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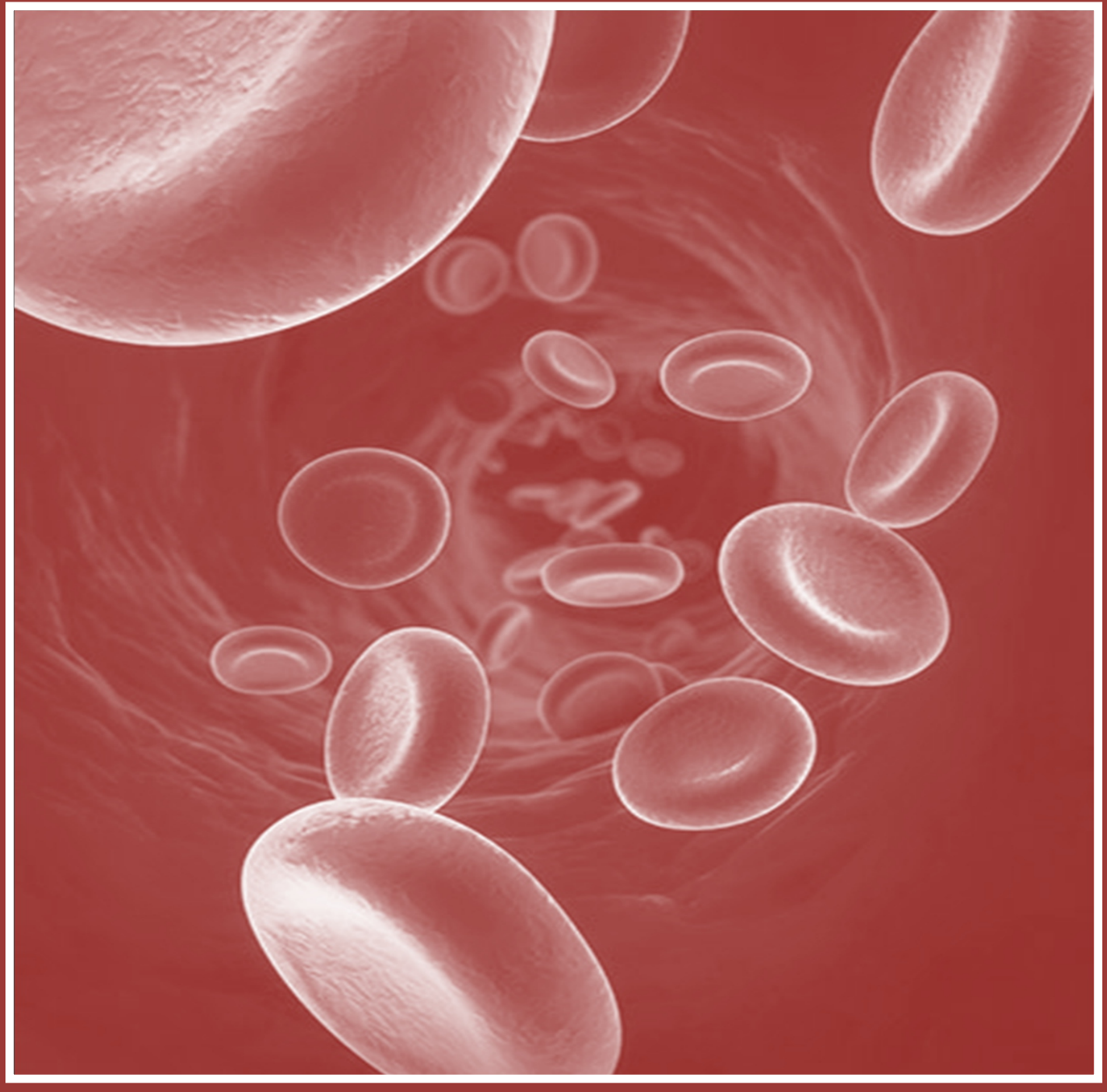

ESSAY COMPETITION ON INDEPENDENCE DAY CELEBRATIONS

PLEDGE CEREMONY DURING SWACHH BHARAT ABHIYAN

Hepatitis C Infection : Prevalence, Diagnosis and Treatment – An Overview

Priya Yabaji, Aruna Shankarkumar

HCV was first identified in 1989 after its isolation from the serum of an individual with non-A, non-B hepatitis by Choo *et al* [1]. Hepatitis C virus causes a liver disease which cannot be prevented by vaccines like hepatitis B & E for which the vaccines are available. World celebrated Hepatitis Day on 28th July, 2016. Globally, 130-150 million people are infected with chronic hepatitis C, of which 3-6 million people are from India, leading to death of approximately 700000 people. Hepatitis C is called viral time bomb by WHO (World Health Organisation).

