Rickettsioses in Australia

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ABSTRACT: Australia, an island continent in the southern hemisphere, has a range of rickettsial diseases that include typhus group rickettsiae (*Rickettsia typhi*), spotted fever group rickettsiae (*R. australis*, *R. honei*), scrub typhus group rickettsiae (*R. tsutsugamushi*), and Q fever (*C. burnetii*). Our knowledge of Australian rickettsiae is expanding with the recognition of an expanded range of *R. honei* (Flinders Island spotted fever) to Tasmania and southeastern mainland Australia (not just on Flinders Island), and the detection of a new SFG species (or subspecies), tentatively named "*R. marmionii*" in the eastern half of Australia. This rickettsia causes both acute disease (7 cases, recognized so far) and is also associated (as a "*R. marmionii*" bacteriaemia) with patients having a chronic illness. The significance of the latter is under investigation. It may be a marker of autoimmune disease or chronic fatigue in some patients.

KEYWORDS: *rickettsiae*; *Australia*; *R. marmionii*

INTRODUCTION

The first rickettsial disease recognized in Australia was louse-borne epidemic typhus (*Rickettsia prowazekii*). Louse-infested convicts began to arrive by ship from England in 1788 (the first permanent settlement of Europeans in Australia). This condition prevailed for about 100 years and many outbreaks of epidemic typhus were recorded. However, the disease never became established in Australia, probably because of the sunny climate and the opportunity to wash clothes regularly.

The Portuguese who occupied the nearby colony of East Timor had been granted permission by Pope Alexander VI, as part of an agreement with Spain (the treaty of Tordesillas in 1494), to occupy any land to the east of longitude 129°E (Greenwich). The land to the west of this line ("the Pope's line") was "granted" to Spain.[1] Hence, when the English settled in eastern Australia in 1788 they only claimed the "Spanish" part of the Australian land mass (as Spain

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was then a British enemy) and did not claim the western part of the Australian land mass (as Portugual was a British ally). This line of demarcation still exists to this day as the current border between Western Australia and the rest of Australia. The Portuguese did not settle in Western Australia and it was eventually colonized (in 1829) by the British.

TYPHUS GROUP (TG) RICKETTISAE

Murine typhus (*Rickettsia typhi*) was recognized as a separate disease from the louse-borne epidemic typhus by two groups working independently—Hone,[2] a public health doctor, working in Adelaide, South Australia, and Maxcy and Havens, working in Montgomery, Alabama.[3] However, Hone's article appeared a year earlier (1922) than the other (1923). Thus murine typhus was first described in Australia.

The original Australian reports were in men who were loading bags of wheat onto ships, in rodent-infested circumstances. Later cases were associated with persons living in rodent-infested houses, especially after a disturbance of the rodent nests. This action is now known to generate infectious aerosols of *R. typhi*-infected rodent flea feces. These are inhaled by the patient. Murine typhus outbreaks have also been associated with mouse plagues in rural Queensland. These days, intermittent cases occur regularly in all parts of Australia (especially Queensland and Western Australia), so that the disease is considered to be Australia-wide. Unfortunately, no Australian isolates of *R. typhi* have been made. Diagnosis of cases has been by serology (initially by Weil-Felix test and later by micro-immunofluorescence).

SPOTTED FEVER GROUP (SFG) RICKETTSIAE

There are two definite SFG rickettsiae in Australia: *R. australis* (Queensland tick typhus), and *R. honei* (Flinders Island spotted fever).

A recently discovered third rickettsia ("*R. marmionii*") is currently being investigated as a new species or new subspecies of *R. honei.*

A. *R. australis* is transmitted by two species of ticks, *Ixodes holocyclus* and *I. tasmani*. The disease occurs down the eastern seaboard of Australia from the Torres Strait islands in the north to the southeastern corner of the Australian land mass (Wilson's Promontory).

The rickettsia is a very atypical SFG rickettsia and is a phylogenetic outlier of this group. It has probably undergone a long period of independent evolution in Australia.

