



Rickettsia typhi central nervous system infection

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ABSTRACT

A 39 year-old male was residing along the south coast of Texas, the USA, presented with fever, myalgias, headaches, and weight loss for ten days. Symptoms and manifestations progressed to include nuchal rigidity, photophobia, hyponatremia, thrombocytopenia, and transaminitis despite the intravenous administration of ceftriaxone and azithromycin. A lumbar puncture performed in the Emergency Department yielded pleocytosis and glucose cerebrospinal fluid/serum ratio of 0.35, suggestive of meningoencephalitis. Conglomerate data raised the suspicion of meningitis secondary to a zoonotic acquired infection, which was later confirmed to be *Rickettsia typhi*. Doxycycline is the drug of choice for the suspected *Rickettsia* disease. After doxycycline administration, the patient improved and was discharged home asymptomatic.

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Introduction

The *Rickettsia* genus consists of gram-negative obligate intracellular bacteria. Infections manifest clinically in their initial stages as an acute, nonspecific, febrile illnesses, often indistinguishable from other infectious and noninfectious etiologies. The severity of this infection can vary depending on the particular species, host, and duration of symptoms. Transmission occurs by multiple vectors, including ticks, fleas, lice, and mites [1].

The *Rickettsia* genus consists of four groups identified as ancestral, spotted fever, typhus, and transitional. The latter three are well-established pathogens. The typhus group consists of *R. typhi*, also known as murine typhus or endemic typhus and *R. prowazekii*, known as epidemic typhus. Murine typhus has been reported worldwide. However, *R. typhi* thrives best in coastal areas [2]. Most recently, *Rickettsia typhi* cases have increased within the United States, with Texas yielding the highest percentage of flea-borne typhus cases annually. According to the Texas Department of State Health Services and the US Census Bureau, there were 157

cases reported in 2008, and 738 cases reported in 2018. Adjusted for Texas's population in 2008, this was the equivalent of 0.646 cases per 100,000 people, and 2.57 cases per 100,000 people in 2018.

The lack of pathognomonic clinical signs during the initial presentation and limited diagnostic options are the most significant challenges for general practitioners to diagnose murine typhus. Promoting education and awareness, prompt administration of empirical treatment in a suspected diagnosis, and waiting for confirmation testing will make for a significant improvement in overall patient outcomes.

Case presentation

The patient was a 39-year-old Hispanic male residing in coastal south Texas who developed a low-grade fever, malaise, and myalgias for ten days. Within 24 h of the onset of symptoms, he took an azithromycin 5-day dose pack that he had at home, but his symptoms did not improve. The patient visited a local emergency department seven days after his symptoms first appeared, with fever, fatigue, myalgias, and weight loss.

The physical exam revealed an oral temperature of 36.4 C, peripheral pulse 87 beats per minute, 18 breaths per minute, blood pressure 115/73 mmHg, and an oxygen saturation of 98 % at room air. The patient was coherent and oriented to person, place, and time. The lungs were clear to auscultation. The heart had a regular heart rate and rhythm without murmurs, gallops, or rubs. Chemistry diagnostics revealed sodium 129 mmol/L, potassium 3.0 mmol/L, chloride 95 mmol/L, lactate dehydrogenase 255 IU/L,

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alanine aminotransferase 59 IU/L, and aspartate aminotransferase 50 IU/L. Automated complete blood count showed white blood cell count 65,000/ μ L, platelets 119,000/uL lymphocytes 13.10 %; neutrophils 77.2 %. Urinalysis showed protein 1+, specific gravity 1.015, trace blood, and 2–4 epithelial cells. Influenza A, influenza B, and rapid strep test for group A streptococcus screens were all negative.

A single view chest radiograph did not reveal an acute cardiopulmonary process, and computed tomography without contrast of the abdomen and pelvis did not show an acute intra-abdominal or pelvic finding. The patient was discharged home with a lower respiratory infection and encouraged to continue supportive care with rehydration, ibuprofen, and acetaminophen. The symptoms progressively worsened despite the use of over-the-counter therapy.