Virology

HCV is enveloped, single positive stranded ribonucleic acid (RNA) virus from genus Hepacivirus, family Flaviviridae with a diameter of 50 nm in size [2]. The genome consists of a single open reading frame (ORF) which is 9600 nucleotide bases long [3].

The ORF is translated into a single protein product of about 3000 amino acids long, which is then further processed to produce smaller active proteins. Untranslated regions (UTR); 5' and 3' ends of the RNA are necessary for replication of the viral RNA. The ORF encodes a polyprotein which is comprised of 10 viral proteins named as Core (C), E1, E2, P7, NS2, NS3, NS4A, NS4B, NS5A and NS5B. Three structural proteins are C, E1 and E2, while seven non-structural proteins are P7, NS2, NS3, NS4A, NS4B, NS5A and NS5B. Core protein modulates gene transcription, cell proliferation, cell death, liver steatosis etc. HCV envelope proteins are glycosylated and play a major role in cell entry. Protein P7 is responsible for ion channel and virus assembly. The NS3 region encodes serine proteinase which is responsible for cleavage of polyprotein into NS4a, NS4b, NS5a, and NS5b.Second proteinase encoded by NS2 is responsible for cleavage of polyprotein in NS2/NS3. The NS5B protein is viral RNA dependent RNA polymerase replicates viral RNA by using positive strand as its template and catalyzes polymerization of ribonucleoside triphosphates (rNTP) [4]. Figure 1 shows schematic representation of HCV genome organization.

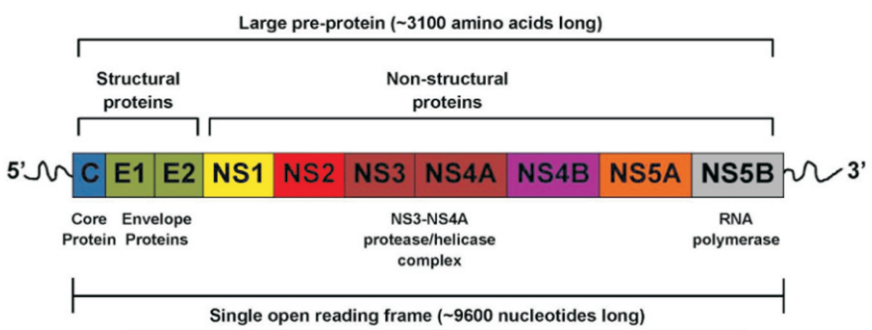

Figure 1: Schematic representation of HCV genome (Adapted from William Ho et al, 2012)

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Global prevalence and Routes of HCV transmission :

Health-care associated transmission

In Developing countries HCV infection is mostly associated with unscreened blood transfusions, unsafe injection practices and procedure such as renal dialysis [5, 6]. According to the latest WHO report on blood safety (2011), 39 countries do not routinely screen blood transfusions for blood borne viruses [7].

In Egypt, HCV RNA prevalence was 14.6% in some regions in 2015 which is the most well documented example of health-care associated transmission [8]. Persons who received untested blood products prior to the introduction of screening of blood for HCV in high-income countries were also at increased risk of infection.

Transmission among people who inject drugs

In middle- and high-income countries, most HCV infections occur among people who use unsterile equipment to inject drugs and contaminated drug solutions. It is estimated that of the 16 million people in 148 countries who actively inject drugs, 10 million have serological evidence of HCV infection [9].

Mother-to-child transmission

The risk of transmission of HCV from an infected mother to her child occurs in 4-8% of births [10,11] and the risk is strongly associated with HCV viraemia as against absence of RNA antenatally [12]. Earlier studies have demonstrated that vertical transmission rate of HCV increases by 2- 4 fold if coinfected with HIV [13, 14]. Till date there is no antiviral treatment recommended for HCV-infected women [15].

Sexual transmission

Sexual transmission of HCV occurs infrequently in heterosexual couples and is more associated with HIV-infection, especially in homosexual men [16,17].

Other

Other routes of transmission of HCV include intranasal drug use, cosmetic procedures (such as tattooing and body piercing), scarification and circumcision procedures [18,19].

Co - infections

- **HIV and HCV co-infection**

  Both HIV and HCV have common routes of transmission. A recent study estimates that 2.3 million people are co-infected with these two viruses across the globe [20]. Although antiretroviral therapy (ART) has reduced the risk of HIV-related opportunistic infections, however, end stage liver disease due to HCV is a leading cause of death in some high-income countries[21].

