



HEPATITIS C : THE INDIAN SCENARIO



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Hepatitis C virus (HCV) is the major cause of chronic liver disease and known to infect approximately 170 million people worldwide. There are about 12.2 million HCV carriers in our country. The natural history of infection by HCV in the northern hemisphere indicates that 80% or more of infected individuals become chronic carriers. Infection is currently defined by the presence of specific anti-HCV antibodies, with or without the presence of detectable viral RNA. Since the discovery of hepatitis C virus in 1989 by Choo and coworkers, there has been an explosion of research and information on the viral epidemiology, mode of transmission, diagnostic, natural history and treatment. HCV is a RNA virus and is heterogeneous in nature, showing multiple genotypes and subtypes, with the basic structure and genome organization being conserved. Transmission of this virus is mostly by parenteral and nosocomial routes. Patients with HCV are at risk of long-term complication, including liver cirrhosis and hepatocellular carcinoma. Though there is great improvement in treatment of HCV in recent years, but in many cases the therapy fails to eradicate the virus. Vaccination is an important alternative way to control viral disease, however, neither previous HCV infection nor vaccination with HCV-derived antigen protects against reinfection.



Keywords

Hepatitis C, virus

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Hepatitis C : The Indian Scenario

Hepatitis C Virus

Hepatitis C virus belongs to the family Flaviviridae. The genome of HCV comprises a single-stranded positive sense RNA of approximately 9.6 kb in length and contains a single open reading frame (ORF) that encodes for a non-functional polyprotein of approximately 3000 amino acid in length. The virus shows extensive genome heterogeneity and has been classified into 6 genotypes with over 100 subtypes having definite geographic distribution. The core protein may have a role in immunity and pathogenesis. Envelope protein has a highly variable region producing immune escape mutants, thus leading to chronicity. Over 70% of HCV genotype that is found in India is.

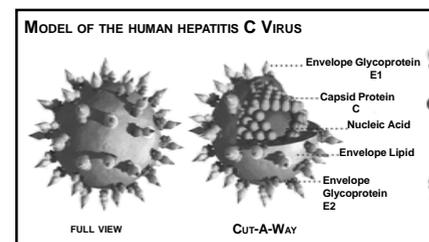


Fig. 1 : Model of Hepatitis C virus

Epidemiology

Today worldwide HCV is the commonest cause of post-transfusion hepatitis. The seroprevalance rate of HCV among the blood donor population in India is 1.8% - 2.5 %, and the community seroprevalence has been reported to be 0.87%. HCV is the etiological agent in about 20% of patients with chronic hepatitis in northern India. The prevalence of HCV varies greatly in

different countries. For example, in the Scandinavian countries <0.5% of the population is infected, where as in Egypt >20% of the population is infected with HCV because of the use of parenteral anti-schistosomal therapy. The highest prevalence has been reported in Ukraine and in the central African countries of Gabon and Cameroon. The HCV carrier rate among the general population in India is nearly the same as in developed countries. High prevalence of HCV infection ranging from 20 - 80% is reported in patients of chronic renal failure on maintenance haemodialysis, multi-transfused patients including patients with haematological disease, professional plasma donors, and renal transplant recipients.

Pathobiology

Virtually all HCV patients develop liver cell injury as shown by raised alanine amino transaminase (ALT) levels. A majority of patients are asymptomatic and anicteric. Only 25-40% of the patients develop malaise, weakness and anorexia and some become icteric. Anti HCV can be detected during the course of illness, 50-70 % of the patients at the onset of disease symptoms and in approximately 90% of the patient three months after the onset of infection. HCV is self-limited in only 15% of the patients. Recovery is characterized by disappearance of HCV-RNA and normalization of ALT. About 85% of the HCV-infected individuals fail to clear the virus by six months and develop chronic hepatitis with persistent and sometimes intermittent viremia. A majority of patients have

elevated ALT levels that can fluctuate widely. However, antibodies to HCV or circulatory HCV-RNA can be demonstrated in virtually all patients. In chronic hepatitis C, inflammatory cells infiltrate the portal tracts and parenchyma cells. The margin of the parenchyma and portal tract may become inflamed, leading to liver cell necrosis. When the disease progresses the inflammation and liver cell death may lead to fibrosis, such fibrosis can progress to cirrhosis in 20% of the patients within two decade of the onset of infection. Once cirrhosis (Fig. 2) is established complications such as jaundice, ascites, variceal haemorrhage and encephalopathy may develop during the end stages. It is estimated that about 2 - 3 % of HCV related cirrhotic patient develop Hepatocellular carcinoma (Fig. 3).

