



A Systematic Literature Review of Syphilitic Hepatitis in Adults

Jiaofeng Huang¹, Su Lin¹, Bo Wan² and Yueyong Zhu*¹

¹Liver Research Center of the First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian, China;

²Institute of Neurology, University College London, London, UK

Abstract

Syphilitic hepatitis in adults is not frequently found in the population and is easily misdiagnosed. The incidence of viral hepatitis is increasing year by year, concomitantly increasing the importance of obtaining a systematic understanding of the clinical features and treatment strategies for this disease. There is, however, a lack of published definitive data regarding the clinical characteristics, diagnosis and standard treatment options for this disease. Searches were made using the MEDLINE database of PubMed and OVID for syphilitic hepatitis publications from 1951 to 2017 in an attempt to analyze and summarize the clinical characteristics.

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Introduction

Syphilis is a sexually transmitted infection induced by the spirochete *Treponema pallidum*, which has a huge impact on people's physical and mental health. In its natural course, the disease progresses from primary syphilis to secondary syphilis and tertiary syphilis if left untreated. A chancre is often seen in primary syphilis. Secondary syphilis is characterized by a distinctive rash, while tertiary syphilis is typified by neurosyphilis, cardiovascular syphilis or gummatous syphilis.¹

An infectious venereal disease with multiple organs involved, syphilis has been described as "the great imitator".^{2,3} The liver is one of the organs that can be affected.⁴ Liver disease due to syphilis infection has rarely been reported and little is known about syphilitic hepatitis (SH). Maryam *et al.*⁵ reported a case of a male with SH who showed multiple liver lesions, while the case published by Aggarwal *et al.*⁶ presented with raised alkaline phosphatase levels. Syphilis, especially in its early stages, is often asymptomatic and easily misdiagnosed.⁷ The increasing incidence of syphilis will result in more SH,⁸ therefore it is important to improve the understanding of this disease. Fehér *et al.*⁹ reported 17 pathologically-confirmed cases of SH from 175 patients with syphilis, in

1975. However, coinfection with hepatitis C virus cannot be ruled out from this population. In 2004, Mullick *et al.*¹⁰ defined SH in detail, however, the reports of this disease are still rare.

There is still a lack of definitive data published about the clinical characteristics, diagnosis and standard treatments of SH. To this end, we searched the MEDLINE database for SH publications from 1951 to 2017, analyzing and summarizing the clinical characteristics through a systematic literature review.

Methods

We searched the MEDLINE database of PubMed and OVID for case reports, case series and descriptions of adult-onset SH. The electronic databases were searched for publications up to January 2017 with the following MeSH terms: "syphilitic hepatitis", "syphilis and liver", "syphilis and jaundice", "syphilis and hepatitis". We also manually searched the references and related reviews of each included study for other possible citations. The searches were restricted to English-language publications.

Results

Finally, a total of 73 articles containing 144 cases of SH in adults with medical records were discovered^{2,3,5,6,10–78} (Fig. 1). The earliest article dated back to 1951⁷⁸ and the latest was published in 2016.¹¹ The largest contribution came from the study by Jung *et al.*³⁶ with 19 patients. Only 129 of the total 144 patients had complete demographic information. The mean age of the 129 cases with information available was 40.5 years, ranging from 14 to 76. The majority were male (130/144, 90.3%), with a sex ratio of 9.3 (130/14, male/female). The number of homosexual patients were 56 out of 103 recorded (54.4%), and all of them were men who had sex with men. Only 127 of the 129 patients had provided information on human immunodeficiency virus (HIV) infection. The number of patients coinfecting with HIV and syphilis were 78 out of 127 with information available (61.4%). The stage of syphilis was recorded for all of the 144 patients, and included 128 (88.9%) with early syphilis (including primary and secondary syphilis), 7 (4.9%) with latent syphilis, and 9 (6.3%) with tertiary syphilis.

