

Murine typhus returns to New South Wales: a case of isolated meningoencephalitis with raised intracranial pressure

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Murine typhus (MT) occurs worldwide, but, in Australia, is only regularly diagnosed in south-west Western Australia. Meningoencephalitis is an uncommon complication of MT, often accompanied by rash or systemic involvement. We report a case of MT presenting exclusively with meningoencephalitis, raised intracranial pressure, papilloedema and bilateral 6th cranial nerve palsies. MT should be considered in patients with "aseptic" meningitis or meningoencephalitis, even in the absence of other typical features of a typhus-like illness. (MJA 2011; 194: 652-654)

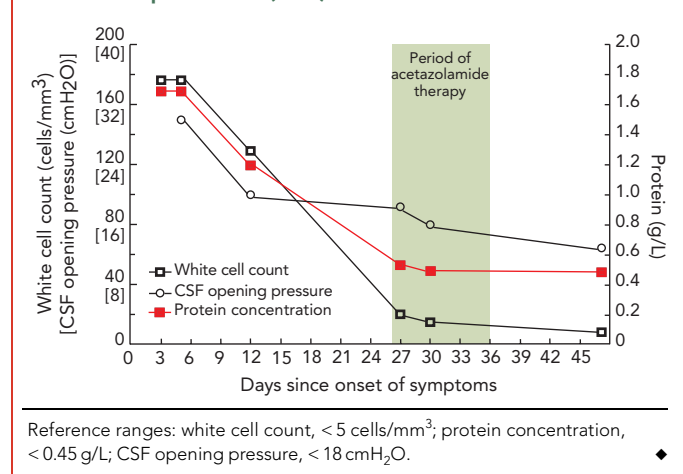
Clinical record

In June 2010, a 20-year-old man who worked as an apprentice chef developed a progressively severe, non-pulsatile global headache without report of additional neurological symptoms, rash, fever or other constitutional features. After 3 days of headache he woke with severe headache and associated nausea and vomiting. A short time later, while standing in the shower, he developed paraesthesiae, starting initially in his fingers and toes, then spreading quickly up his limbs, trunk and finally involving his face and tongue. He subsequently collapsed onto the bathroom floor and was unable to move or speak, although he did not lose consciousness. While he was being transported to hospital, a speech disturbance was noted, with fluent but nonsensical speech. On initial assessment he was noted to be febrile at 39°C and confused, but without rash, organomegaly, lymphadenopathy or other signs on complete physical examination. There were no additional findings on neurological examination.

This patient was normally well, had no prior significant medical history and took no regular medications or complementary therapies. He did not smoke, drank alcohol rarely and denied using cannabis or other recreational substances. He lived with his family on a small acreage in a rural area of the mid-north coast of New South Wales. Two dogs and two horses lived on the property, and an aviary containing parrots and an enclosure housing chickens were contained within the yard. There were no cats on the property. The patient reported that rats and mice were frequently seen around the chicken enclosure, but he had not been in its vicinity for several weeks before his illness. About a week before the onset of the headache, he had visited a friend who kept a pet rat indoors. He had never travelled outside NSW, and his travel within NSW was limited almost exclusively to infrequent travel between his home and Sydney. He did not recall any flea or other insect bites.

He was diagnosed with meningoencephalitis after a lumbar puncture on the day of admission showed a predominantly lymphocytic pleocytosis of 180 lymphocytes/mm³ (reference range [RR], <5 lymphocytes/mm³) with an elevated protein level of 1.7 g/L (RR, <0.45 g/L) and a normal glucose concentration (Box 1). He was admitted to the intensive care unit (ICU) and remained there for a week because of fluctuating confusion and fever. During that week he had two further episodes like the one described before his presentation, including on Day 10 of admission requiring readmission to the ICU. Empiric treatment with a number of antimicrobial medications was commenced at standard doses in the following order: ceftriaxone (intravenously, Days 3 to 17 of

