Acta Tropica 166 (2017) 16–24

Contents lists available at ScienceDirect

Acta Tropica

journal homepage: www.elsevier.com/locate/actatropica

Clinical and laboratory characteristics, epidemiology, and outcomes of murine typhus: A systematic review

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ARTICLE INFO

Article history:
Received 19 September 2016
Received in revised form 23 October 2016
Accepted 26 October 2016
Available online 29 October 2016

Keywords:
Rickettsia typhi
Murine typhus
Endemic typhus
Triad
Doxycycline

ABSTRACT

Murine or endemic typhus, a febrile disease caused by *Rickettsia typhi*, is often misdiagnosed due to its non-specific presentation. We sought to evaluate all available evidence in the literature regarding the clinical and laboratory manifestations, epidemiological characteristics, and outcomes of murine typhus. Pubmed was searched for all articles providing available data. In an effort to incorporate contemporary data, only studies from 1980 were included. Thirty-three case series including 2074 patients were included in final analysis. Available evidence suggests that the classic triad of fever, headache and rash is encountered in only one-third of patients. Other frequent symptoms were chills, malaise, myalgia, and anorexia. A tetrad of reported laboratory abnormalities consisting of elevated liver enzymes, lactate dehydrogenase, erythrocyte sedimentation rate and hypoalbuminemia was detected. Complications were observed in one-fourth of patients, reported mortality was extremely low, but untreated patients had notably longer duration of fever. Among epidemiological characteristics, a seasonal distribution with most cases reported during warmer months, was the most prominent finding. Murine typhus in children exhibits several different characteristics, with abdominal pain, diarrhea, and sore throat reported more commonly, higher frequency of anemia, lower frequency of hypoalbuminemia, hematuria and proteinuria and a much lower rate of complications. This systematic review of published evidence provides a thorough description of the clinical and laboratory features of murine typhus and highlights important differences in children.

Contents

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http://dx.doi.org/10.1016/j.actatropica.2016.10.018
0001-706X/

1. Introduction

Murine or endemic typhus is a febrile disease caused by *Rickettsia typhi* (previously known as *R. mooseri*), an obligate intracellular gram-negative organism. It is primarily transmitted to humans from rodents through fleas, although other reservoirs are also reported (Azad et al., 1997; Civen and Ngo, 2008; Gikas and Tsioutis, 2010). Due to its non-specific presentation and uneventful clinical course, the disease often evades suspicion (Gikas and Tsioutis, 2010). Furthermore, the low specificity of older laboratory methods that were used for diagnosis (Civen and Ngo, 2008; La Scola and Raoult, 1997), questions the validity of actually proven cases in older studies. In children, large studies are few, but several differences from adults have been noted (Gikas et al., 2009; Whiteford et al., 2001). However, the scarcity of studies and the small number of included cases preclude safe assumptions.

The aim of this systematic review is to evaluate all available evidence in the literature regarding the clinical and laboratory manifestations, epidemiological characteristics, and outcomes of murine typhus.

2. Methods

2.1. Data sources and search

This review has adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). We developed a search strategy with the following combination of text-words: "Typhus, Endemic Flea-Borne"[Mesh] OR ("flea-borne typhus"[tw] OR "murine typhus"[tw] OR "endemic typhus"[tw] OR "rickettsia infection*[tw]). References of retrieved articles were hand-searched. We searched Pubmed MEDLINE for studies published from 1980 and onwards; day of last search was March 31 st 2016.

2.2. Study selection

We included all studies reporting clinical and/or laboratory data on infection due to *R. typhi*. Studies with any of the following were excluded from analysis: cases diagnosed with the Weil-Felix agglutination test (due to lack of sensitivity and specificity (La Scola and Raoult, 1997); review articles, case reports and case series with fewer than 10 patients. No language restriction was imposed.

Two investigators (CT, EP) independently reviewed the titles and abstracts of the citations for potentially relevant articles using Abstrackr (Wallace et al., 2012); the full text publications of potentially relevant articles were retrieved and rescreened by the same two investigators. Disagreements were resolved by consensus.

2.3. Data extraction

Data from each eligible study were independently extracted by three investigators (CT, MZ, AA). We extracted data on study design and methodology, epidemiological characteristics, patient characteristics, clinical and laboratory manifestations of the infection, complications related to the infection, treatment given, and outcomes. We used a standardized extraction form in an Excel® spreadsheet.

2.4. Outcome measures

The primary outcome recorded was the presence of the classic triad (fever, rash, headache). Secondary outcomes were clinical and laboratory manifestations, complications related to the infection, epidemiological data (seasonal variation, history of exposure to fleas and animals), treatment given, and infection-related outcomes (duration of fever, mortality rates). In order to highlight differences, data in children (≤16 years of age) are reported separately where feasible.

2.5. Definitions

Hypoalbuminemia was defined as serum albumin levels <3.5 mg/dL. Hyponatremia was defined as serum levels of sodium <135 mEq/mL. Thrombocytopenia was defined as platelet count <150,000/μL; anemia was defined as hemoglobulin levels <12 g/dL in women and <14 g/dL in men; white blood cell count <5,000/μL was defined as leukopenia and >10,000/μL was defined as leukocytosis. Complications related to the infection were defined as organ failure or requirement for hospitalization during the course of murine typhus.

3. Results

3.1. Literature search

Fig. 1 summarizes our search yield. We screened 613 citations, excluded 505 as irrelevant and 108 articles were retrieved for full-text review. Finally, we included 33 studies: 16 were prospective, 14 were retrospective and 3 did not describe study design.

3.2. Study characteristics

Table 1 summarizes the characteristics of included studies (Adjemian et al., 2010; Anyfantakis et al., 2013; Aouam et al., 2015; Bernabeu-Wittel et al., 1999; Blanton et al., 2015a,b; Brown et al., 1988; Chaliotis et al., 2012; Chang et al., 2012; Dumler et al., 1991; Fergie et al., 2000; Gikas et al., 2009, 2004; Gray et al., 2007; Hamaguchi et al., 2015; Hernández-Cabrera et al., 2004; Hidalgo et al., 2008; Kaabia et al., 2006; Koliou et al., 2007; Miguélez et al.,