- **HBV and HCV co-infection**

  Dual hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are common in HBV or HCV endemic countries of Asia, sub-Saharan Africa and South America [22].

HCV prevalence in India

In India, mandatory screening of blood for Hepatitis C was made effective in 2001 under the National Blood Policy.

In 2015, the first review article included 109 studies from India, highlighted HCV prevalence in various population groups and summarizing an overview of HCV as an emerging infection, its transmission pattern and need to create public

awareness to decrease future burden of HCV infection in India [23]. Highest serologically positive HCV frequency of 51.22 % (95% CI: 50.80 – 51.64) was found in Injecting Drug Users followed by multitransfused thalassemic cases with a frequency of 22.78% (95% CI: 22.00 – 23.55) suggesting the re-use of needles among IDUs and failure of proper screening of blood transfused to thalassemiacs (Figure 2).

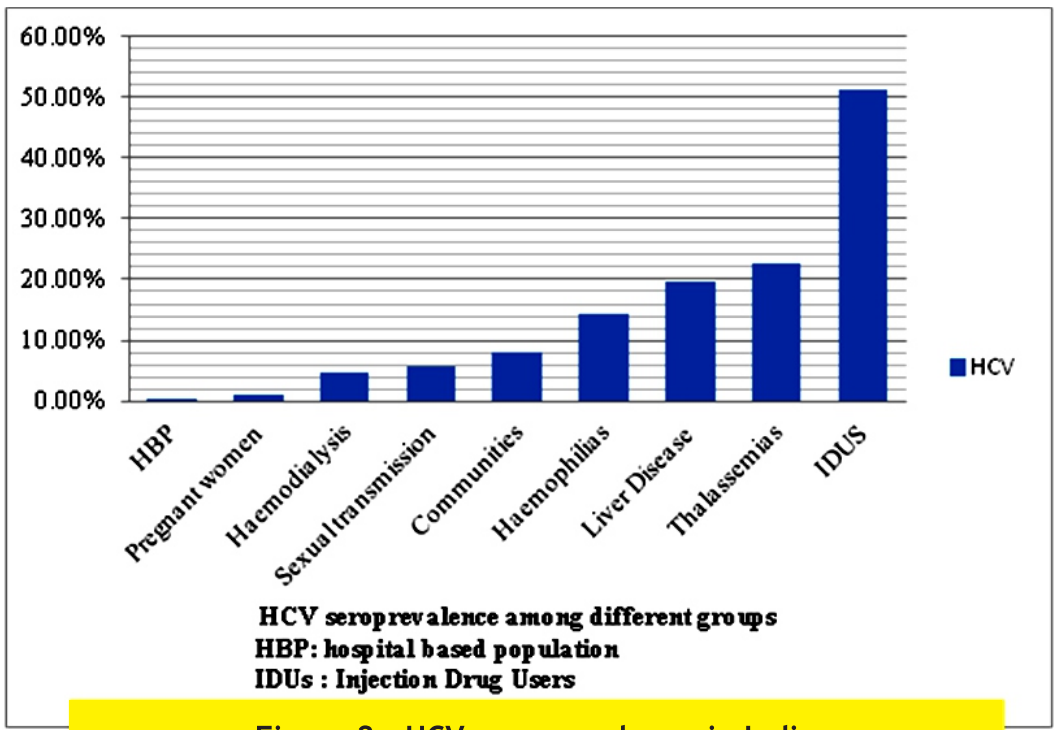

Figure 2 : HCV seroprevalence in India

Natural history of HCV infection

The incubation period of HCV, though ranging up to several months, averages 6-8 weeks. Humans are the only natural hosts of HCV. The HCV genome does not enter cell nucleus. HCV-RNA replication occurs in cytoplasm of hepatocytes[24].

Hepatitis C can present as acute or chronic hepatitis. Most of the cases of acute hepatitis C are asymptomatic with patients unaware of the underlying infection. Symptomatic acute hepatitis with jaundice is seen in only 25% of patients. The worrying aspect of acute hepatitis C infection is spontaneous viral clearance which is unusual with nearly 54-86% of infected individuals progressing to chronic hepatitis. Among these 20% to 30% will develop progressive disease leading to liver cirrhosis and hepatocellular carcinoma (HCC) over the course of two or more decades. A general view of progression of hepatitis C infection is given in Figure 3. Chronic HCV infection is also associated with a number of extra-hepatic manifestations.

