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Acute viral hepatitis – Should the current screening strategy be modified?

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ABSTRACT

Background: The epidemiology of viral hepatitis has changed. Since the introduction of safe and effective vaccines for hepatitis A and B in 1980s, the incidence of acute infections caused by these viruses has been declining in the UK. At the same time, hepatitis E virus (HEV) has been recognised as an increasingly important cause of acute hepatitis, but testing is not widely available.
Objectives: The aim of this study was to establish the viral causes of acute hepatitis, and use that data to modify the current diagnostic algorithm.
Study design: A Cognos search was performed to collate subjects tested for HAV, HBV, HCV, HEV, EBV and CMV between June 2010 and December 2012. Information included virological result and their ALT level if done within 5 days from virological testing.
Results: From 3462 subjects with suspected acute viral hepatitis, only 25% had biochemical evidence of acute hepatitis ($n = 854$; ALT > 100 IU/l). The frequency of detection of acute HEV infection (25/409) was over 31-times higher than that of HAV (6/3462), and 7-times higher than that of HBV (24/3462). Most cases of acute HAV, HEV, EBV and CMV infections presented with abnormal ALT levels. Most EBV infections were associated with lymphadenopathy (23/34); in comparison most of CMV infections were not associated with lymphadenopathy (18/22).
Conclusions: HEV screening should be included in the initial testing panel for acute hepatitis and screening at least for HAV and HEV might be limited to those with abnormal ALT levels.

1. Background

Viral hepatitis is one of the most common of the severe infectious diseases. The five most established viral causes include hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV) and hepatitis E virus (HEV) [1]. These diverse viruses are members of different virus families. They are all are associated with acute hepatitis, and typically target hepatocytes leading to their destruction. Several herpes viruses, such as cytomegalovirus (CMV) and Epstein–Barr virus (EBV), can also cause hepatitis in addition to other symptoms including fever, sore throat and lymphadenopathy. All these viruses can produce an acute illness characterised by discrete onset of nausea, fever, malaise, abdominal pain and jaundice, often associated with an increase in peripheral blood enzymes released from damaged hepatocytes such as alanine aminotransferase (ALT) levels. The severity of acute viral hepatitis can range from asymptomatic infection to fulminant hepatic failure. In addition, HBV, HCV and HDV can cause chronic infections, which can lead to cirrhosis and hepatocellular carcinoma. More recently, chronic HEV infection has been reported in immunocompromised individuals [2–4].

The features of acute viral hepatitis are clinically indistinguishable between viruses and thus laboratory tests are needed to identify the specific viral cause of illness [1]. Individuals with suspected acute viral hepatitis are usually initially tested for HAV IgM, HBV surface antigen (HBsAg) and HCV IgG. Other viruses including HEV, CMV and EBV are subsequently screened based on the clinical details. Individuals with a travel history to endemic countries, occupational or water exposure within the past 9 weeks are thought to be at increased risk of acute HEV infection [5], whereas signs of lymphadenopathy point towards acute CMV or EBV infection.

The epidemiology of viral infections is constantly changing. Since the introduction of safe and effective vaccines for against hepatitis B in 1981 and hepatitis A in 1995, the incidence of acute infections caused by these viruses has been declining in the UK [6–8]. At the same time, HEV has been recognised as an increasingly

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Table 1
Laboratory confirmation of viral cause of acute hepatitis.

Virus	Laboratory confirmation
HAV	IgM antibody for HAV positive
HBV	HBsAg positive and IgM antibody for HBV core antigen (anti-HBc) positive
HCV	HCV Ag or PCR positive, and HCV antibody negative in previous testing (if done)
HEV	IgM antibody for HEV positive, and HEV IgM immunoblot positive or HEV PCR positive
EBV	IgM antibody for VCA positive, and EBNA IgG negative or EBV PCR positive (if done)
CMV	IgM antibody for CMV positive, and low IgG avidity or IgG seroconversion (if done)

important cause of acute hepatitis [5,9–11], but testing is not widely available.

2. Objectives

The aim of this study was to establish the viral aetiology of hepatitis in Lothian region, South-Eastern Scotland, to collect clinical data and to use that information to modify the diagnostic algorithm currently followed in the Specialist Virology Centre at the Royal Infirmary Edinburgh, which conducts routine testing for the region.

3. Study design

A total of 3426 serum samples obtained from individuals with acute hepatitis were submitted to the Specialist Virology Centre at the Royal Infirmary of Edinburgh between July 2010 and December 2012. The subjects tested for HAV, HBV, HCV, HEV, EBV and CMV were identified from the laboratory database. The information collected included name, date of birth, specimen number, hospital number, location, virological test result as well as ALT level if done within 5 days from virology testing. Clinical details on IgM-positive, or in case of HCV, PCR- or Ag-positive individuals were collated from laboratory database and electronic patient notes. Acute hepatitis was defined as an acute illness with jaundice or elevated ALT level (defined as >100 IU/l). In comparison, the number of acute HCV infections was also estimated according to the Centre for Disease Control and Prevention case definition in which elevated ALT level is defined as >350 IU/l [12]. Population incidence has been calculated based on the estimated Lothian population size of 800.000 people.