He returned to the emergency department two days later, complaining of a significant headache and persistent fever and malaise. A brain CT scan was normal. Repeated laboratories demonstrated persistent hyponatremia of 132 mmol/L, albumin 3.4 g/dL, and elevated alanine aminotransferase of 59 IU/L. The patient received intravenous ceftriaxone and was placed in observation. However, the patient continued to have elevated temperatures with progressive lethargy in the morning. The patient was transferred to another facility for a higher level of care because of clinical deterioration.

Upon arrival to the emergency department following the transfer, the physical exam revealed an oral temperature of 37.9 C, pulse 96 bpm, 16 breaths per minute, blood pressure 128/80 mmHg, and an oxygen level 99 % at room air. There was bilateral photophobia with a +1 Kernig sign and bilateral hyper-reflexia of his patellar tendons. A lumbar puncture spinal fluid analysis showed a pleocytosis of 28 cells/ μ L with a lymphocyte percentage of 52 % and PMNs at 27 %. CSF protein was 40 mg/dL, and there was hypoglycorrhachia of 57 mg/dL. Compared to the patient's serum glucose of 161 mg/dL, this represented a ratio of 0.35. CSF cultures were negative, including for acid-fast bacilli, cryptococcus, and fungus.

The patient received intravenous ceftriaxone, acyclovir, and doxycycline at the moment of admission to the hospital. The meningeal inflammation was treated with dexamethasone 4 mg intravenously. A presumptive diagnosis of murine typhus was established based on presenting clinical manifestations and endemic awareness. Doxycycline 100 mg was administered intravenously due to clinical suspicion of rickettsia infection. Later results from the zoonotic panel were positive for *Rickettsia* (quantitative titer of 1:512). Blood serology was negative for typhus, dengue, malaria, histoplasmosis, cryptococcosis, Q fever, and ehrlichiosis.

For the next five days, the patient improved dramatically, including the resolution of his headache and fever. The transaminitis resolved after treatment of the infection. The patient

worked outside in dense brush areas and was also dealing with a flea infestation of his dogs. On the physical exam, he had several patches of xerosis that resembled small insect bites. At discharge, the patient had complete resolution of his symptoms. The patient received doxycycline 100 mg orally twice a day for a total of 14 days as an outpatient. There were no symptoms at follow up in the clinic one week after discharge. The neurologic exam was normal, without evidence of residual weakness, loss of balance, derangement of cranial nerves, visual changes, or general sensation.

Discussion

Rickettsia sp. infections are attracting growing interest from Public Health organizations due to increasing awareness of their ongoing clinical presence and the severity of their impact on community health [3]. Interest has also heightened due to the potential development of the genus as a bioterrorism weapon. Reference centers like the CDC for Tropical Diseases of the University of Texas at UTMB and the Medical Branch of the University of Texas at Galveston have established protocols to prevent and promote recognition of this species on potential lethal febrile diseases. The outbreaks related to this genus in the United States corresponded with the appearance of vectors or via ecological changes.

Over the last decade, the Texas Department of State Health Services and the CDC have seen an escalating incidence of *R. typhi* in Texas, specifically in the south coastal counties [2]. A new rise in clinical cases demonstrates a parallel increase in virulence of the organism, which has led to critical presentations, prolonged admissions, and detrimental consequences secondary to delayed treatment [4].

R. typhi has a well-recognized zoonotic life cycle orbiting around the peridomestic cycle of the cat flea (*Ctenocephalides felis*) or the rat flea (*Xenopsylla cheopis*). These are the most common vectors that infect a human. Humans acquire the infection through the skin by inoculation of the feces of the infected flea after a bite, by autoinoculation of feces while scratching the skin, or through mucosal surfaces like the conjunctivae or the oral mucosa [5]. The increasing rates in murine typhus-infected human cases over the past decade has allowed us to reevaluate the significance of what was once considered an infection with a low mortality rate. This type of infection has generated an increase in awareness among healthcare providers in areas most susceptible to murine typhus [6].