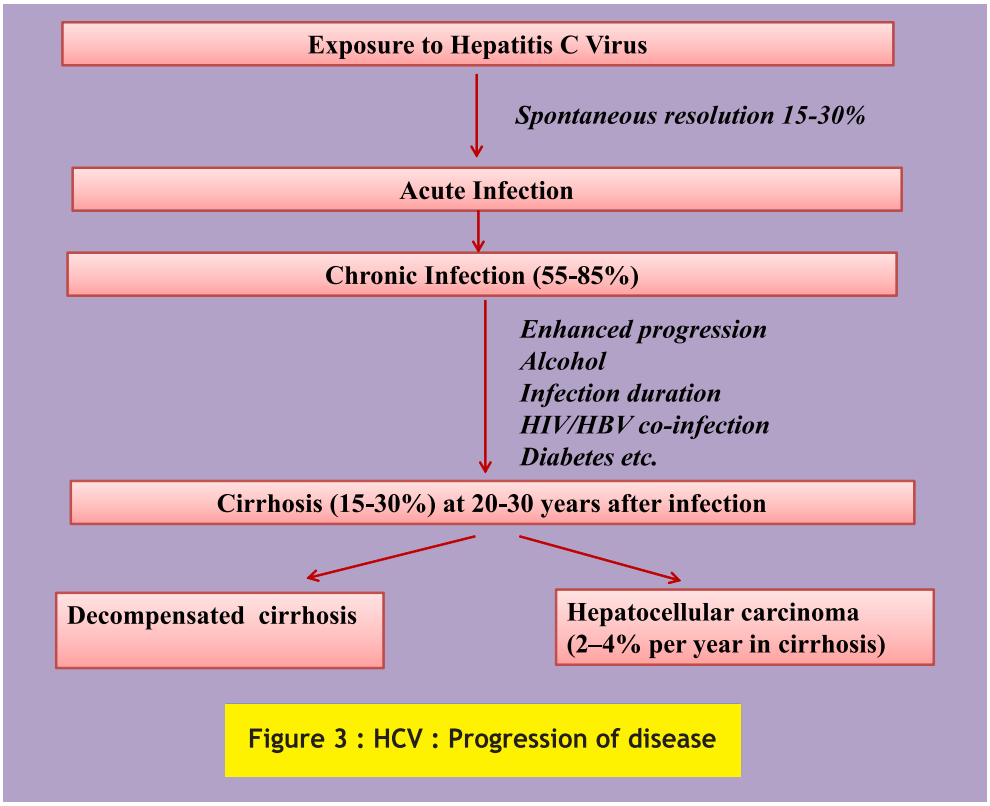

Figure 3 : HCV : Progression of disease

Global Distribution of HCV genotypes:

HCV strains are classified into six to seven genotypes (1-7) on the basis of phylogenetic and sequence analyses of whole viral genomes [25]. HCV strains, belonging to different genotypes differ at 30-35% of nucleotide sites. Within each genotype, HCV is further classified into subtypes that differ at <15% of nucleotide sites [26].

The distribution of HCV genotypes and sub-genotypes varies substantially in different parts of the world. Global distribution of HCV genotypes is shown in Figure 4.

Genotypes 1 and 3 accounts for the majority of HCV infections worldwide. In Africa and Middle East, the most prevalent genotype is 4. Genotypes 5 and 6 are most common in South Africa and Asia [27, 28]. Genotype 1a is most prevalent in the United States and Northern Europe, while 1b is the most common genotype worldwide [29]. In Europe and Japan, genotypes 2a and 2b are most prevalent, while 2c subtype is most frequent in Northern Italy.. Genotype 3a is most common in Pakistan in comparison to 3b and 1a [30]. The diversity of genotypes also varies considerably across countries. The highest diversity is observed in China, South-East Asia, Western Europe and Australia while in countries like Egypt and Mongolia, almost all HCV infections are due to single genotype [31].

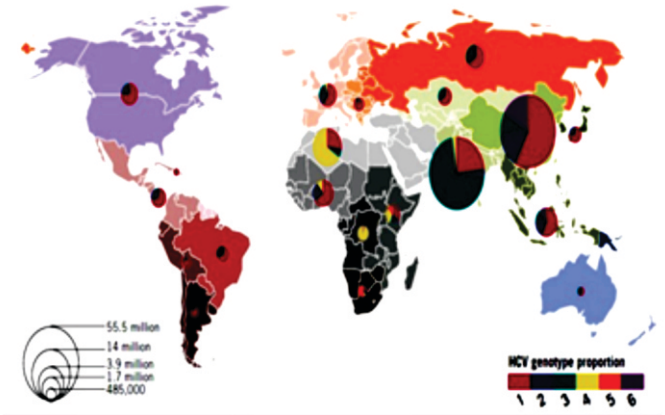

Figure 4 : Global distribution of HCV genotypes (Adapted from WHO HCV guidelines 2016)

Distribution of HCV genotype in India

Genotyping of HCV is helpful for predicting the likelihood of response and duration of treatment.

