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Original articles

Liver function test abnormalities in murine typhus in Greece: a retrospective study of 165 cases

Alterazione dei test di funzionalità epatica in pazienti affetti da tifo murino in Grecia: studio retrospettivo di 165 casi

Dimitrios Anyfantakis[1], Stephanos Doukakis[2], Michael Papadakis[2], Domniki Triantafyllidou[2], Konstantina Bambili[2], Georgia Polimili[2], Serafim Kastanakis[2]

[1]Primary Health Care Centre of Kissamos, Chania, Crete, Greece;
[2]First Department of Internal Medicine, Saint George General Hospital of Chania, Crete, Greece

INTRODUCTION

Murine typhus is an acute febrile illness caused by *Rickettsia typhi*, an obligate intracellular parasite that lives and multiplies in the cytoplasm of the host's endothelial cells [1]. It is often referred as endemic typhus and occurs in hot and humid as well as in cold and mountainous environments [2, 3].

Infection by *R. typhi* causes a systemic illness with various clinical and laboratory characteristics [4]. Mild hepatic injury in the context of murine typhus occurs frequently [1].

In 1993, a prospective study has been launched in the region of Chania, Crete with the aim to explore clinical and laboratory characteristics of murine typhus and advance awareness of this frequently misdiagnosed disease [1]. In the current study we aim to investigate the incidence and variations of liver function tests abnormalities in patients with a diagnosis of murine typhus over a 15-year period, from January 1993 to February 2008.

Corresponding author
Dimitrios Anyfantakis
E-mail: danyfantakis@med.uoc.gr

PATIENTS AND METHODS

This is a hospital based retrospective study of the patients diagnosed with murine typhus in the Saint George General Hospital of Chania, Crete, Greece. The prospective study was approved by the institutional research ethical committee of the Saint George General Hospital of Chania, Crete, Greece. All patients were informed about the aims of this study. Informed consent was obtained from all participants prior to any blood sample collection. Laboratory results were also made available to the participants [1].

Inclusion criteria of acute infection were considered: the presence of antibody titres against *R. typhi* of IgG ≥1:960 or IgM ≥1:400, and/or a 4-fold increase in the titres between the acute phase and convalescent phase serum specimen [1]. The minimal presumptive diagnostic criteria of acute infection with *R. typhi* were the presence of fever >38°C, and/or headache, and/or skin rash [1].

Three serum samples were then obtained in the majority of patients: the first on admission, the second in a meantime of 2 weeks after admission and the third about one month later [1]. Biochemical parameters including serum concentrations of aspartate aminotransferase

(AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) were then measured. We retrospectively reviewed the patients' medical charts for abnormal liver function laboratory tests, i.e., ALT, AST and LDH. Cut-off value for AST was considered 47UI, for ALT, 37 UI and for LDH, 480 U/L. Data regarding information on clinical details were also recorded.

RESULTS

One hundred and sixty five patients, 94 males (57%) and 71 females (43%) were diagnosed with murine typhus during the aforementioned period. Number and counts of patients with elevation of AST, ALT and LDH are recorded in 10) with murine typhus presented a >1 fold elevation of AST (AST Table 1. It is remarkable that on admission most of the patients (approximately 9 out of, mean value 82 U/l). A similar trend was recorded for ALT with approximately 7 out of 10 patients having abnormal levels (ALT, mean value 52 U/l), and more than 8 out of 10 with elevated levels of LDH (LDH, mean value 338) (Table 2). Hepatomegaly diagnosed with abdominal utrasonography was detected in 37 (22,4%) patients and splenomegaly in 8 (4.8%) patients. Spleen and liver enlargement was present in six patients (3.6%).
Two weeks later the percentage of patients with abnormal hepatic biochemical parameters was equally high (Table 1). One month later the liver function parameters tended to return to normal levels in the majority of the patients. More specifically only 8.4% (n=14), 7.2% (n=12) and 4.8% (n=8) of the patients were found with abnormal values of AST, ALT and LDH respectively. The mean values of AST, ALT and LDH variations on the examined serum samples are shown in Table 2. Clinical course was complicated in 5 patients (3%) with acute renal failure and in 6 patients (3.6%) with formation of pulmonary infiltrates.

DISCUSSION

Murine typhus is a worldwide distributed infectious disease with an underestimated incidence [5, 6]. The disease was first described in Greece by Lepine in 1932 and by Lorandos in 1934 [1, 7, 8]. In 1948 Dimisas reported 1420 cases with 17 deaths in Greece [9]. In Europe the disease was first reported in 1986, and more specifically with 49 cases of murine typhus identified in the island of Euboia, Greece [10]. Endemic cases are also reported in Chania, Crete [1]. Remarkably in the city of Chania the incidence of the disease has been reported to be 3 cases per 100000 inhabitants in 1993, 12 in 1994, 28 in 1995 and 6 in 1996 [1].
Our study disclosed that biochemical hepatic injury through elevation of liver enzymes is prevalent. In the same direction Gray et al., in a retrospective study of patients with murine typhus admitted to a regional hospital of New

Table 1 - Patients with abnormal values of AST, ALT and LDH.

Serum samples	*N. (%) with AST elevation*	*N. (%) with ALT elevation*	*N. (%) with LDH elevation*
First sample*	142/165 (86%)	114/165 (69%)	136/165 (82.4%)
Second sample**	126/165 (76.3%)	112/165 (67.8%)	117/165 (70.9%)
Third sample***	14/165 (8.4%)	12/165 (7.2%)	8/165 (4.8%)
At admission*, within a mean of 2 weeks after admission**, and about 1 month later***.			