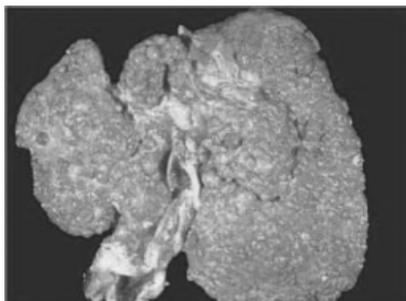


Fig. 2 : Cirrhosis of Liver

Extra-hepatic Manifestation

Hepatitis C infection may affect not only the liver but various non hepatic tissues as well. Many extra-hepatic manifestations, such as lichen planus, oral cancer, membranous-glomerulonephritis, lymphocytic sialadenitis, Mooren's



Fig. 3 : Hepatocellular Carcinoma

corneal ulcer, idiopathic pulmonary fibrosis, uveitis, sicca syndrome, low grade B cell lymphoma etc. have been described. In addition, autoimmune disease, viz autoimmune thyroiditis and mixed cryoglobulinemia are also found to be associated with HCV infection. HCV-RNA has been detected in 90% of patients with "essential" mixed cryoglobulinaemia, and cryoglobulins have been found in 30 -50% of patients with chronic hepatic C virus infection. Porphyria cutanea tarda also has a strong association with chronic HCV, although there appears to be a marked geographic variation in the rate of HCV positive patients with porphyria. A study in the United States found that 16 of 17 porphyria patients tested positive for anti-HCV, whereas of 17% in Northern Europe, 20% in Australia and New Zealand, and 65% in Southern Europe tested positive.

Mode of Transmission

HCV is transmitted primarily through the parenteral route and source of infection include injection, drug abuse, needle-stick accidents and transfusion of blood and especially blood products in patients with hemophilia, solid-organ transplant,

chronic renal failure or cancer patients requiring chemotherapy. However, nonparenteral or nonapparent parenteral exposure probably is also likely to occur. Although it appears that HCV can be transmitted by mucosal exposure, compared with HBV infection, this route is very inefficient. Sexual transmission of HCV is not as common as it is with hepatitis B virus, but seems to occur. Sexual transmission of hepatitis C between monogamous partners appears to be uncommon. Though HCV is a member of the Flaviviridae family, there is no epidemiologic or experimental evidence for transmission by an insect vector, although it remains theoretically possible. The single most important mode of transmission of HCV in most of the western countries is the illicit use of injectable drugs. Dentists practicing oral surgery, practitioners of folk medicine and those involved in hairdressing, ear-piercing and tattooing are also at high risk of HCV transmission. Maternal-infant transmission is not common. In most studies, only 5% of infant born to infected women become infected. The disease in newborns is usually mild and free of symptoms. The risk of maternal-infant spread rises with the amount of virus in the mother's blood. Breast feeding has not been linked to HCV's spread.

Diagnosis

A variety of diagnostic tests based on the detection of either the anti-HCV antibodies or HCV-RNA in patient sera has been developed. Third generation

ELISA that incorporates antigens from the core, NS 3, NS 4 and the NS 5 proteins of HCV representing about 60% of the total amino acid profile of the HCV polyprotein, is available in the market. Although this ELISA is significantly sensitive, a major drawback of this assay is that it fails to differentiate between active and post-infection cases. Antibodies tests often fail to detect acute infection i.e. patients in the window period between the time of infection and the time of appearance of antibody detectable by the assay. In addition third-generation ELISA cannot be used to detect the viral infection owing to genotype variations. To overcome this problem, sensitive diagnostic peptide based enzyme immunoassay using monoclonal antibodies for the detection of the core antigen of HCV (HCVcAg) has been developed with the claim of sensitivities comparable to nucleic acid amplification systems. Presently, an indigenous peptide based HCV EIA kit is available (Xcyton™, Bangalore, India). The RNA of hepatitis C virus can be detected by highly sensitive test based on RT-PCR or other nucleic acid amplification techniques. These techniques can detect HCV even in the window period.

Treatment of HCV

Until the mid-1990s, interferon-2 α (IFN-α) was the only available treatment for HCV. The addition of ribavirin, a nucleoside analogue, substantially improved the response; however, viral

genotype remains an important determinant of response rate. Although cure remains the primary objective, the benefits of treatment are not necessarily restricted to those patients who achieved eradication of the HCV. It seems that interferon treatment alone or in combination may prevent progression of, or even reverse, hepatic fibrosis in infected patients even if cure is not achieved. Although ribavirin alone does not seem to be active against HCV, the combination resulted in much improved and sustained biochemical, virological and histological response rates. Recent studies have shown that long-acting pegylated interferon (modified form of interferon) have better viral response than standard IFN- α preparations and in combination with ribavirin, achieved sustained viral eradication rates of 54 - 56%. A short course (six months) of INF- α commonly led to transient normalization of serum ALT, loss of detectable virus in blood and reduction of inflammation in liver. Unfortunately, relapse occurred in many cases when treatment was stopped. It was later shown that prolonging the duration of treatment with interferon for at least 12 months doubled the sustained response rate and this longer regimen was subsequently approved as the standard of care. The end treatment virological response and sustained virological response (SVR) is much higher in patient with genotype 2 and 3 compared with patient with genotype 1. Studies have shown about 70 - 80% patients with