Earlier studies suggest that genotype 3 is the most common genotype in India, accounting for 54%-80% of cases [32-33]. Within genotype 3, subtype 3a is the more frequent in most of the studies, but a recent report found subtype 3b to be the most prevalent [34]. Studies from northern, eastern and western India have uniformly shown predominance of genotype 3; however, in southern India, both genotypes 1 and 3 are prevalent [35, 36]. Genotype 4 is identified in some cases from southern and western India while genotype 6 infection is reported from eastern and north-eastern parts of India [37-38]. In a study of 75 isolates from the north-eastern part of India with predominant tribal population, genotype 4 is reported to be the most common genotype (31%) followed by genotype 6 accounting for 13.6% of the cases [39]. Two cases of genotype 5a have also been reported [40,41].

Virological assessment

The investigation of HCV diagnosis starts with serological assays for detecting antibodies to HCV followed by molecular assays for detecting HCV RNA as given in Table 1.

Table 1: Various diagnostic test available for detecting HCV infection.

a) Serology
• Rapid test
• ELISA (Enzyme Linked Immunosorbent Assays)
• RIBA (Recombinant Immunoblot Assays)
b) Molecular
• **Detection of HCV RNA**
Qualitative detection of HCV RNA
Quantitative detection of HCV RNA
• **HCV** Genotyping
Direct sequencing
RFLP (Restriction Fragment Length Polymorphism)
INNO LiPA II (Innogenetics)

Serologic assays:

- **Rapid test**

  Rapid immunoassay tests do not require complicated instrumentation or skilled technical staff, generating results within an hour and therefore may be used for point of-care testing.

  These assays are based on recombinant antigens derived from core, NS3, NS4, and NS5 proteins in an immunochromatographic format with a specificity of >99% and sensitivity ranging from 86% to 99% [42] . Rapid kits are extensively used for surveillance purposes; they are not well suited for high risk groups and immunocompromised patients [43].

- **Enzyme Immunoassay**

  Initial screening for HCV infection is done by serologic method by determining anti HCV antibody via an **Enzyme Immunoassay** (EIAs) or by immunoblot assays.

  Three generations of EIA antibody testing are developed since 1989. First-generation assays, developed in 1992, incorporated an epitope from the NS4 region (C100-3) of the HCV genome which lacked sensitivity and specificity[44]. The second generation EIA-2 included antigens from the core, NS3, and NS4 regions which markedly improved sensitivity and specificity [45]. Presently, a third-generation ELISA that incorporates antigens from the core, NS3, NS4 and the NS5 proteins of HCV is used [46]. The diagnostic specificity of third-generation assays is >99% [47]. EIA method is relatively inexpensive and highly sensitive but has disadvantage of giving wrong (false positive) results in routine blood donors and asymptomatic adult [48]. For this reason, Centres for Disease Control and Prevention has recommended the supplementary tests like Recombinant Immunoblot Assay (RIBA) or Polymerase Chain Reaction (PCR) based methods to confirm positive ELISA tests [49].

- **Recombinant Immunoblot assay**

  The recombinant immunoblot assay is used to confirm HCV infection. In RIBA assays, multiple HCV antigens are individually displayed on a nitrocellulose strips as bands [50]. Reactivity with $\geqslant$ 2 proteins indicates a positive result; the test result is considered as indeterminate if reactivity to only one protein is detected. Indeterminate result may be due to nonspecific cross-reacting antibodies or indicative of recent HCV infection that has not yet triggered a broad humoral response. Since positive cases in RIBA, show two bands they are considered more sensitive than EIA.

  False-negative serological results may be seen in acute infection, immunocompromised patients wherein further RNA-based testing should be considered.

Liver biochemistry:

Liver function tests are insensitive for predicting disease progression. Serum alanine aminotransferase (ALT) can be elevated in patients without significant histological abnormality. Similarly, normal values do not exclude progressive liver disease or cirrhosis.

Liver assessment:

When assessing a patient it is important to ascertain the risk of developing liver fibrosis. This can be difficult as available tests have limitations and clinicians often rely on a combination of approaches. Liver ultrasound may demonstrate a coarse echo texture or a nodular margin to the liver if there is significant fibrosis. Splenomegaly may indicate portal hypertension. A normal ultrasound scan does not exclude cirrhosis. Liver biopsy is a gold standard method, associated with an element of risk, but offers the advantage of detecting concurrent disease processes (e.g. steatosis, iron overload) contributing to hepatic injury and affecting treatment response.