Table 2 - Mean values and range of AST (reference interval 0-38 U/l), ALT (reference interval 0-36 U/l), and LDH (reference interval 240-480 U/L).

Serum samples	*AST Mean value (range) (U/l)*	*ALT Mean value (range) (U/l)*	*LDHMean value (range) (U/l)*
First sample*	82.0 (33-302)	74.0 (19-295)	338 (45-655)
Second sample**	52.0 (18-245)	53.5 (31-290)	333 (90-560)
Third sample***	28.0 (15-113)	24.0 (25-98)	142 (30-502)
At admission*, within a mean of 2 weeks after admission**, and about 1 month later***.			

Zealand reported that liver function test abnormalities were found in approximately all the patients [11]. In parallel with this, abnormal liver enzymes levels were frequently documented among 97 Texas pediatric patients with murine typhus [12]. Additionally, during an outbreak of *R. typhi* infection in Texas, 7 out of 10 of the diagnosed patients presented impaired liver function in terms of elevated levels of aspartate aminotransferase, alanine transaminase, alkaline phosphate, bilirubin, and/or lactate dehydrogenase [13]. Similar high percentage of liver involvement in terms of serum aminotransferase elevation has been reported by Silpapojakul et al. [14].

Remarkably, hepatic biochemistry disorders were recorded in more than 9 out of 10 patients with murine typhus infection at the time of initial evaluation. Interestingly, in one fourth of them a >5 fold elevation of AST and ALT was documented [14].

Murine typhus represents a potential life-threatening disease if untreated with reported mortality rates reaching up to 4% with reduction to lower than 1% after the institution of appropriate therapy with antibiotics [1, 5, 15]. Delayed diagnosis, hepatic or renal dysfunction, male sex, African origin, glucose 6-phosphate dehydrogenase deficiency, older age and central nervous system abnormalities are considered risk factors that predispose to a more severe clinical course [4, 16].

Clinicians maintain a low level of diagnostic suspicion for the disease, especially in United States [15]. Furthermore, physicians' awareness of the clinical and laboratory features of the disease is limited [15]. This is probably attributed to the restricted geographic regions that are characterised as endemic for the disease (Texas and California) as well as to its non specific clinical presentation [15]. Furthermore, the disease can mimic a variety of other severe infections such as Rocky Mountain spotted fever, Lyme borreliosis, brucellosis, leptospirosis, viral or bacterial meningitis and Q fever making establishment of initial diagnosis challenging for physicians [17, 18].

Delays in the timely diagnosis and management of murine typhus may increase the risk of severe complications such as seizures, respiratory failure, and persistent frontal and temporal lobe dysfunction [4, 13]. For this reason physicians have to be aware of the laboratory features of murine typhus infection and consider the possibility of murine typhus or other rickettsial infection in a patient presented with fever with or without skin rash and mild hepatic injury expressed with elevated serum aminotransferase levels. This is more challenging in countries such as Greece where the disease is endemic.

Keywords: murine typhus, liver function, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase.

Conflict of interest declaration

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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SUMMARY

The aim of this study was to analyse data relating to the liver function profile during acute infection from murine typhus in the city of Chania in the island of Crete (Greece). A retrospective study of the files of all the cases with a diagnosis of murine typhus admitted to the Saint George General Hospital of Chania over a 15-year period (1993-2008) was performed. Variations in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) levels were recorded from three consecutive examined serum samples. A total of 165 patients were diagnosed with murine typhus during the above time period. Serum aminotransferase and lactate dehydrogenase were abnormal in most of the first examined samples. Remarkably on admission, serum levels of AST, ALT, and LDH recorded an increase above the cut-off point in 142 (86%), 114 (69%) and 136 (82.4%) patients respectively. More than two out of every ten patients presented hepatomegaly. In conclusion, liver dysfunction occurs frequently in patients with murine typhus. A high level of physicians' awareness is required for the liver biochemical abnormalities caused by this worldwide zoonotic disease, especially in endemic areas such as Greece.

RIASSUNTO

Il presente studio è stato intrapreso al fine di analizzare i dati relativi ai parametri della funzionalità epatica in corso di tifo murino nella città di Chania, nell'isola di Creta. É stato condotto uno studio retrospettivo delle cartelle cliniche di tutti i casi con diagnosi di tifo murino ricoverati presso il Saint George General Hospital di Chania, Creta, Grecia relative a un periodo di 15 anni (1993-2008). L'osservazione della variazione dei livelli di alanina amino transferasi (ALT), aspartato aminotransferasi (AST) e lattato deidrogenasi (LDH) è stata effettuata su tre campioni consecutivi di siero.
Nel suddetto periodo, 165 pazienti hanno ricevuto una diagnosi di tifo murino. I livelli di AST, ALT e LDH sieriche sono risultati alterati nella maggior parte dei primi campioni esaminati. In particolare, al ricovero, un aumento dei livelli sierici di AST, ALT e LDH superiore al cut-off è stato registrato in 142 (86%), 114 (69%) e 136 (82,4%) pazienti, rispettivamente. Epatomegalia è stata rilevata in oltre in 20% dei pazienti.
La disfunzione epatica è di frequente riscontro nei pazienti affetti da tifo murino. È necessario che i clinici pongano grande attenzione alle alterazioni biochimiche provocate da questa zoonosi presente in tutto il mondo, soprattutto nelle aree endemiche quale la Grecia.

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