The *Rickettsia* genus infection results in an initial direct infection of endothelial cells with the ability to progress to multi-organ endothelial inflammation and subsequent capillary leak and complications such as acute respiratory adult distress syndrome (ARDS), myocarditis, vasculitic skin lesions, meningo-encephalitis, and liver, renal and gastrointestinal involvement may become evident. An increase in capillary permeability may trigger

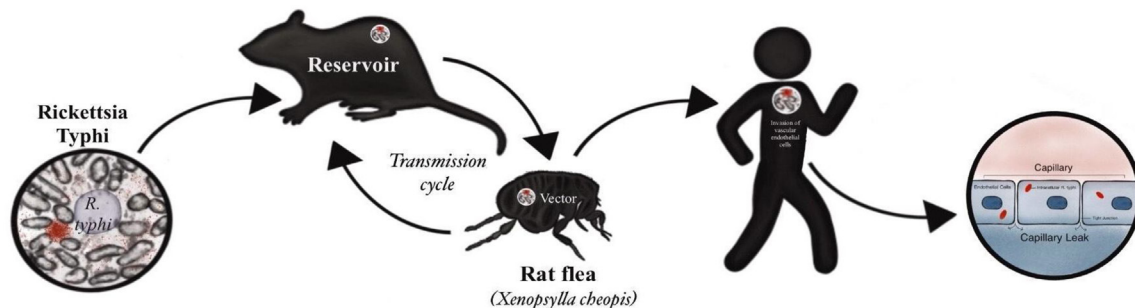


Fig. 1. Illustrates the mechanism of transmission of *R. typhi* from the reservoir to the vector and subsequently infecting a human. Direct invasion of endothelial cells increases permeability leading to a capillary leak.

Table 1
Cases of *Rickettsia typhi* Meningitis.