Molecular assays:

Active infection is diagnosed by the detection of HCV RNA in the blood by a PCR-based assay. Highly sensitive, quantitative, commercial assays are available for detecting virus and for monitoring responses during and after treatment. Molecular diagnostic assays are an integral part in the management of HCV patients. These tests for hepatitis C specifically detect HCV RNA and the process is commonly referred as a Nucleic Acid Test (NAT) or Nucleic Acid Amplification Test (NAAT). The HCV NAT becomes positive approximately 1 to 2 weeks after initial HCV infection. The NAT can determine whether a patient with a positive HCV antibody test has current (active) or resolved HCV infection.

Qualitative HCV RNA:

Qualitative HCV assays involve viral RNA isolation, complementary DNA (cDNA) synthesis, PCR amplification and detection of PCR amplicons. Qualitative HCV RNA test detects the presence of HCV circulating in blood and is most sensitive test available [51]. The qualitative HCV RNA test has higher sensitivity, but it can only determine the presence or absence of HCV RNA, not HCV RNA level and thus cannot be used for monitoring response to therapy.

Quantitative HCV RNA:

HCV quantitative assay is used to determine the number of international units of HCV RNA per millimeter of serum or plasma (IU/mL) in known HCV positive patients. At present real time PCR based detection systems are widely available, having a very low limit of detection and broad dynamic range [52].

Genotyping assays:

Genotypes are very useful for determining the duration of treatment regimens and predicting treatment response. Genotyping is done by direct sequence analysis, reverse hybridization to genotype-specific oligonucleotide probes, or restriction fragment length polymorphisms (RFLPs). Though many commercial kits are available, the gold standard for HCV genotyping is nucleotide sequencing, by using core (C), envelope (E1), or the non-structural (NS5B) regions, amplified by reverse transcription followed by polymerase chain reaction [53].

Most diagnostic assays commonly target the 5' UTR but in research settings, core and or

NS5B region is usually sequenced as this region is more conserved amongst all genotypes. Unless re-infected, genotypes do not change during the course of infection.

Treatment

Available therapy until 2011

The antiviral properties of interferon (IFN) were discovered in 1957. Interferon treatment was approved for HCV in 1991 by FDA. Until 2011, the standard of care for HCV was a combination therapy with pegylated interferon-alpha by subcutaneous injection once weekly and oral ribavirin daily (PEG-IFN/RBV) [54]. Interferons are naturally occurring cytokines with antiviral effects. Pegylation refers to the attachment of polyethylene glycol that enhances half-life of the interferon when compared to its native form. Ribavirin, a purine nucleoside has antiviral effect only against HCV, when combined with interferon-alpha. A treatment duration and success rate with this regimen depends on viral and host factors. HCV genotypes 1 and 4 are considered as difficult to cure whereas; genotypes 2 and 3 have higher cure rates. A patient with genotypes 2 or 3 is generally treated for only 24 weeks as against genotype 1 treatment is for 48 weeks[55]. Both interferon and ribavirin are not only expensive but can also have serious side effects .The regimen is expensive and associated with drug adversities such as flu like symptoms, nausea, diarrhea, major depression, insomnia, irritability and hair loss, suppression of bone marrow function [56].

Available therapy until 2014

A major milestone in the treatment of HCV occurred with the approval of first direct acting antivirals (DAA) such as telaprevir and boceprevir targeting protease. This treatment when combined with PEG-IFN/RBV lead to a high 70% Sustained virologic response (SVR) in genotype 1 , treatment-naive patients and offered benefit to some patients who had previously failed dual PEG-IFN/RBV treatment [57,58].SVR is defined as aviremia 24 weeks after completion of antiviral therapy for chronic hepatitis C virus (HCV) infection.

Available therapy from 2015

The next major breakthrough was approval of Sofosbuvir , a NS5B polymerase inhibitor in combination with PEG-IFN/RBV for just 12 weeks with 89% SVR in treatment-naive patients with genotype 1 infection and 83-100% in treatment-experienced patients with genotypes 2/3 [59].

Experience at NIIH

A total of 97 cases which includes 30 HCV seropositive, 32 HCV seropositive haemophilia, and 35 HCV seropositive thalassaemia cases were enrolled. Haematological and serological tests were done for HCV, HIV and HBV infections in all cases. HCV viral load testing was done using Cobas Taqman on sera aliquots stored at -80 degree C to diagnose active viral infection.