A total of 97 cases had detailed clinical data available. The symptoms of SH were nonspecific in nature. Rashes were the most common clinical manifestations of SH (74/97, 77.9%), followed by fatigue or poor appetite (55/97, 56.7%), icterus (34/97, 35.1%), fever (25/97, 25.8%), weight loss (22/97, 22.7%), abdominal pain (21/97, 21.6%), phallo-dynia (13/97, 13.4%),

Keywords: Syphilis; Hepatitis; Liver enzyme; Granuloma.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; HCV, hepatitis C virus; SH, syphilitic hepatitis; TBIL, total bilirubin.

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*Correspondence to: Yueyong Zhu, Liver Research Center of the First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian 350001, China. Tel: +86-591-87981656, Fax: +86-591-87982526, E-mail: zhuyueyong@fjmu.edu.cn

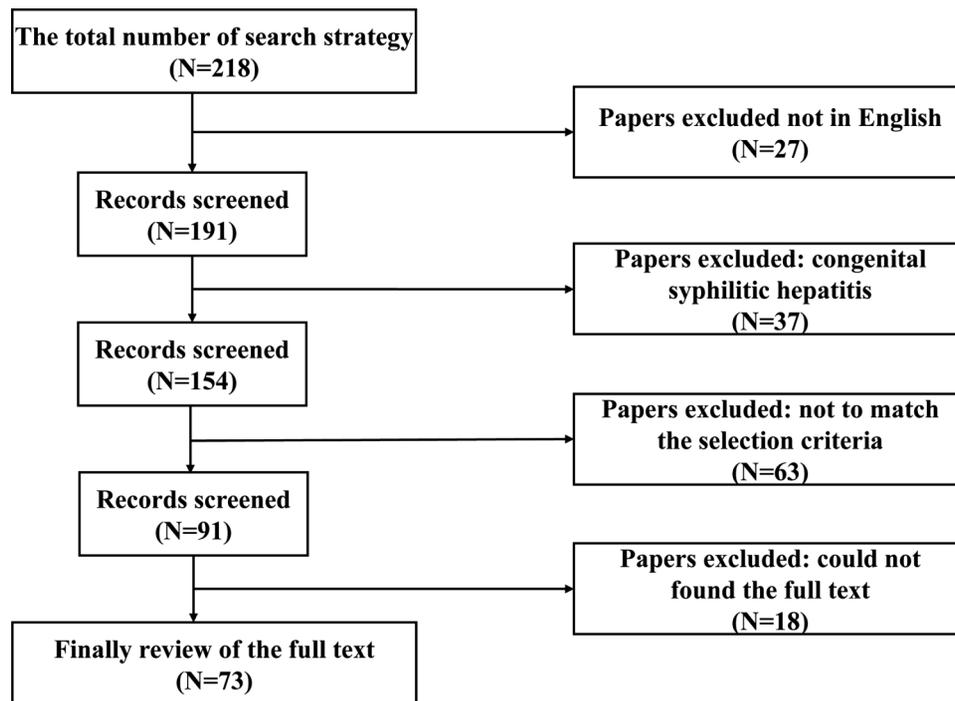


Fig. 1. A flow chart of the procedure followed for this systematic review.

sore throat (8/97, 8.2%), headache (7/97, 7.2%) and arthralgia or myodynia (6/97, 6.2%). In addition, physical examination revealed cases of hepatomegaly (52/97, 53.6%), lymphadenopathy (30/97, 30.9%), splenomegaly (14/97, 14.4%) and uveitis (8/97, 8.2%).

Information of the liver laboratory values was available for 99 out of the 144 patients (68.8%). The mean and 95% confidence interval (CI) of laboratory values have been summarized in the diagram below (Fig. 2). The mean for the laboratory values were 82.5 $\mu\text{mol/L}$ (total bilirubin, TBIL), 314.5 U/L (alanine aminotransferase, ALT), 253.0 U/L (aspartate aminotransferase, AST), 684.5 U/L (alkaline phosphatase, ALP) and 561.8 U/L (gamma-glutamyl transpeptidase, GGT). We found an obvious rise in ALP and GGT outside of the normal ranges and slight elevations of ALT and TBIL.

