Murine Typhus with Presentation of Unilateral Abducens Nerve Palsy: A Case Report

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Abstract

Neurologic complications of murine typhus were uncommon but included aseptic meningitis, meningoencephalitis and rarely if ever, cranial nerve deficit. We report a rare case of murine typhus complicated with increased intracranial pressure and isolated abducens nerve palsy in a 31-year-old returned traveler. The patient developed right abducens nerve palsy in the absence of other neurologic symptoms or signs within 12 hours following receipt of a lumbar puncture. Murine typhus was diagnosed by serology using indirect immunofluorescence assay. The patient received 8-day antibiotic therapy with favorable response. His abducens palsy resolved completely without adjuvant therapy in 3 months. Literature was reviewed focusing on pathogenesis and management. (J Intern Med Taiwan 2014; 25: 36-40)

Key Words: Murine typhus, Neurologic complications, Abducens nerve palsy

Introduction

Murine typhus, a zoonosis caused by *Rickettsia typhi* and mainly transmitted by rat fleas, is distributed worldwide. It is not infrequently seen in Asian beach resorts with abundant urban rats. Classical triad consisting of fever, headache and rash might not be present at all times and diagnosis is often made by clinical suspicion. The clinical course is generally benign and self-limited. Complications were uncommon but included jaundice, pneumonia, renal insufficiency and meningitis[1]. The neurologic complications of murine typhus occurring in 2-10% of patients, encompass aseptic meningitis, meningoencephalitis and rarely if ever, cranial nerve deficit[2,3]. We report a rare case of murine typhus complicated by increased intracranial pressure and reversible unilateral abducens palsy in a returned traveler from the island of Bali, Indonesia.

Case report

A 31-year-old previously healthy male engineer was admitted to the emergency room with a 2-day history of fever, diffuse myalgia, and headache 10 days after returning from a 5-day trip to Bali. He denied any upper respiratory tract symptoms but was initially treated as a flu like illness with minimal improvement. He revisited the ER in 2 days due to persistent fever and headache. The patient reported a history of contact with snakes and sea turtles during the trip. On examination, he was alert and his neck was supple. He had a fever of

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39°C and tachycardia of 112/min. The blood pressure was 148/96 mmHg. No rash or lymphadenopathy was noted. Neurologic examination including fundoscopy was normal. The rest of the physical examination was unremarkable. Laboratory results were as follows: leukocyte count 4790/mm^3, neutrophil count 3592/mm^3, hemoglobin 12.5g/dl, platelets 190000/mm^3, ALT 74 U/L (normal 0-35), AST 62 U/L (normal 5-40), and LDH 283 U/L (normal 106-211). Chest radiography and abdominal ultrasonography were normal. Serology for syphilis and HIV was negative. Computed tomography of the brain was normal. A lumbar puncture using a 22-gauge needle on day 2 of admission showed clear cerebrospinal fluid (CSF) with opening pressure 23 cm H_2O and closing pressure 19.9 cm H_2O, but biochemistry and cell count of CSF did not show any abnormality. Cultures from blood and CSF were sterile. CSF serology for *Cryptococcus neoformans* was also negative. Between 9-12 hours following receipt of a lumbar puncture, he noticed double vision. Total right abducens palsy in the absence of other neurologic symptoms or signs was noted (Fig 1). Magnetic resonance imaging (MRI) with and without gadolinium enhancement of the brain on the sixth hospital day failed to show any brain stem and cavernous sinus lesion or signs of CSF volume depletion and intracranial hypotension. (Fig 2) The TSH level was normal. A repeat fundoscopy one week apart showed mildly blurred optic disc margins but there was no reduction of visual acuity. Treatment with doxycycline 100mg po bid