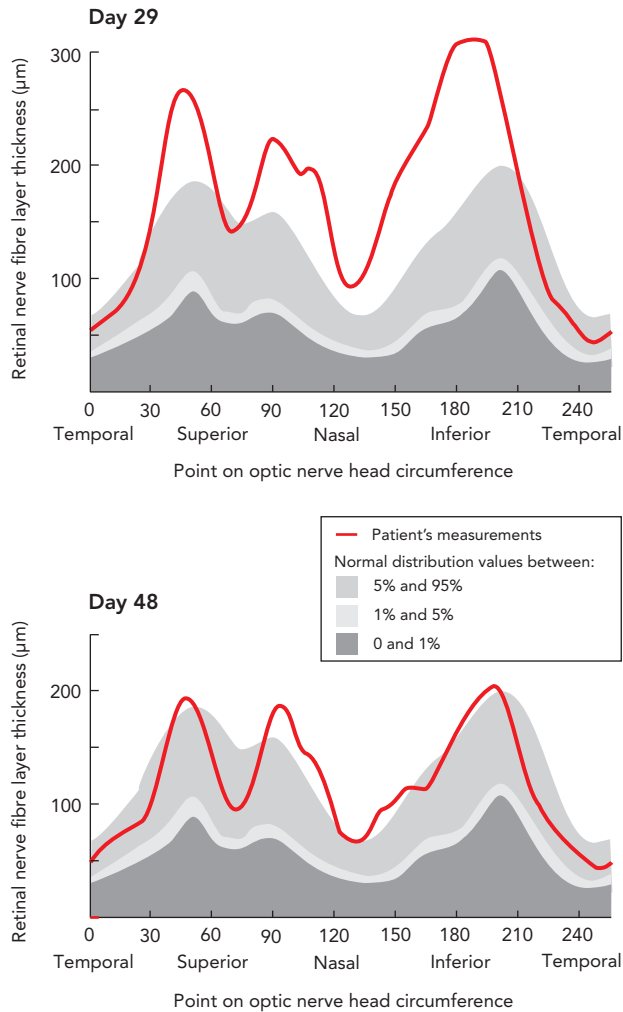
1 Serial findings on examination of the patient's cerebrospinal fluid (CSF)



illness); ampicillin (intravenously, Days 4 to 9); aciclovir (intravenously, Days 4 to 17); vancomycin, oseltamivir and azithromycin (intravenously, Days 10 to 17). Phenytoin therapy (1000 mg intravenous loading dose, followed by 300 mg orally, daily) was commenced on the day of admission owing to the possible seizure activity before presentation. He was discharged from hospital on Day 17 of the illness after the fever and headaches resolved.

On presentation, the results of blood investigations including a full blood count, liver function tests, a C-reactive protein test, renal function tests and electrolyte level measurements were normal. A transient leukocytosis developed after admission and peaked on Day 6 of admission at $14.0 \times 10^9/L$, with a predominant neutrophilia. At no time was there significant derangement of liver function tests. Findings on brain imaging, including gadolinium enhanced magnetic resonance imaging of the brain on two occasions, magnetic resonance venogram and magnetic resonance angiogram were all normal. Serial lumbar punctures were performed (Box 1) showing the reducing white cell count and protein level. Cerebrospinal fluid (CSF) opening pressure was elevated to 30 cmH₂O (RR, <18 cmH₂O) measured on Day 5 and this normalised by Day 27. Results of serological tests for human immunodeficiency virus, leptospirosis, Q fever, mycoplasma, brucellosis, psittacosis, and Ross River fever, which were performed during both the acute and convalescent phases of the illness, were negative. Repeated tests of the CSF for cryptococcal antigens were

2 Serial ocular coherence tomography of retinal nerve fibre layer thickness showing improving papilloedema from Day 29 to Day 48



negative. CSF cultures for bacteria, fungi and mycobacteria were also negative, as was polymerase chain reaction testing for herpes viruses and enterovirus. Indirect immunofluorescence detecting total antibody against rickettsiae in the typhus group (*Rickettsiae typhi* and *R. prowazekii*), spotted fever group (*R. honei* and *R. australis*) and scrub typhus (*Orientia tsutsugamushi*) was performed in parallel on serum collected on Days 9 and 41. Antibodies against *R. typhi* were detected at a titre of 1/256 on Day 9, rising to $\geq 1/1024$ on Day 41. Antibodies in each CSF specimen showed cross-reactivity with *R. prowazekii* at equivalent titres, but not with other rickettsial species.