First Author	Year	Sex/Age	Location	Presenting Symptoms	CSF Analyses	Confirmatory Methods	Treatment	Outcome
Silpapojakul [12]	1991	26/M	Songkla, Thailand	Meningoencephalitis, rash, seizure (10d)	Mono cells 27; PMN 0; Pro 0.55; Glu 36	Weix-Felix Titers >2560	Doxycycline	Recovered
Silpapojakul	1991	60/F	Songkla, Thailand	Fever, HA & Myalgia (10d), AMS, Scleral injection, Diffuse crepitations, maculopapular rash to BUE (on exam)	Mononuclear cells 45; PMN 9; Pro 1.85; Glu 69	Serology Titers 1:1600	Ampicillin, Amikacin, Chloramphenicol	Died (cardiac arrest)
Silpapojakul	1991	70/M	Songkla, Thailand	Aseptic meningitis, alcoholism, jaundice, renal insufficiency (4d)	Mono cells 5; PMN 10; Pro 1.04; Glu 39	Serology Titers 1:12800	Doxycycline	Recovered
Masalha [13]	1998	18/F	Beer-Sheva, Israel	HA, Fever, Abd pain, Visual blurring, Vomiting (2wk); Splenomegaly, nuchal rigidity, bilat papilledema, R-sided hemiparesis (on exam)	Press 310; Cell 83–640 (5d); %mono cell 90–98; Pro 101; Glu 45	Serology Titers Positive for IgM, specifics not reported	Antituberculous tx; IV doxycycline (after 14d)	Recovered, residual R hemiparesis
Masalha	1998	22/F	Beer-Sheva, Israel	HA, Malaise, Fever (2wk); Bilat papilledema, R lateral rectus palsy, horizontal nystagmus (on exam)	Press 50, Cell count 10, % mono cell 90; Pro 75; Glu 64	Serology Titers Positive for IgM, specifics not reported	IV Doxycycline (started on 5th day of admission)	Recovered
Masalha	1998	25/F	Beer-Sheva, Israel	HA, visual blurring (3wk) Fever, papilledema (on exam)	Press 220; Cell count 16; % mono cell 95; Pro 38; Glu 58	Serology Titers Positive for IgM, specifics not reported	IV Doxycycline (started on 4th day of admission)	Recovered, secondary optic atrophy
Masalha	1998	25/M	Beer-Sheva, Israel	Fever (10d); Rt hemiparesis (on exam)	Press 200; cell count 97; % mono cell 95; Pro 65; Glu 55	Serology Titers Positive for IgM, specifics not reported	IV doxycycline (3rd day of admission)	Recovered
Masalha	1998	28/M	Beer-Sheva, Israel	Fever, Drowsy (2wk); papilledema (on exam)	Press 210; cell count 95; % mono cell 85; Pro 65; Glu 55	Serology Titers Positive for IgM, specifics not reported	IV ceftriaxone, IV doxycycline (on 7th day of admission)	Recovered
Galanakis [14]	2002	04/F	Crete, Greece	Fever 40C, chills, myalgia, malaise, rash (8d); pharyngitis, conjunctivitis, lymphadenopathy, hepatosplenomegaly, systolic murmur (on exam); nuchal rigidity (4th day of admission)	RBC 22; WBC 22; %lymph 75; Pro 24; Glu 53	Serology Titers IgG 1:30720 IgM 1:400	IV Immunoglobulin, aspirin (at admission)	Recovered
Galanakis	2002	14/M	Crete, Greece	fever, chills, HA (6d, transfer from hospital); rash (4th day of admission at other location)	RBC 145; WBC 20; %lymph 95; Pro 29; Glu 50	Serology Titers IgG 1:61440 IgM 1:25600	Penicillin G; Vibramycin for 10d	Recovered
Vallejo-Maroto [15]	2002	50/M	Seville, Spain	Fever, myalgia, asthenia, abd pain (7d); maculopapular rash (on exam)	Cell count 86; Lymph% 75; Pro 1 g/L ² ; Glu normal	Serology Titers IgG 1:512 IgG 1:16384	IV doxy for 2wks; Ciprofloxacin 750 mg BID for 2wks on readmission	Recovered initially, readmit for aseptic meningitis, then recovered fully
Vander [16]	2003	22/M	Beer-Sheva, Israel	Fever, HA (7d); nuchal rigidity, L peripheral facial palsy (on exam)	Press 23; Pro 58; Glu 48; WBC 136; Mono# 97	Serology Titers IgG 1:960 IgM 1:400	IV ceftriaxone & doxycycline	Recovered
Simon [17]	2011	20/M	South Wales	HA (3d), N/V, paresthesia, aphasia (on 3rd day, transported to hospital by EMS); Fever, AMS (on exam)	Press 30; Lymph count 180, Pro 1.7 g/L; Glu WNL	Serology Titers 1:256	Ceftriaxone (day 3–17), Ampicillin (day 4–9), Acyclovir (Day 4–17), Vancomycin, oseltamivir and azithro (day 10–17)	Recovered
Carr [18]	2014	17/F	Tampa, Florida	Fever, HA, rash, vomiting, myalgia, weakness (12d); dehydrated (on exam); Vomiting, HA, diplopia (8wks after initial admission)	WBC 184; %lymph 97; Glu 49; Pro 83; RBC 0 (done at 2nd admission)	Serology Titers IgG 1:1024 IgM 1:256	Not Stated	Not Stated
Stephens [19]	2018	46/M	San Antonio, Texas	Convulsion, Hypotension, Tachycardia	Pressure 30; Lymph 66; Pro 170 mg/dL; Glu normal	Serology Titers IgG 1:256 IgM 1:4096	Doxycycline	Died
Collins	2020	39/M	Victoria, Texas	Fever, Headache, Photophobia, Unintended Weight Loss		Serology Titers IgG 1:512	Doxycycline, Acyclovir, Ceftriaxone	Recovered