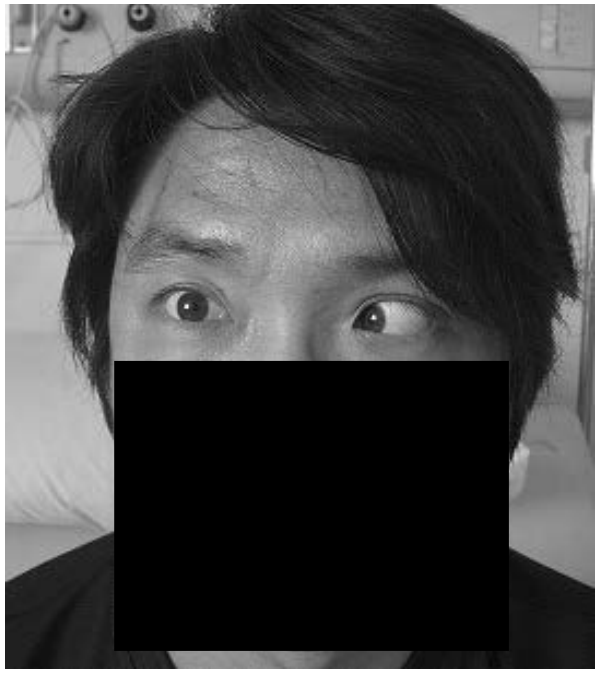

Figure 1. Total right abducens nerve palsy.

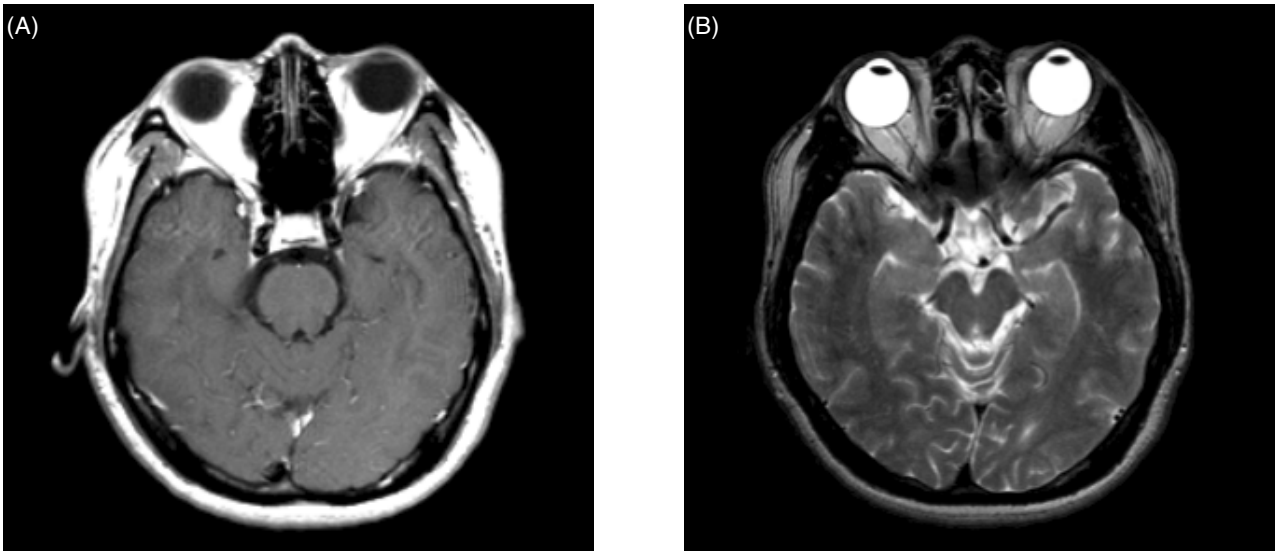

Figure 2. Magnetic resonance imaging of the brain failed to show any abnormality. (A) T1-weighted axial image with Gd enhancement. (B) T2-weighted axial image.

was started on the fourth hospital day. Following one day of oral doxycycline, therapy was switched to intravenous levofloxacin 500mg per day. Fever with headache abated on the second day of antibiotic switch and levofloxacin was continued for a total of 7 days. Serology for specific antibodies to leptospirosis, *Rickettsia typhi*, *Orientia tsutsugamushi*, *Rickettsia japonica*, and *Rickettsia coronii* was performed at the Centers for Disease Control, Taipei, Taiwan (Taiwan CDC). Murine typhus was diagnosed by an IgM titer of 1:160 and an IgG titer of 1:640 (*R. typhi* IFA slide kit; SCIMEDX) on the 12th day after fever onset. The rest of the serology was negative. A repeat serologic test using the same method for *R.typhi* 8 days apart revealed an IgM titer > 1:160 and an IgG titer > 1:640. His abducens palsy started to resolve after 2 months and recovered completely 3 months after symptom onset in the absence of adjuvant steroid therapy.

Discussion

Murine typhus has a wide geographic distribution and was thus not infrequently seen in international travelers. Central nervous system complications of murine typhus are less commonly encountered than those of epidemic typhus or spotted fever rickettsiosis[4]. The serologic test used to diagnose murine typhus is indirect immunofluorescence assay (IFA). We tested for *Rickettsia japonica* and *Rickettsia coronii* because the patient had a history of overseas traveling and cross reactions on IFA have been described[5,6].