genotype³ attained SVR after a 6 month of combinational therapy. In India, the percentage of sustained responders is higher due to a predominant prevalence of hepatitis C genotype, which is interferon sensitive. A six-monthly treatment regimen is now followed for eradication of HCV in our country. Many other factors viz. age at the onset of infection, immune status at the time of infection, viral load, genotype³, obesity, alcoholism, co-morbid illness, however, are also important for achieving desirable therapeutic response. In a developing country like India the cost of combinational therapy of interferon for chronic hepatitis C treatment may cost something around Rs. 1.5 - 4.5 lakhs. Since a majority of the population is not covered by health insurance, financial constraints become a major obstacle for many patients to initiate therapy.

Both interferon and ribavirin are not only expensive but can also have serious side effects. The combination therapy is contraindicated in the following conditions:

1. Patients with co-morbid illness (unstable cardiac or peripheral vascular disease, chronic renal failure, haemoglobinopathies.
2. Evidence of decompensated cirrhosis.
3. Auto-immune disease.
4. Tuberculosis.
5. History of severe or untreated depression.

6. Thyroid function abnormalities.
7. Active alcohol or drug abuser.
8. Uncontrolled diabetes.
9. Pregnancy.

At present, treatment is not recommended for children under 18 years of age as the natural history of HCV in children is not well defined. Co-infection with HIV or HBV is not a contraindication for treatment, and HIV-infected patient with good CD4 levels have responded adequately to therapy.

Treatment of non-responders

While waiting for new treatment strategies able to eradicate HCV in patients who do not have a virological response with currently available therapy, it has been suggested that such patients could be benefited from long-term administration of interferon, with the aim of reducing disease activity, fibrosis progression and abnormal hepatocyte proliferation, thus reducing or delaying progression to cirrhosis and development of hepatocellular carcinoma. This is still a quite controversial issue as several retrospective cohort studies suggest that virological non-responders have marginal benefits from long-term administration of interferon.

Alternative approaches for HCV treatment

A significant proportion of HCV patients have cirrhosis and thrombocytopenia at the time of presentation and are prone

to develop infection and reduced Glomerular Filtration Rate. Also many patients are unable to tolerate the combinational treatment regimen due to adverse side effects. Newer adjuvant therapies to manage these patients are now being tried.

Glycyrrhizin, a major component licorice root, *Glycyrrhiza glabra* or *Glycyrrhiza uralensis* has been found to have anti-viral properties through endogenous interferon induction as well as hepatocytoprotective effect. Clinical trials using Glycyrrhizin among patients with chronic hepatitis C have demonstrated normalization or decrease in ALT values as well as histological improvement. Glycyrrhizin has also been shown to inhibit RNA viruses through a hitherto unknown mechanism. The Indian Council of Medical Research (ICMR) is now conducting a multi-centric open randomized controlled clinical trial to evaluate the efficacy and safety of combined therapy with oral Glycyrrhizin and ribavirin for the treatment of decompensated HCV induced cirrhosis.

In a recently concluded trial by ICMR on the efficacy of glycyrrhizin vis-à-vis ribavirin, the unpublished preliminary data indicates that glycyrrhizin can be as effective as ribavirin. This ICMR study was conducted in various institutes all over India viz. All India Institute of Medical Sciences, New Delhi, PGI Chandigarh, Sanjay Gandhi PGI, Lucknow, Center for Liver Research & Diagnostic, Hyderabad, Metro Center

for Liver and Digestive Disease, Noida etc.

Conclusion

In the absence of efficient anti-HCV screening among blood donors in our country, post-transfusion HCV-induced chronic liver disease is likely to increase. Also, HCV infection from other sources will continue to add to the disease pool. HCV is a silent disease and in many patients have end stage liver disease at presentation. HCV can be managed well if it is detected and treated early. Awareness about HCV in general public and doctors in primary health care sectors can be an important key to increase detection rates. Large number of HCV infected people in our country is not yet diagnosed. In our institute we have started Patient Awareness Lecture (PAL), patients and their family members are invited for an interactive lecture session on HCV management. Some blood banks in Delhi have now taken initiative to inform donors if their blood sample is found positive for HCV. Such practices should be followed by other blood banks throughout the country. Government should take steps to advertise the harmful

and long term consequences of HCV in electronic media. Also effort should be made to identify carriers by testing high-risk individuals, and implement stringent public health measures to prevent spread.

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