All samples were screened for HAV IgM antibodies, hepatitis B surface antigen (HBsAg) and HCV IgG antibodies using the Architect Assays (Abbott, USA) (Table 1). HBsAg positive samples were tested also for hepatitis B core IgM/IgG antibodies and hepatitis B e-markers (antigen and IgG antibody) using the Architect Assays (Abbott, USA) as well as for HBV DNA and HDV RNA. Similarly, HCV IgG-positive samples were further tested for the presence of HCV RNA, and since August 2011 for HCV Ag. Repeated samples were requested from HBsAg positive or HCV IgG positive to confirm identity, and to established those with a chronic infection. Any samples submitted from the Department of Hepatology at Royal Infirmary of Edinburgh or from individuals with a history of travel, or since 2011 with ALT levels over 100 IU/ml, were additionally tested for HEV IgM and IgG with recomWell assays ($n = 409$; Mikrogen, Germany). All IgM positive results were confirmed with recomWell IgM Immunoblot assay (Mikrogen, Germany), and some of those samples were also tested by HEV PCR.

A subset of samples ($n = 835$) was tested as a part of routine diagnostic service for EBV and CMV infection. Samples were tested for Viral Capsid Antigen (VCA) IgM and IgG antibodies by Liaison assays (Diasorin, Italy), for CMV IgG by Architect assays (Abbott, USA) and CMV IgM by VIDAS assays (Biomerieux, France). Data on seroconversion, Epstein–Barr Nuclear (EBNA) IgG antibodies (Diasorin, Italy) and CMV IgG avidity (Biomerieux, France) testing as well as EBV PCR testing was also collected. Additional EBV and CMV testing was requested by clinical virologists if clinical features were suggestive of EBV or CMV infections (i.e. lymphadenopathy). Based on these test results individuals could be classified as having acute EBV infection (defined as EBV IgM and IgG positive, and EBNA IgG negative if done) and acute CMV infection (defined as CMV IgM positive, and low CMV avidity <50% or CMV IgG seroconversion on follow-up sample if done).

Statistical analysis of proportion was performed using Fisher's exact test, whereas a non-parametric Kruskall Wallace test was used to compare independent groups of sampled data. A p-values less than 0.05 were considered statistically significant. The study was approved by the East of Scotland Research Ethics Committee (10/S1402/33).

4. Results

A total of 3426 samples obtained from individuals with suspected acute hepatitis were examined during the 30-month study period. Of those, 25% had biochemical evidence of acute hepatitis ($n = 854$; ALT > 100 IU/l), 43% had marginally abnormal ALT levels ($n = 1492$; ALT >50 IU/l and <100 IU/l), 10% had normal ALT levels ($n = 334$; ALT < 50 IU/l) and 22% had not had ALT measured ($n = 782$).

All 3426 samples were screened for HAV, HBV and HCV, a subset of 409 samples were screened for HEV and a subset of 835 samples were tested for EBV and CMV. This testing revealed 6 cases of acute hepatitis A (6/3426, 0.2% or in those with abnormal ALT 6/854, 0.7%), 24 cases of acute hepatitis B (24/3426, 0.7%), 16 cases of acute hepatitis C (16/3426, 0.5%) and 25 cases of acute hepatitis E (25/409, 6.1%) (Table 2). No cases of acute hepatitis D infections were identified. In addition, 34 cases of acute EBV infections (34/835, 4.1%), and 22 cases of acute CMV infections (22/835, 2.6%) were found. From those, 22 from 34 acute EBV infections and 8 from 22 CMV infections were confirmed by further diagnostic testing (Table 1).

All individuals with confirmed acute hepatitis due to HAV, HCV, HEV, EBV or CMV, and over 90% of individuals with acute hepatitis B (22/24) presented with abnormal ALT levels over 100 IU/l. The highest ALT levels were associated with HBV infection (median 2445 IU/l), followed by HAV (1782 IU/l), HEV (1697 IU/l) and HCV (706 IU/l) (Fig. 1). Most patients with acute hepatitis A, B or E were jaundiced compared to only 19% of individuals with hepatitis C. Abnormal ALT levels were also found in acute EBV and CMV infections (median 306 and 141 IU/l, respectively). Individuals with EBV and CMV infections were rarely (2/34) or never jaundiced, respectively.

The median age of all individuals subjected to acute hepatitis screening was 42 years (Fig. 2). Most individuals with a viral cause identified were younger with median ages of HAV infection of 28 years, HBV of 31 years, EBV of 24 years and CMV of 30 years. The individuals with acute HCV or HEV infections were significantly older with the mean of 49 and 48 years, respectively (pairwise p-values from 8.5×10^{-6} to 0.012 by Kruskall Wallace non-parametric test).

The likely sources of infections were evaluated in individuals infected with hepatitis A, B, C or E. Half of acute hepatitis A (3/6) infections were travel related, but the source of remaining acute HAV infections was unclear. One third of acute HBV infections were linked to a recent travel (8/24) and one third to a recent sexual contact with HBV-positive individual (7/24), whereas the source of infection was not identified in the remainder. Most of the acute HCV infections were diagnosed in IDUs (9/16), while one had acquired

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