HCV viral load range was found to be higher in hemophiliac cases as compared to other two groups. HCV- thalassaemia cases though

being half the age as compared to the HCV seropositive group showed almost similar viral load range indicating the possibility of added liver injury due to iron overload.

Conclusion

Molecular diagnostic testing for HCV has provided a crucial tool for addressing significant controversies in HCV management. NAT for detecting HCV RNA remains the gold standard method for detecting HCV infection in individuals in high risk group population which confirms active state of viral infection, *i.e.*, the virus is in replicating state in the patient's body. However, in developing countries due to financial constraints and lack of technical expertise in clinical settings, these tests are difficult to perform and time consuming. In these settings, the most widely employed screening tests are the HCV rapid immunoassays. However, it is the need of an hour to effectively design strategies to detect HCV infection even in sero-conversion period.

Although few patients are cured at initial stages, the activated virus after some time become uncontrollable and can cause human death. No proper vaccine and antiviral drugs are available to control HCV. The initial focus should be on prevention including safe injection practices in hospitals, safe blood supply and guidance to the injection drug abuser or intravenous drug users about the risk of HCV. Health education and special awareness programs should be launched for prevention of the disease. Safe blood test and other laboratory tests are necessary for an early diagnosis of HCV.

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NIIH HAPPENINGS

Department of Pediatric Immunology & Leukocyte Biology

Dr Manisha Madkaikar, Scientist F

1. Invited for Technical specification committee meeting for Flowcytometer held at GCRI Ahamedabad on 15th June 2016.
2. Invited to deliver a lecture on 'Flowcytometry-Basics' in CPD training course for Transfusion Medicine held at Mumbai on 11th July 2016.
3. Invited to deliver a lecture on 'Diagnostic challenges in PID" during PHOCON meeting held at Hyderabad on 15th July 2016.
4. Invited to deliver a lecture on diagnostic challenges in HLH during CME on HLH at Harkisan Das Hospital, Mumbai on 7th August 2016.
5. Invited to attend RAPSAC meeting of CDFD, Hyderabad from 11th to 12th August 2016.
6. Invited to deliver a lecture for ' Life at War series II-HLH-Immunity at Civil war' at Wadia Children's Hospital, Mumbai on 21st Aug 2016.

Maya Gupta,TA

1) Invited to chair a session on *Diagnosis of HLH* at Immunology symposium on "Life at War: series 2 - HLH - Immunity at Civil War" held on 21st August 2016 at Bai Jerbai Wadia Hospital for Children, Mumbai.

Dr Snehal Shabrish, PDF

1) Invited as a speaker to deliver talk on "Diagnosis of HLH (Molecular)" at Immunology symposium on "Life at War: series 2 - HLH - Immunity at Civil War" held on 21st August 2016 at Bai Jerbai Wadia Hospital for Children, Mumbai.

Department of Hematogenetics

Dr Malay Mukherjee, Scientist E

1. Attended Review meeting on New Born Screening programme among the tribal groups of Gujarat and Madhya Pradesh held at Valsad Raktadan Kendra, Valsad on 6th May 2016.
2. Visited Bulsar Raktadan Kendra, Valsad and Seva Rural Hospital, Jagadiha, Baruch in relation to New Born Screening programme among the tribal groups of South Gujarat from 2nd to 3rd June 2016.
3. Attended Expert Group Meeting held at Chandrapur on 9th June 2016.
4. Invited as speaker in the "National Seminar on Sickle Cell Anemia: Advances in Clinical Care and Research" organized by SRM University and NAWA, held at Chennai on 19th June 2016 and delivered a lecture on "Sickle cell anemia in India: Dimension of the problem".
5. Invited to attend Consultative meeting on Newborn Screening in Maharashtra held at Director of Health Services, Arogya Bhavan, Mumbai on 19th August 2016.
6. Invited as an expert in the Brainstorming meeting for the CSIR Mission Mode Project on "Sickle Cell Anemia" held at CSIR Science Centre, New Delhi on 24th August 2016.

Dr Anita Nadkarni, Scientist E

1. Delivered a lecture on "Laboratory diagnosis of hemoglobinopathies and problems encountered" in 3rd Association of Practicing pathology conference held at Mumbai on 11th June 2016.

Dr Prabhakar Kedar, Scientist D

1. Invited as a chairperson in the Mumbai Hematology Group quarterly meeting held at Fortis Hospital, Mumbai on 19th of June 2016.