The patient first noticed diplopia and reduced visual acuity on Day 10, which peaked on Day 20 of his illness. At this point, bilateral partial 6th nerve palsies and papilloedema were noted. Because of persistent visual symptoms and papilloedema, therapy with 250 mg acetazolamide orally, twice daily was commenced on Day 26. Papilloedema was documented on Day 28 by ocular coherence tomography (OCT), a measure of retinal nerve fibre layer thickness and indicative of the degree of optic disc swelling (Box 2). The 6th nerve palsies resolved after Day 30 and regular

fundoscopy and repeat retinal OCT showed the papilloedema continued to resolve (Box 2). Acetazolamide therapy was ceased on Day 35. The patient had not experienced recurrence of the headaches or neurological symptoms at 6 months after the onset of the illness.

Discussion

We present the first case of murine typhus (MT) reported in NSW since the 1940s. Perhaps even more notably, we have now reported the first case of MT causing proven, isolated meningoencephalitis with raised intracranial pressure (ie, rarely reported complications without other typical clinical features) in Australia.

MT (endemic typhus) was first described in 1922 with a series of cases from South Australia.¹ There have been further outbreaks in the Darling Downs region of south-east Queensland and south-west Western Australia.² In each series, exposure to rodents was reported in a significant proportion of cases. MT has been reported worldwide in diverse geographic areas.³ Several areas continue to regularly report new cases including Perth in WA,⁴ South-East Asia,⁵ and Texas in the United States.⁶ The first case of MT in Victoria was recently reported,⁷ and no locally acquired cases of MT have been reported from NSW since 1944.⁸

The disease is caused by *R. typhi*, which is an obligate intracellular gram-negative bacterium with an incubation period of 7–14 days. There are two major sources of transmission. The major route of infection worldwide is the rat–flea–rat cycle.⁹ Rat fleas (*Xenopsylla cheopis*) transmit *R. typhi* to a roof or Norwegian rat (*Rattus rattus* and *Rattus norvegicus*, respectively). Humans are infected when flea faeces containing *R. typhi* are inoculated into the site of a flea bite. Alternatively, the organism may be inhaled from an environment contaminated with flea faeces. Another transmission cycle has been identified, which involves predominantly cats and opossums and their fleas (*Ctenocephalides felis*).¹⁰ In the case we present here, it is likely that the patient was infected as a consequence of close contact with rodents, with a respiratory route of infection being most likely.

Although serological testing does not separate MT and epidemic typhus, MT has been distinguished by its milder course and the lower associated mortality.¹ Fever is almost universal, and about 75% of affected patients complain of headache. Rash is observed in about 50% of cases, and is usually a macular or maculopapular rash that starts on the trunk and spreads to the extremities. A number of other features may accompany the illness, including myalgia, arthralgia, gastrointestinal symptoms, jaundice and hepatic dysfunction.¹¹ Among the antibiotics given to our patient, azithromycin was the only one with activity against rickettsiae, and may have altered the course of the illness. However, without treatment, MT is usually a self-limiting illness, with symptoms resolving after 2 weeks.¹

Neurological complications like those described in this report are uncommon in MT. Aseptic meningitis or meningoencephalitis has been reported in 2%–14% of cases.^{12,13} There is often a coexisting rash or other systemic features of typhus,¹² and isolated meningitis or meningoencephalitis has been reported previously in only six patients.^{13,14} Papilloedema and raised intracranial pressure can occur with the meningitis, and 6th nerve palsy has been reported in a single case.¹³ Facial nerve palsy has also been described in association with meningitis in MT.¹⁴ Neurological dysfunction is usually reversible, but long-lasting deficits have been reported.^{13,15} In affected patients, the CSF typically shows a

predominantly monocytic pleocytosis with variable elevation of protein concentration.¹³ The raised intracranial pressure and optic disc swelling in our patient were transient, and it is likely that intracranial pressure changes associated with meningitis are monophasic like MT infection generally. This has important implications for the extent and duration of treatment of associated raised intracranial pressure.

This is the first report of MT causing proven, isolated meningoencephalitis with raised intracranial pressure in Australia. The clinical manifestations documented represent rarely reported complications of MT without other typical clinical features. The case illustrates that MT should be considered in the differential diagnosis of a patient presenting with “aseptic” meningitis or meningoencephalitis with or without raised intracranial pressure. This is particularly relevant in areas where MT is regularly observed, like south-west WA. However, it should also be considered in other areas of Australia. The absence of other typical features of a typhus-like illness such as rash should not preclude testing for *R. typhi*, as antibiotic therapy may reduce the duration and severity of the illness, and establishing the diagnosis of MT provides valuable information about the likely course and prognosis of the illness.

Competing interests

None identified.

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