Acta Tropica 156 (2016) 130–136

Contents lists available at ScienceDirect

Acta Tropica

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

Evaluation of aminotransferase abnormality in dengue patients: A meta analysis

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ARTICLE INFO

Article history:
Received 20 August 2015
Received in revised form 22 December 2015
Accepted 23 December 2015
Available online 29 December 2015

Keywords:
Dengue
Liver injury
Aminotransferase
Meta analysis

ABSTRACT

Dengue virus is a type of flavivirus transmitted by Aedes mosquitoes. The symptoms of infection by this virus range from asymptomatic or mild symptomatic dengue fever (DF) to dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). Significant abnormality in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) has been shown in a large number of dengue infection cases and to be indicator for liver injury provided that there are no other combined infections or liver injury. This study aims to assess the abnormal levels of liver aminotransferase in dengue patients. The related literature was searched in multiple databases, including PubMed, Embase, Google Scholar and Cochrane Library. The literature was selected through strict inclusion and exclusion criteria, and the quantitative synthesis of the liver aminotransferase abnormality was performed with R software. The fixed or random effects model was employed based on the results of the statistical test for homogeneity. In total, 15 studies were included. The proportion of AST abnormality with 95% confidence interval (95% CI) was 0.80 (95% CI: 0.56–0.92) in DHF patients and 0.75 (95% CI: 0.63–0.84) in DF patients; the proportion of ALT abnormality was 0.54 (95% CI: 0.34–0.73) in DHF patients and 0.52 (95% CI: 0.41–0.63) in DF patients. Serum ALT and AST levels may be indicators for evaluating liver injury in dengue infection and for diagnosis and treatment effect.

Contents

Abbreviation: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DENV1–4, dengue virus serotypes 1–4; DF, dengue fever; DHF, dengue haemorrhagic fever; DSS, dengue shock syndrome; 95% CI, 95% confident interval.

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http://dx.doi.org/10.1016/j.actatropica.2015.12.013
0001-706X/

1. Background

Dengue is one of the most common and widespread mosquito-borne infections in the world. It is caused by the dengue virus, which belongs to *flavivirus* and is subdivided into four serotypes, DENV-1, DENV-2, DENV-3 and DENV-4 (Gupta et al., 2012; Mishra et al., 2015). Dengue infection presents menifestations that range from the classic dengue fever (DF) with no or mild symptoms to severe dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) (Mishra et al., 2015). It is estimated that 390 million dengue infections are believed to occur each year, among which nearly 100 million show manifestations at different severity levels (Bhatt et al., 2013).

Dengue virus has been shown to infect diverse cells or tissues in humans and some animal models (Pattanakitsakul et al., 2007; Petitdemange et al., 2014; Hoang et al., 2010; Hapugoda et al., 2010; Paes et al., 2009; Onlamoon et al., 2010). Substantial clinical observations have implied the involvement of the liver in the pathogenesis of dengue infection (Aye et al., 2014). In most clinical cases of dengue infection, the elevated serum ALT and AST was observed (Kuo et al., 2010; Roy et al., 2013). Evidence of dengue viral RNA was detected in patients who died of acute dengue hemorrhagic fever (Aye et al., 2014) and liver injuries were already noted post infection in experimental animal model (Paes et al., 2009). The degree of elevated ALT and AST in dengue infection is associated with the severity of the illness (de Souza et al., 2007; Ahmed et al., 2014).

It was previously reported in dengue cases that the incidence of ALT and AST abnormality ranged from 7% to 73% and 11% to 88%, respectively (YouSaha et al., 2013; Riaz et al., 2009). To evaluate the liver injury caused by dengue infection more objectively, the related literature was retrieved and the data were extracted. In addition, the overall proportion of abnormal ALT and AST were weighted with a meta analysis.

2. Materials and methods

2.1. Search strategy

The literature was retrieved from databases including PubMed, Embase, Google Scholar, Cochrane Library. The studies were searched using the following keywords: "dengue" or "dengue fever" or "dengue hemorrhagic fever" or "dengue shock syndrome" and "alanine aminotransferase" or "aspartate aminotransferase".