Along the long course of the abducens nerve, possible pathophysiological mechanisms responsible for nontraumatic isolated abducens palsy include pontine lesion, cavernous sinus syndrome, increased intracranial pressure and withdrawal of CSF during lumbar puncture. Abducens palsy after diagnostic lumbar puncture can be uni- or bilateral, usually occurs 4-14 days after lumbar puncture using large-bore needles (< 20-gauge) and results from CSF hypotension due to persistent spinal fluid leakage through the puncture site[7]. The reported incidence of extraocular muscle paralysis after lumbar puncture varies from 1 in 400 to 1 in 8000[8]. Our patient developed abducens palsy within 12 hours after lumbar puncture using a standard-gauge needle. The gap between opening and closing pressures following lumbar puncture was close and both pressures were not way above normal limits. In addition, findings of imaging study and fundoscopy were not correlated with CSF hypotension, which makes this explanation more unlikely.

An earlier review by Brooks reported that typhus-related ocular abnormalities might involve every part of the eye. 20% of the 2031 patients had ocular findings, but only 11 of them (0.5%) had extraocular problems[9]. The authors described the pathology of typhus fever as primarily a disease of the blood vessels. Microscopically, there is a generalized proliferative endangiitis involving mainly small vessels. However, the diagnostic methods and details of clinical characteristics of affected eye movements in relation to specific cranial nerves were not given in this review. Manor and colleagues report 2 cases of papilledema in the absence of elevated intracranial pressure in endemic typhus[10]. The fundus changes subside with abating of fever and are thus ascribed to ocular vessel inflammation. Our patient's fundus examination showed bilateral blurred optic disc margins after fever had disappeared, suggesting that papilledema might partly be due to increased intracranial pressure.

Rickettsial invasion of the central nervous system can be part of the involvement of the endothelium of the vascular system in multiple systems. Among the rare neurologic complications such as cranial nerve deficit, facial paralysis or hearing impairment due to murine typhus has been reported in limited numbers[11]. Complications could occur within one to two weeks after disease onset. In 1986, Wenzel and colleagues reported five cases of

acute febrile cerebrovasculitis as a presumed *R.typhi* infection[12]. Evidence of increased intracranial pressure was noted in all of the five cases who had received lumbar puncture. One was complicated by a cranial nerve VI deficit but the clinical course and treatment were not described. The authors inferred that there was a causative link between transient oculomotor signs and brainstem microvascular involvement. Our patient presented with isolated increased intracranial pressure without CSF pleocytosis, which suggested a different mechanism other than primary meningitis. Due to the long course of the abducens nerve, it is also vulnerable to the increase in intracranial pressure. Despite that we did not use a more sensitive method such as angiography to detect small vessel abnormalities in the brain stem and the affected eye, we propose that combination of the two mechanisms: increased intracranial pressure and rickettsial invasion of endothelium of the brain stem with or without concomitant ocular involvement and a secondary immune response, contributes to this rare complication.

Therapy of murine typhus with suspected CNS complications included timely effective antibiotics and adjuvant agents. Effective antibiotics used in published case series included various classes of antibiotics such as tetracyclines, macrolides and fluoroquinolones. However, no comparative efficacy or outcome was described within different classes of antibiotic use in these reports.

The value of coadministration of adjuvant systemic corticosteroids with antibiotics for alleviation of neurologic complications caused by rickettsioses is still debated. Analysis of efficacy and timing of adjuvant therapy has been difficult due to rarity of such complications, which makes the anecdotal reports less applicable in clinical practice.

In summary, clinicians should be alert and include rickettsial infection as one of the infectious causes of febrile eruption with suspected cerebrovasculitis in a returning traveler from endemic areas. Adequate prompt antibiotics usually result in good prognosis without neurologic sequela.

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地方性斑疹傷寒合併單側外旋神經麻痺：病例報告

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摘　要

斑疹傷寒合併神經學併發症並不常見，若併發外旋神經麻痺更是罕見。我們報告一例31歲男性病患在巴里島感染斑疹傷寒併發顱內壓升高與單側外旋神經麻痺的個案。病患在腰椎穿刺後不到12小時出現右側外旋神經麻痺。經過單用適當抗生素治療後，病患恢復良好。外旋神經麻痺3個月後完全緩解。