2. Participated in the "Workshop on Human Genome and Transcriptome Analysis" held at Institute of Bioinformatics, Bangalore from 25th to 28th July 2016.

Dr. Prashant Warang, TA

1. Presented a paper entitled "Combined glucose-6-phosphate dehydrogenase and pyrimidine 5'nucleotidase deficiency can alter clinical outcome : Case report" in MHG Quarterly Meeting, held at Fortis Hospital, Mumbai on 19th June 2016.

Ms. Priya Hariharan, SRF

1. Presented a paper entitled "Effect of Delta globin gene variations on HbA2 levels" in MHG Quarterly Meeting, held at Fortis Hospital, Mumbai on 19th June 2016.

2. Presented a poster entitled "Effect of genetic modifiers in clinical outcome of beta thalassemia syndromes" in HbE-Beta thalassemia Conference held at Bangkok, from 4th to 5th August 2016.

Dr. Dipti Upadhye, Scientist

1. Awarded third best prize for a poster entitled "Spectrum of hemoglobinopathies identified during newborn screening programme in North East, Tripura" presented in "Best of European Hematology Conference 2016" held at Mumbai from 22nd to 24th July, 2016.

3. Presented a poster entitled "Newborn screening for HbE disorders and G6PD and Pyruvate Kinase deficiencies and their co-inheritance in the north eastern region in Tripura" in HbE- Beta thalassemia Conference held at Bangkok, from 4th to 5th August 2016.

Department of Transfusion Medicine

Dr Ajit Gorakshakar, Scientist F

1. Organised an Essay and Drawing competition under the theme "Yad Karo Kurbani" to celebrate 70 years of Independence on 19th August 2016 at NIIH, Mumbai.

2. Attended the meeting of the Research Advisory Committee of Seth G S Medical College and KEM Hospital held at KEM hospital Mumbai on 22nd August 2016.

3. Awarded Second prize at 41st Annual National Conference of Indian Society of Blood Transfusion and Immunohematology held at Pune from 26th to 28th August 2016 for a paper entitled "A novel FUT1 mis-sense mutation identified in an Indian with para Bombay phenotype".

4. Awarded Runners up prize at 41st Annual National Conference of Indian Society of Blood Transfusion and Immunohematology held at Pune from 26th to 28th August 2016 for a paper entitled "Analysis of Duffy

Blood Group Genotypes in Agri, Kolis and Pathare Prabhus from Maharashtra".

5. Attended National Healthcare Assessment Meet organized by WHO Collaborating Center for Priority Medical Devices and Health Technology Policy, National Health Systems Resource Center, Ministry of Health and Family Welfare, Govt of India at Tirupati, on 30th August 2016 to discuss the assessment and to demonstrate RDB kit.

Department of Hemostasis

Dr. Shrimati Shetty, Scientist E

1. Invited to participate in Haemophilia Symposium-2016 organized by Christian Medical College, Vellore from 11th to 12th June held at New Delhi.

2. Invited to deliver a talk on " Factor assays-trouble shooting" at Coagulation Workshop update – Western edition organized by Kokilaben Ambani Hospital, Mumbai from 1st to 3rd of July 2016

3. Invited by the World Federation of Hemophilia (WFH) to attend the special session on the WFH Humanitarian Aid Program during the WFH XXXII World Congress in Orlando, Florida, USA from 24th to 28th July, 2016.

Dr. Bipin Kulkarni, Scientist C

1. Selected for the ICMR- International Fellowship award for Young Biomedical Scientists, for the year 2016- 2017.

Department of Cytogenetics

Dr V Baburao, Scientist E

1. Visited Radiation Biology Center, Kyoto University, Kyoto Japan, under DST-JSPS collaborative project, from 18th to 26th May 2016.

2. Invited as Chairman of the selection Committee to select SRF at NIRRH, Mumbai, on 28th June 2016.

3. Invited as a Member of selection committee to select Ph.D candidates at NIRRH, Mumbai, from 12th to 13th July 2016.

4. Attended Advanced workshop on Good clinical practices in clinical research for ethics committee members at NIRRH, on 23rd August 2016.

5. Attended executive committee meeting of Molecular Pathologists Association of India at SRL laboratories, Mumbai on 24th August 2016.

Ms. Avani Solanki, SRF, visited Radiation Biology Center, Kyoto University,Kyoto, Japan under DST-JSPS project from 18th to 31st May 2016.

Library & Information Science

Mr Vijay G Padwal, ALIO

1. Attended Orientation/Refresher training workshop of ICMR Library and Information Professionals at National Institute of Virology, Pune from 11th to 12th August 2016.

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