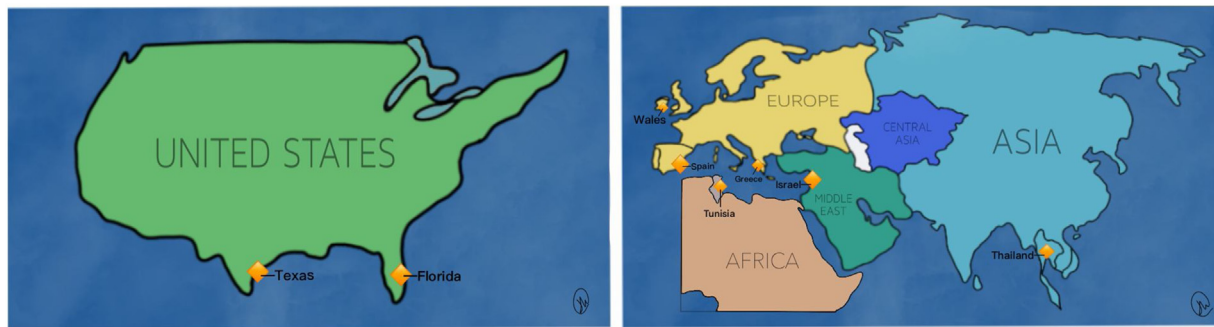


Fig. 2. Distribution of *Rickettsia typhi* meningitis cases worldwide. At the left: United States; Texas [19], and Florida [18]. At the right: Thailand [12]; Israel [13]; Greece [14]; Spain [15]; Wales [17]; Tunisia [20].

edema, hypotension, distributive shock, hypoalbuminemia, and secondary prerenal insufficiency (Fig. 1).

A potential complication following direct infection of the endothelial cells, by binding to outer membrane protein (Omp) A and B, is the progression to a multi-systemic vasculitis. Unlike the remainder of the typhus group, *R. typhi* binds to OmpB only, without binding to OmpA. This fact makes *R. typhi* slower to progress to systemic infection and may explain the relatively increased lead time to the development of symptoms [7].

CNS infection caused by *R. typhi* is rare. CNS microbial invasion may occur by the following postulated pathways: transcellular, paracellular, and intracellular (otherwise known as the "Trojan horse" approach). The mechanism of intracellular invasion is, presumably, the most favored pathway for crossing the blood-brain barrier, given the particular intracellular requirements of the rickettsial organism [8].

The incubation period of *R. typhi* is 7–14 days, and typical initial clinical manifestations are fever, arthralgia, headache, and a transient exanthem. The vague clinical presentation of *Rickettsia typhi* naturally leads to vast differential diagnosis and can be confused with other tropical diseases like dengue and malaria. Hematologic manifestations may include thrombocytopenia due to platelet consumption, lymphocytosis, leukopenia, and anemia. An elevation of gamma-glutamyl transpeptidase and alkaline phosphatase occurs after hepatic inflammation. Hydroelectrolytic alterations, like hypoalbuminemia, hypokalemia, hyponatremia, and hypocalcemia, are attributed to microvascular injury [9].

The described case progressed from febrile illness to a full-blown meningoencephalitis over ten days. The vague initial presentation confused physicians on two separate occasions. Likewise, the patient himself felt that his illness was nothing major and opted to self-medicate for an extended length of time. The infection had evolved to definite central nervous system involvement, which was confirmed via lumbar puncture yielding pleocytosis, hypoglycorrhachia, and elevated protein in the CSF. The patient received doxycycline in addition to acyclovir and ceftriaxone because of the high prevalence of rickettsial infection in south Texas. Lumbar puncture suggestive of meningeal inflammation, lack of response to antimicrobials (azithromycin and ceftriaxone), endemic location, and laboratory data (hypokalemia, hyponatremia, increased hepatic enzymes, and thrombocytopenia) led to clinical suspicion of rickettsiosis. Afterward, there was a serological confirmation of *R. typhi*. Treatment correlated well with the patient's resolution of symptoms, including fever and headaches.

