Editorial on viral hepatitis

INTRODUCTION

With the first ever World Health Organisation (WHO) Global Elimination Strategy on Viral Hepatitis set for its likely adoption at the World Health Assembly in May 2016, it will be a pivotal year for viral hepatitis. On World Hepatitis Day, i.e., 28th July, the birth anniversary of Nobel Laureate Baruch Samuel Blumberg, www.NOhep.org will be officially launched to achieve the theme for 2016: Elimination. This will be the first time national governments sign up and commit to the goal of eliminating viral hepatitis as a public health threat by 2030.[1]

DISEASE BURDEN AND PREVALENCE

Viral hepatitis is a global public health problem, particularly in resource-poor countries.[2]

Indian scenario

The Integrated Disease Surveillance Programme of the National Centre for Disease Control (NCDC) received notification of 290,000 cases of acute viral hepatitis in 2013[3] and of 81 outbreaks of viral hepatitis out of 1562 (5.19%) outbreaks in 2014.[4]

Blood-borne viral hepatitis

Hepatitis B virus (HBV) is the second most common cause of acute viral hepatitis after hepatitis E virus (HEV) in India.[3] Population prevalence of chronic HBV infection in India is around 3–4%. There is a wide variation in hepatitis B surface antigen (HBsAg) prevalence in different geographical regions in India.[2] Hepatitis D virus (HDV) infection is observed in 10–20% of HBV positive patients.[3] The population prevalence of chronic hepatitis C virus (HCV) infection in India is 1%. However, there are pockets of areas where prevalence of hepatitis C has been observed to be relatively higher in Punjab, Haryana (22.6%), Andhra Pradesh, Puducherry, Arunachal Pradesh (1.4–7.89%) and Mizoram (71.2% among active injecting drug users).[2] Genotypes 1 and 4 of HBV and genotypes 1 and 3 of HCV are more prevalent in India.[3] Recent outbreaks: One of HBV, HCV from February 2014 to April 2015;[5] one of HCV in February 2016.[6]

Water-borne viral hepatitis

HEV is the most important cause of epidemic hepatitis though hepatitis A virus (HAV) is more common among children.[3] HAV and HEV are responsible for 10–30% and 10–40%, respectively, of acute hepatitis and 5–15% and 15–45%, respectively, of acute liver failure cases in India.[2] Genotypes 1 and 3 of HAV and genotype 1 of HEV are the predominant strains in India.[3] Recent outbreaks of HEV: One each in the period November 2012 to July 2013,[7] in December 2015 and in February 2016;[6] one outbreak of HAV in April 2014.[8]

CURRENT TRENDS IN LABORATORY DIAGNOSIS

Primary diagnosis of HBV and HCV infection is made using serological tests for detecting antigens and antibodies against these viruses. To confirm the primary diagnosis, to quantify viral load, to determine genotypes and resistance mutants for antiviral treatment, qualitative and quantitative molecular tests are used.

Hepatitis B virus

To detect HBV markers, various serological techniques have developed such as radioimmunoassay (RIA), electrochemiluminescence immunoassay (ECLIA), microparticle enzyme immunoassay (MEIA) and chemiluminescent microparticle immunoassay (CMIA). However, EIA, CLIA and rapid point-of-care tests are the commonly used tests.

The evolution of the development of nanoscience and nanotechnology has increased the development of immunosensors for HBV diagnosis – one with a limit of detection of 0.01 IU/ml – about forty times lower than

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that of the EIA method; yet others with detection of 0.001–0.015 ng/ml of HBsAg.

Molecular assays with high sensitivity are clearly important for the diagnosis of chronic hepatitis B without hepatitis B e antigen detection in serum, and occult HBV, where viral loads can be quite low. Currently, real-time polymerase chain reaction (PCR) has become the standard technique of choice to detect and quantify HBV deoxyribonucleic acid in clinical practice.

HBV genotyping is important for designing appropriate antiviral treatment and determining HBV disease progression. Among the several methods available, PCR-restricted fragment length polymorphism is widely used to genotype HBV since it is inexpensive and simple.

For the past twenty years, fluorescence-based quantitative PCR chemistries have revolutionised nucleic acid diagnostics and become the gold standard for viral load quantification.[9]

Hepatitis C virus

The mainstay in diagnosing infection with HCV is to initially screen high-risk groups for antibodies to HCV (anti-HCV) in blood samples,[10] usually done by third generation ELISAs.