The disease (Queensland tick typhus) was first recognized among soldiers training in the Australian jungle during World War II.[4] Several were rickettsiaemic and *R. australis* was isolated by animal inoculation.

This is now recognized as a fairly common disease in urban areas of eastern Australia (especially Sydney and Brisbane), where native bush is present and ticks commonly bite people.

The disease is a typical SFG illness, except that the rash may be vesicular and the disease misdiagnosed as chicken pox. There have been a few reported deaths, usually due to misdiagnosis or late diagnosis.

Native mammals such as the bandicoot and various rodent species are the normal vertebrate hosts of *R. australis*.

B. *R. honei*. On Flinders Island, in Bass Strait, the body of water between mainland Australia and Tasmania, the sole medical practitioner (Stewart) recognized a summer syndrome of fever, headache, and rash. Many patients recalled a tick bite.[5] It was subsequently shown to be a spotted fever group rickettsial infection[6] and named *R. honei* in honor of Frank Hone, the Australian discoverer of murine typhus.[7] Further studies revealed that *R. honei* was associated with the reptile tick, *Aponomma hydrosauri*.[8] This was a surprising observation, as reptile ticks had not previously been implicated in the transmission of human rickettsial diseases. *A. hydrosauri* ticks on blue-tongue lizards, tiger snakes, and copperhead snakes all contained *R. honei*. Humans are accidental hosts.

R. honei has now been shown to cause human disease in Tasmania and southeast mainland Australia,[9] as well as other parts of the world (Thailand, Texas [USA], and Sicily [Italy]). It may well have a worldwide distribution. Other tick species are likely to be involved.

Phylogenetically, *R. honei* is a mainstream SFG rickettsia. The disease it causes is relatively mild and no deaths have been reported.

C. *R. honei* subsp. *marmionii* or "*R. marmionii*." This is a new SFG rickettsia detected in Australia. Seven cases of acute illness have been detected so far. The main features are fever and headache. Only three patients had a rash and only two of these had an eschar. These cases occurred in widely diverse regions of Australia—Torres Strait islands (×3), north Queensland (×2), Tasmania (×1), and near Adelaide (×1). All cases were confirmed by PCR (7/7), culture (5/7), seropositivity (5/7), or serconversion (2/7). The polymerase chain reaction test was a real-time assay. Targeting the citrate synthase gene of *Rickettsia sp.* it was extremely sensitive (1–10 copies detectable) and extremely specific (no reactivity with *Orientia sp*., *Ehrlichia sp*., *Bartonella sp*.). All tested members of the SFG and TG were detected, with the exception of *R. bellii*.

Amplified gene sequence comparisons (16S, citrate synthase, 17kDa, ompA) showed that *R. honei* and *R. japonica* were its closest relatives. It remains to be seen whether "*R. marmionii*" is a new species of SFG rickettsia or a subspecies of *R. honei.* It was named in honor of Barrie Marmion, an Australian rickettsiologist, whose lifetime of work on Q fever has led to many advances, including the development of a Q fever vaccine.

It appears to grow best in the laboratory at 28°C in XTC-2 (amphibian) cells. The tick vector(s) is (are) not yet known, although one patient was bitten by *Haemophysalis novaeguineae* in north Queensland.

"*R. marmionii*" has also been associated with chronic illness in 14 patients. Many hundreds of patients with a variety of chronic illnesses (some undiagnosed) were tested for rickettsial disease by their doctor. Rickettsial serology, PCR, and culture were performed. Three percent of the group were rickettsaemic by real-time PCR targeting the citrate synthase gene (the assay mentioned previously). Of these 14 patients, 5 were also positive by conventional PCR targeting the 17 kDA antigen gene of *Rickettsia sp*. Sequencing of this amplified gene, in all 5 patients showed all to have 100% homology with "*R. marmionii*." A group of 400 control patients, from a different medical practice, were negative for rickettsiaemia, and this difference was statistically significant ($P < 0.001$).