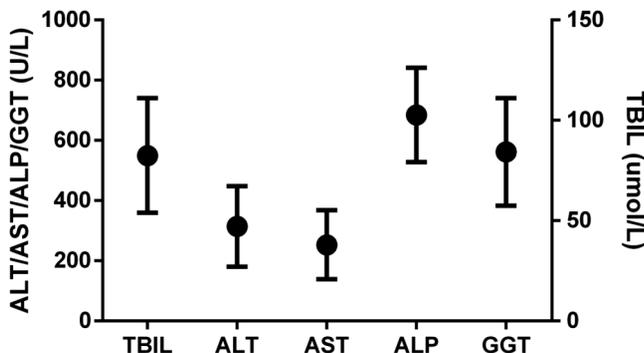


Fig. 2. The mean and 95% CI of laboratory values. Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; CI, confidence interval; GGT, gamma-glutamyl transpeptidase; TBIL, total bilirubin.

A total of 55 cases had liver biopsy taken. The hallmark histopathological features found in the hepatic tissue included inflammatory cell infiltration of portal areas or hepatic lobules (48/55, 87.2%), hepatocellular necrosis (25/55, 45.5%), granuloma with multinucleated giant cells (11/55, 20%), cholestasis (27/55, 49.0%) and fibrosis (10/55, 18.2%). Immunohistochemical staining or Warthin–Starry staining were performed in 28 cases. In 19 of the 28 cases, treponema spirochetes were visualized in liver tissue, 15 of which were discovered by immunohistochemical staining and 4 by Warthin–Starry stain.

All the patients received antibiotic therapy. Among the 144 cases, 129 took intramuscular or intravenous penicillin therapy, 5 took oral doxycycline, 7 had oral amoxicillin hydrate and 3 used ceftriaxone. Jarisch–Herxheimer reaction occurred in 7 patients, with 6 of them responding to penicillin and one to amoxicillin hydrate treatment. All patients responded well to treatment.

Discussion

This systematic review showed that liver damage usually occurred in early syphilis, which was easily missed as a diagnosis because of the nonspecific nature of presenting symptoms. The results also found that SH was more often diagnosed in men, especially those who had sex with men, which could be linked to the route of sexual transmission. There were four large studies carried out to explore the relationship between SH and autoimmune deficiency syndrome, with a total of 54 patients.^{34,36,48,49} The studies showed that SH is common in HIV-positive patients with syphilis infection. Syphilis should be included in the differential diagnosis of HIV patients presenting with liver test abnormalities, rash and/or sexual risk factors. Liver damage is very common in HIV-infected patients

because of their use of antiretroviral therapy, opportunistic infections and increased malignancy rates.¹⁰ In light of this, clinicians should try to maintain a broad list of differential diagnoses.

The clinical manifestations of SH in adults are often non-specific and multifaceted. Rashes, fatigue or poor appetite, hepatomegaly and icterus were the most common. The rashes often presented as multiple nonpruritic, erythematous, non-confluent maculopapular lesions, generally concentrated on the trunk, palms and soles of the feet. Hepatosplenomegaly is often found on physical examination or imaging. The laboratory tests of SH will show abnormal liver enzymes with a marked increase of ALP and GGT, in contrast to a mild elevation in ALT or AST levels. Histological features of SH include bile duct inflammatory infiltration, which may be linked to the elevated blood ALP and GGT levels. Hepatic granuloma is another feature of SH.⁷⁹ It is very difficult to identify the spirochetes in liver tissue among these patients. Only 19 patients showed spirochetes in the liver tissue on immunohistochemical staining^{11,16,24} or Warthin–Starry staining.^{43,51,52}

This is the first systematic review of SH. The results will help clinicians better understand this disease. The main limitations of this study were the retrospective design and the heterogeneous sources of the data. The heterogeneity and lack of data may cause bias.

Conclusions

The clinical characteristics of SH were its nonspecific presentation, elevated liver enzymes, especially ALP and GGT and bile duct inflammation or granuloma formation as seen by hepatic histopathology. Together, these facets of SH can provide some direction for clinicians regarding the approach to diagnosis of this disease.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Independently carried out the reference selection and data selection, performed analysis and interpretation of the findings, and drafted the article (JH), designed the study (BW), manuscript preparation (SL), served as third investigator for resolution of discrepancies through a consensus meeting (YZ), revised the final article for important intellectual content (SL, YZ).

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