HCV seropositivity may occur several weeks to months after virus exposure; hence, there is a potential delay in diagnosis. This resulted in blood bank adaptation of nucleic acid-based testing (NAT) shortening the window period from up to 13 weeks with EIA-based testing to three days with NAT-based assessment. This reduced the risk of transfusion-related HCV infection.[11]

The NAT test has become the gold standard supplemental test for patients who have a positive HCV EIA screening test[12] as the latter does not differentiate whether the person has resolved or current HCV infection. For persons who are immunocompromised, testing for HCV RNA is to be considered. The qualitative HCV RNA test can be done by PCR and transcription-mediated amplification.[11] There are ultrasensitive HCV quantitative RNA assays that detect as few as five copies/ml.[12]

An alternative to quantitative HCV RNA measurement is HCV core antigen testing, but it is not as sensitive or precise.[11]

Other immunoassays for anti-HCV detection include ECLIA, CMIA, CLIA and MEIA,[9] Food and Drug Administration-approved OraQuick HCV Rapid Antibody test.[12]

- Biosensor technology has emerged as an alternative technique with low detection limit, higher selectivity and sensitivity and faster responses for anti-HCV detection[9]
- Recently, in November 2015 at the American Association for the Study of Liver Diseases conference, a one-step HCV antigen test on urine or blood was presented by Dr. Ke-Qin Hu. It is licensed to DiligenMed, Inc.[13]

Hepatitis D virus

The diagnosis of HDV infection rests on detection of antibody to HDV antigen (anti-HDV) by EIA or RIA.

The presence of IgM anti-HDV does not distinguish acute from chronic HDV infection: as IgM anti-HDV also persists in chronic infection and high titres are often found in patients with severe liver inflammation.

HDV antigen in the liver (by immunoelectron microscopy [IEM]) and HDV RNA in serum and liver can be detected during HDV replication but are not routinely used for diagnosis.[2]

Hepatitis E virus

Diagnostic tests consist of direct evidence by detection of virus itself by IEM,[2] and a recent attempt at culture in human hepatoma cells.[14] Diagnosis in the immunocompetent patients can be based on serology.[15] Anti-HEV IgM assays can be used as first-line diagnostic assays.[16] Antibody tests are not useful in the diagnosis of chronic HEV. However, if a patient is noted to have anti-HEV IgG in the serum, testing for HEV RNA should be performed to detect underlying chronic HEV.[17]

However, in immunocompromised subjects, RNA detection is essential as they may not develop antibodies[17] or seroconversion could be delayed.[18] Detection of viral nucleic acid from blood and other body fluids is by reverse transcriptase (RT)-PCR,[17] the gold standard for specificity in acute infection[19] or by loop-mediated isothermal amplification.[17] There is a wide variation in sensitivity (100–1000-fold) of various assays for detection of HEV RNA.[18] HEV genotype detected by one assay may not be detected by another assay and vice versa.[17] Recently, a WHO international standard (genotype 3a) was established, which is an important step in both standardisation of HEV RNA detection and accurate quantification.[16]

In 2014, a new taxonomic scheme for the classification of HEV has been proposed with genotypes 1–4 infecting humans.[20]

Tests for hepatitis E should therefore be included in evaluations of all patients with increased levels of liver transaminases, particularly immunocompromised individuals because chronic hepatitis E has been observed in HIV-positive patients and organ transplant recipients.[18]

Currently, there is a wide variation in the tests for diagnosis of HEV, and there is a need for standardisation of the assays.[17]

Caution is needed in interpreting seroprevalence data obtained using different HEV assays. Highly discrepant results are probably due to variation in sensitivity since many diagnostically relevant epitopes are conformation dependent, the virus is genetically heterogeneous, and there is a wide variation in duration of antibody response.[21]

Hepatitis A virus

IEM, antigen assays (RIA, EIA), RT-PCR can be used to detect HAV in faecal samples.[22] There are EIA to detect IgM, IgG and total anti-HAV.

As part of a new national hepatitis initiative in 2014, led by the NCDC as the nodal agency, 10 medical colleges have been identified to carry out surveillance for hepatitis. The activity will be initiated in a phased manner, and at the end of five years, a network of 10 laboratories would be established.[3]

Data on viral hepatitis obtained from 12 centres in Kerala have been presented in a special article in this issue.[23] It is important to collect, compile and share data in a common reporting format to get a perspective on the existing scenario and help in awareness, screening, policies and prevention.

To achieve the 2016 theme of elimination, greater awareness, increased diagnosis and key interventions including universal vaccination, blood and injection safety, harm reduction and treatment are all needed. This means every activity that addresses viral hepatitis is a step towards elimination.[1]

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