can arise if the blood vessels of the stomach, intestines, liver and pancreas become infected [10.11]. Symptoms include nausea, vomiting, and abdominal pain.

DIAGNOSIS

Laboratory diagnosis

Serological testing is the best diagnostic method at present. Methods used include indirect immune Ouores cent antibody assays (IFA), indirect haemagglutination assays (IHA), latex agglutination and enzyme-linked immunosorbent assays (ELISA). However, diagnosis is not usually early enough to

influence the management of the illness, as specific antibodies to R. rickettsii are not usually produced during the acute stage of the disease'. Therefore, serology should only be used as confirmation.

Cultivation and isolation of R. rickettsii from clinical specimens is not a practical diagnostic method because of the specified growth requirements of the organism, and the highly infectious nature of the pathogen in laboratory environments.

R. rickettsii DNA has been identified in acute phase specimens using PCR (Polymerase Chain Reaction) technology[12,13]. This allows the amplification and identification of the pathogen's nucleic acid in minute quantities in a very short period of time.

Differential diagnosis

Diagnosis of RMSF, especially in the early stages, is very difficult because of the non-specific symptoms and range of different manifestations. The classic signs of fever, rash and history of tick bite only appear together in three per cent of patients in the first three days[3,5].

RMSF may be confused with influenza, measles, Gram-negative bacterial sepsis, Staphylococcal sepsis, toxic shock syndrome, rubella, leptospirosis, typhoid fever, gastroenteritis, acute surgical abdomen, bronchitis, atypical pneumonia, meningoencephalitis, viral encephalitis, immune complex diseases (e.g.: SLE), infectious mononucleosis, drug hypersensitivity reactions, other rickettsial diseases, viral syndrome, or secondary syphilis[14,15].

Treatment

Fatalities from RMSF are low if treatment is started promptly. Death within the first four days of onset of symptoms is rare, even without antibiotic treatment, but the initiation of antibiotic therapy after six days is associated with a mortality rate of around 50 percent [16].

Most antibiotics have no effect on R. rickettsii - tetracycline and chloramphenicol are the recommended drugs.

RECOMMENDED THERAPY

Twenty-five to fifty mg/kg/day of Tetracycline OR 50 mg/kg/day of chloramphenicol[17] OR 25 mg/kg of oral tetracycline followed by 500 mg every 6 hours until 24 hours after the patient has become afebrile[18] OR 100 mg of doxycycline even 12 hours[19].

SUSCEPTIBILITY OF POPULATION

Males account for around 60 percent of cases. Higher incidences are reported in children between five and nine years and males over 50 years old. Fatality rates are increased in American black males (due to a genetic condition in 12 percent of this population).

PREVENTION

No effective vaccine is available. Killed R. rickettsii derived from ticks, and cell and embryonated egg culture have failed to protect humans from challenge with a virulent strain of the pathogen.

Chemical vaccines involving two R. rickettsii surface proteins have been shown to protect mice and guinea pigs from RMSE Guinea pigs have also been protected from RMSF by vaccination with a recombinant surface protein of R. conorii.

Avoid tick bites would appear to be the most effective means of preventing RMSE.

Immunity acquired after an infection is usually solid and appears to involve both humoral and cell mediated mechanisms.

POTENTIAL AS BIOLOGICAL WARFARE AGENT

Although the pathogen is highly infectious in aerosol form, it loses virulence quite rapidly outside the cellular environment. It would therefore only be infectious for a limit period of time after release.

There is a delay of about one week before symptoms start to appear, so the pathogen would be of little use if a rapid onset of disease was the objective of the attack. Mortality is usually low, particularly if treatment is prompt. However, the illness can be quite debilitating and may seriously reduce effective manpower and strain medical resources. The symptoms are non-specific, and rapid laboratory diagnosis is not yet available. Any delay incorrect identification and initiation of effective therapy increases the chance of the patient developing potentially fatal complications.

FUTURE DIRECTIONS

An effective vaccine and rapid diagnostic procedures should be developed. Recombinant and subunit vaccines are currently being developed and show some potential.

REFERENCES

1. Walker DH. Rocky Mountain Spotted Fever - a disease in need of microbiological concern. Clin Microbiol Rev 1989; 2: 227-240.
2. Hayes SF, Bergdorfer W Reactivation of Rickettsia rickettsii in Dermacentor andersoni ticks: an ultrastructural analysis. *Infect Immunity* 1982; 37: 779-785.
3. Walker DH, Fishbein DB. Epidemiology of rickettsial diseases. *Europ Epidemiol* 1991; 7:237-245
4. Rao AK, Schapira M, Clements ML, et al. A prospective study of platelets and plasma proteolytic systems during the early stages of Rocky Mountain spotted fever. *NEJM* 1988; 318: 1021-1028.
5. de Borja C, Hrehorovich Yr. Rocky Mountain spotted Fever: often a diagnostic dilemma. *Maryland Med J* 1991;40: 367- 370.
6. Helmick CG, Bernard KW, D'Angelo U. Rocky Mountain spotted fever: clinical, laboratory, and epidemiological features of 262 cases. *J Infect Dis* 1984;150: 480-488.
7. Kaplowitz LG, Fischer jj, Starling PF. Rocky Mountain spotted fever: a clinical dilemma. *Current C/in Topics Infect Dis* 1981; 2:89-108.
8. Stephenson R. Rickettsia in the regiment. *J Roy Army Med Corps* 1989; 135:21-24.
9. Westerman EL Rocky Mountain spotted fever. A dilemma for the clinician. *Arch lntern Med* 1982;142: 12106-1107
10. Adams JS, Walker DH. The liver in Rocky Mountain spotted fever. *Amer J Clin Patho* / 1991;75: 156-161.
11. Randall MR, Walker DH. Gastrointestinal and pancreatic lesions and rickettsia infection in Rocky Mountain spotted fever. *Arch Pathol Lab Med* 1984; 108: 963- 967.
12. McDade JE. Diagnosis of rickettsial diseases; a perspective. *Eur J Epidemiol* 1991; 7: 270-275.
13. Tzianabos T, Anderson BE, McDade JE. Detection of Rickettsia rickettsii DNA in clinical specimens by using polymerase chain reaction technology. *Clin Microbial* 1989; 27: 2866- 2868.
14. Clements ML, Wisseman CLjr, Woodward TE, *et al*. Reactogenicity, immunogenicity, and efficacy of a chick embryo cell-derived vaccine for Rocky Mountain spotted fever.] *Infect Dis* 1983; 148: 922-930.

15. McDonald GA, Anacker RL, Mann RE. Extraction of protective components of Rickettsia rickettsii with n-Octyl-p-0-glucopyranoside. *Rev Infect Dis* 1988; 10 (Suppl. 2): S382-S385.
16. Vishwanath S, McDonald GA, Watkins NG. A recombinant Rickettsia conorii vaccine protects guinea pigs from experimental boutonneuse fever and Rocky Mountain spotted fever. *Infect Immunity* 1990; 58: 646-53.
17. Dumler JS, Wisseman Cljr, Fiset P, Clements ML Cell-mediated immune responses of adults to vaccination, challenge with Rickettsia rickettsii, or both. *Amer J Trop Med Hygiene* 1992;46: 105-115.
18. Breitschwerdt EB, Davidson MG, Aucoin DP, et al. Efficacy of chloramphenicol, cipronoxacin, and tetracycline for treatment of experimental Rocky Mountain spotted fever in dogs. *Antimicrob Agents Chemother* 1991; 35: 2375-2381.
19. Brezina R. Diagnosis and control of rickettsial diseases. *Acta Virologica* 1985; 29:338-349.