A prospective study of 216 patients with confirmed *Rickettsia typhi* concluded that doxycycline was superior to azithromycin in the treatment of uncomplicated murine typhus. Fever clearance, time-temperature in the area under the curve (AUC), and treatment failure frequency were measured and concluded that

azithromycin was inferior to doxycycline. In our case, the patient started azithromycin at the onset of his symptoms without clinical response. He rapidly developed neurological manifestations. Lumbar puncture results supported a meningeal inflammation; therefore, doxycycline was started empirically on his arrival to the emergency department. The patient had significant clinical improvement following doxycycline therapy and was discharged without complications or neurological sequelae [10].

We conducted a literature review of similar cases with the following criteria: lumbar puncture, serological confirmation of *R. typhi* of >1:64 and at least a four-fold increase in IgG, clinical improvement with doxycycline, confirmation of meningeal inflammation defined by pleocytosis of more than five cells, elevated CSF protein, and decreased serum to CSF glucose ratio or brain imaging suggesting an infectious process.

We found 16 cases which are reflected (Table 1). Our search found that this complication has only been reported in 6 countries; Israel was leading with 5 cases followed by Thailand (Figs. 2 and 3). A coastal location was a common factor in the countries, as mentioned earlier. Analysis of the cases revealed that early intervention led to improved outcomes. The case presented here has been the only one identified in which treatment was initiated in the emergency department. This intervention correlated with a directionally proportional manner with the length of stay, complications, morbidity, and mortality. Delay in all these variables could lead to irreversible neurological sequelae or death. Recently, the availability of unbiased, next-generation sequencing-based pathogen detection tests in routine diagnostic laboratories (clinical metagenomics) has demonstrated increased diagnostic yield for syndromic testing [11]. Clinical metagenomics tests enable detection of any relevant pathogen with a clinically relevant turnaround time of one to two days. Metagenomics testing is useful when the differential diagnosis is broad, and pathogen-

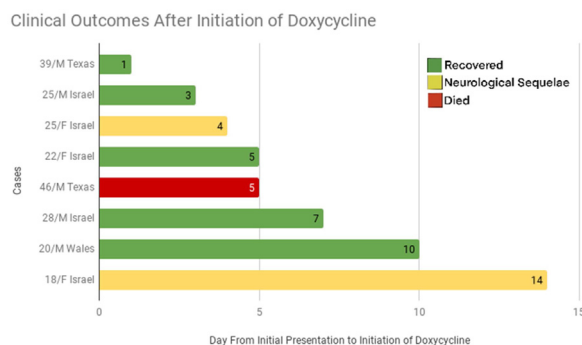


Fig. 3. Days from Initial Presentation to Initiation of Doxycycline Therapy *Cases excluded from table did not include sufficient date in the original publication.

specific tests are not available, such as is the case for murine typhus.

Conclusion

R. typhi infections have increased in coastal Texas in recent years and could be clinically deleterious if the infection is not recognized timely. Diagnostic testing methods for *R. typhi* are shortcoming compared to more popular zoonoses such as Rocky Mountain Spotted Fever and Lyme disease. Early initiation of doxycycline in the early phases of the illness directly affects the morbidity and mortality associated with *R. typhi*, including CNS manifestations.

Declaration of Competing Interest

No conflicts of interest.

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Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Rafael J Deliz: Corresponding author, data analysis, writing, editing graphs, reviewing references, tables and figures

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Brian X Contreras: Data collection, writing, references writing and search

Mark L Stevens: Data analysis, writing, references selection and reading, editing

Miguel Sierra-Hoffmann: Data collection, writing, intellectual contribution by editing, study design

Miriam Castro-Lainez: Writing, Intellectual contribution with comments and editing

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