The 14 rickettsiaemic patients had a variety of chronic diseases, including autoimmune disease (rheumatoid arthritis $\times 5$; Hashimoto's thyroiditis $\times 2$; polymyalgia rheumatica $\times 1$), chronic pain syndrome $\times 7$, and chronic fatigue $\times 7$; the total was >14 due to same symptoms in multiple patients.

The interpretation of these results is difficult. There appear to be three possibilities:

1. All data are spurious due to DNA contamination in our lab. This is unlikely as meticulous extraction and amplification protocols were in place, the master-mix contained UDG to prevent carryover contamination, and all control patient blood specimens were negative.
2. "*R. marmionii*" causes chronic illness. This is a possibility but the data are insufficient to make such a claim at this time.
3. "*R. marmionii*" becomes latent in a patient after primary infection. At some stage later in their life patients develop an immunosuppressive illness or are therapeutically immunocompromised. This allows the latent "*R. marmionii*" to reactivate and establish a low-level rickettsiaemia, which was detectable by our assays.

It is not known whether the circulating "*R. marmionii*" is responsible for any of the patients' symptoms or whether rickettsaemia is just a marker of patient immunosuppression.

This work needs to be repeated with another similar patient cohort in another rickettsial laboratory.

SCRUB TYPHUS (*ORIENTIA TSUTSUGAMUSHI*)

The northern third of Australia is tropical. In the early days of European colonization of Australia (19th century), febrile illness was a major impediment

to people living and working in tropical Australia. Among the various causes of fever, not differentiated at that time, however, was scrub typhus.

The mite *Leptotrombidium deliense* is endemic in tropical Australia and cases have been detected in the Kimberley region of Western Australia, the Top End of the Northern Territory (especially Litchfield Park), coastal tropical Queensland, and the islands of the Torres Strait (especially Darnley Island). In many of these parts of Australia human population density is very low, so cases are not common or there are few doctors to diagnose the cases.

The disease also occurs in Papua New Guinea from where the KARP serotype originated from a soldier during World War II.

Darnley Island, a small island with only 150 people, has an extremely high incidence of rickettsioses, including *O. tsutsugamushi*, *R. australis*, and "*R. marmionii*." Each year there are several cases on the island.

Deaths have occurred from scrub typhus due to the patients' remote location, delayed medical attention, slow evacuation to hospital, or inappropriate antibiotics.

Q FEVER (*COXIELLA BURNETII*)

II Q fever disease is common in central eastern Australia: There are about 500 cases reported in Australia per year. With Australia's population of 20 million, this gives a Q fever incident rate of approximately 25/100,000 population per year.

Most cases occur in adults in the workforce, with certain occupations (associated with sheep, cattle, or goats) being at most risk.

Q fever was first described in Australia in 1937[10] among abattoir workers in Brisbane. It is still a significant health hazard in those abbatoirs that do not immunize their staff against Q fever.

Q fever also occurs among farmers and the farming community. It occurs more commonly in drought conditions since the dust, containing *C. burnetii* in a dessicated but viable form, is blown long distances from the infected source animals.

Many sero-positive persons do not recall an illness compatible with Q fever, so it is possible that asymptomatic sero-conversion can occur. Several species of Australian ticks carry *C. burnetii*, although virtually all human cases are thought to occur via infected aerosols. Pneumonia is a rare manifestation of Q fever in Australia and patients with acute disease usually present with fever, myalgia, headache, and sometimes hepatitis. Chronic Q fever in Australia occurs mainly as endocarditis or post-Q fever chronic fatigue.

CONCLUSION

Australia has a full range of rickettsial diseases, with the exception of louse-borne epidemic typhus (*R. prowazekii*).

Q fever (*C. burnetii*) is the most common, but Queensland tick typhus (*R. australis*), Flinders Island spotted fever (*R. honei*), murine typhus (*R. typhi*), and scrub typhus (*O. tsutsugamushi*) also occur regularly.

A newly recognized SFG rickettsia ("*R. marmionii*") appears to cause both an acute rickettsial illness and to be associated (as a rickettsaemia) in some patients with various chronic (and presumably immunosuppressive) diseases. Its role in chronic illness is not yet clear.

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