2.2. Inclusion and exclusion criteria

The articles were included according to the dengue infection classified by World Health Organization (WHO, 1997). DF is defined by living in or traveling to an endemic region with two or more items of the following: (1) headache and/or retro-orbital pain; (2) nausea and/or vomiting; (3) rash; (4) aches and pains; (5) tourniquet test positive; (6) leucopenia. Any warning signs (abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, liver enlargement, increase in haematocrit, and falling platelet count) with laboratory confirmation are also defined as DF. DHF is graded according to the WHO criteria (WHO, 2009), including grade I (fever accompanied by non-specific constitutional symptoms; the only hemorrhagic manifestation is a positive tourniquet test); grade II (spontaneous bleeding in addition to the manifestations of grade I, usually in the form of skin and/or other hemorrhages); grade III (circulatory failure manifested by rapid and weak pulse, narrowing of pulse pressure—20 mmHg or less-or hypotension, with presence of cold clammy skin and restlessness); and grade IV (profound shock and undetectable blood pressure). The criteria for DSS are the following: (1) severe plasma leakage leading to DSS; (2) fluid accumulation and respiratory distress as severe bleeding, severe organ involvement (liver, central nervous system, heart, kidneys and others).

The studies were classified as brief report, disease surveillance, outbreak survey, cross-sectional study and longitudinal observation. The criteria of abnormal liver function caused by dengue infection was on the basis of clinical reference value. Studies were excluded if the abnormal levels of liver aminotransferases were induced by other reasons, such as other viral hepatitis, fatty liver, alcoholic hepatitis, drug-induced liver injury and hemolysis, rather than dengue infection.

2.3. Data extraction

The following information was extracted from each study: first author, publication year, area of the study, type of patients, sample size and the number of cases with abnormal aminotransferase level. Two reviewers independently collected the data, and for controversial results, they reached a consensus after discussion.

2.4. Statistical analysis

The analysis was performed by R3.1.1 software (Wolfgang Viechtbauer, 2015 http://www.metafor-project.org). The "metafor" package was applied to evaluate the proportion of abnormal ALT and AST resulting from dengue infection, and the data are shown in a forest plot. Heterogeneity was tested by the *I*-squared statistic, which describing the percentage of total variation across the studies resulting from heterogeneity (Higgins and Thompson, 2002). *I*-squared statistic takes 25%, 50%, and 75% as the boundary values to evaluate the literature heterogeneity as low, moderate, and high, respectively. If the heterogeneity is moderate and high, a random effects model is chosen; otherwise, a fixed effects model is selected (Higgins et al., 2003; DerSimonian and Kacker, 2007). Publication bias was described with a funnel plot. The qualitative data extracted from the included studies were analyzed in subgroups to reduce the heterogeneity, as follows: (1) ALT abnormality in DF patients (ALT-DF); (2) ALT abnormality in DHF patients (ALT-DHF); (3) AST abnormality in DF patients (AST-DF); (4) AST abnormality in DHF patients (AST-DHF).

3. Results

3.1. Analysis of the included literature

Based on the inclusion and exclusion criteria, 15 studies were included, and the data from these studies were extracted (Kuo et al., 2010; YouSaha et al., 2013; Riaz et al., 2009; Ray et al., 1999; Mohan et al., 2000; Teichmann et al., 2004; Kularatne et al., 2005; Ooi et al., 2008; Ahmed, 2010; Abdallah et al., 2012; Lee et al., 2012; Ayyub et al., 2006; Nguyen et al., 1997; Sam et al., 2013; Larreal et al., 2005). Among them, there were 11 studies about ALT abnormality in DF patients, 6 studies about the ALT abnormality in DHF patients, 8 studies about AST abnormality in DF patients, 5 studies about AST abnormality in DHF patients (Fig. 1). Details on the first