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RESEARCH ARTICLE

IS HEPATITIS C LIKE A HOT KNIFE THROUGH BUTTER? (A SILENT KILLER).

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Abstract

Hepatitis C virus belongs to the flavi virus family. Hepatitis C virus is known as Non-A and Non-B hepatitis. It exists in six genotypes with different worldwide distribution. It is a curable disease. HCV is the common cause of transfusion and liver transplant-associated hepatitis. It can also be considered as STD and can be transmitted at birth from an HCV infected mother. Acute disease is usually mild but 70% of those infected develop chronic disease. A high percentage of individuals had an asymptomatic disease that leads to cirrhosis and liver failure. Hence each year, the percutaneous injury resulted in around 16,000 HCV and caused about 8000 deaths in the USA. Clinically acute infection with HCV is milder than infection with HBV (1).

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Introduction:-

HCV is a single stranded RNA virus that belongs to the family Flaviviridae and genus hepacivirus. As estimated 130 to 170 million people world wide are chronically infected with HCV, with 3-4 million new infections reported every year and majority of these individuals have low and middle income countries (LMCs) (2)

Worldwide, chronic infection with the hepatitis-C virus is the second most common cause of HCC accounting for 20% of all HCC (3)

Nearly half million HCV infected people die every year annually due to absence of accessible and effective diagnostic and treatment facilities in most of these LMICs (4)

Liver is the primary organ affected by chronic hepatitis C virus (HCV), a broad clinical the spectrum of extra hepatic complications and diseases are associated with this viral infection (5)

WHO mandates acceleration of HCV screening and diagnosis to meet its global goal of eradication of HCV by 2030 (6)

Moreover, outbreaks of hepatitis C among HIV positive homosexual men have been reported 2000 (7)

Prevalence of cirrhosis and mortality seems to be lower in patients with effective antiviral treatment (8,9)

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High incidence of acute hepatitis-C virus infections in Human immunodeficiency virus (HIV) positive men who have sex with men (MSM) has been observed in many European countries, as well as Australia and USA (10,11)

Several recent studies described an incidence of acute HCV infection in Dutch HIV positive MSM of 11/1000 person year of follow up (PYFU)(12)

The Type 1 interferon exerts their action through binding to a specific cell surface receptor complex known as the INF-alfa receptor(INFAR) that consists of IFNAR1 andIFNAR2 chains. The two commercially available IFNs in widespread usage for the treatment of hepatitis C are INF-alfa and INF alfa2b (13)

This is an extremely high incidence in a country where the overall HCV prevalence is estimated at 0.2%.It is described a comparably high incidence of HCV infection among HIV positive MSM in several other European countries(14)

More than 170 million people are chronic carriers of HCV and at high risk of developing liver cirrhosis and/or hepatocellular carcinoma (HCC). Three to 4% of chronically infected individuals develop fatal HCC. Currently, HCC caused by HCV infection is considered an indication for liver transplantation (15)

The faster fibrosis progression in HIV/HCV co-infection patients in particular with declining CD4 cell counts has also prompted many guidelines to prioritize HCV therapy in HCV co-infected subjects (16)

Studies on Chimpanzees reveal, two days after infection, HCV RNA levels rise, followed by a plateau within two days, concomitant with the induction of intrahepatic type 1 INF (17, 18)

Fibrosis is the principal complication of chronic hepatitis C, and it is estimated that 20% of patients develop cirrhosis over a period of 10, 20 or 30 years (19, 20)

History

The first association of blood transfusion with hepatitis was in 1943 (21) Willow brook clarified the transmissibility of a hepatitis agent from human plasma (22) The virus, initially called non-A, non-B hepatitis (NANBH). Inoculation of chimpanzees with blood components from humans having both acute and chronic NANBH resulted in characteristic elevations of transaminases, providing a valuable animal model for NANBH. By the mid-1980s, physicochemical studies of infectious inocula had revealed that the NANBH agent was small, enveloped virus (23) HBV and HCV virus co-infection mostly seen in South East Asia and Mediterranean countries. The two viruses inhibit each other mutually at the same time. Generally one plays a dominant role over the other. Generally HBV dominates HCV. Mostly, HCV strongly suppresses the HBV replication on co-infected patients.

Scientists in the United States and Japan finally identified this major cause of parent rally transmitted hepatitis in 1989 and designated it as the HCV (24,25)

A vaccine against hepatitis C is a remote possibility until recently. However, the outlook for hepatitis C vaccine has improved with advances in our understanding of the correlates of spontaneous immunity (26, 27). The discovery led to significant improvements in diagnosis and improved antiviral treatment (28) The role of antiviral therapy in acute hepatitis C is unclear. Acute infections are usually asymptomatic and found incidentally, such as needle stick injuries in health care workers. It is not clear what % of these cases becomes chronic. Some studies have shown that early treatment with INF or combination therapy decrease the chronicity rate in patients with acute hepatitis C (29) The current standard of care for hepatitis C is pegylated interferon used in combination with ribavirin. Each genotype responds differently to a treatment.(30) The discovery and cloning of HCV have led to a greater understanding of its relationship to acute and chronic hepatitis, cirrhosis, primary liver cancer, and extra hepatic conditions including essential cryoglobulinemia, glomerulonephritis, and serum autoantibody positivity(31)

Researchers discovered the hepatitis C virus in the late 1980s, and they were first able to grow the virus as a cell culture in 2005. Before this, researchers could not study how medications or vaccines might change the virus.

Significant Gap In Research

The current strategy targets the high prevalence population with advanced liver disease at near term risk of HCV associate mortality and cost effective. But it misses younger more recently infected persons. Risk based strategies are currently used to identify persons with HCV not in birth cohort. Risk based testing in addition to birth cohort testing is more effective than either strategy alone (32)

HCV c protein has been implicated in numerous cellular pathways, including altered signaling, transcriptional control apoptosis and cellular transformation (33)

Sub genomic replications were developed in 1999 and proved to be the best broadly useful system for studying HCV RNA replication cell culture (34)

In 2005, production of authentic HCV in cell culture (HCVcc) was achieved the first time. (35)

Needle exchange programs are a vital tool in preventing HCV infection among young persons who inject drugs Massachusetts is experiencing a troubling with an especially sharp rise in the last 2 years of opioid related deaths (36)

Where research go next?

There is no vaccination or prophylaxis against hepatitis C So early identification and treatment of infected individuals is required and has been shown to reduce the risk of developing chronic infection. Increased risk of needle injuries is identified and corrected. The therapeutic vaccine would also be an invaluable adjunct to current treatment options for HCV. Compared with hepatitis C virus single infection, HBV/HCV infected patients tend to have a more severe liver injury, a higher probability of cirrhosis, and hepatocellular carcinoma For those with HCV and low level of HBV viremia, treatment with PEG-INF and ribavirin can be as effective as in HCV mono-infection. To days' gold-standard treatment for HCV consists of pegylated interferon and ribavirin. This has been a remarkable advance in the treatment of HCV and may result in the permanent eradication of the virus in infected people. Nevertheless, it is currently expensive, has extensively side effect and is often ineffective. Several medications, now available to treat hepatitis C. While medication assistance is available, and some insurance companies pay for treatment, preventing the disease would be significantly more cost-effective (37)

)In US and Europe nearly 34% infected persons are co-infected with both HIV and HCV. In chronic infection, HCV RNA levels are higher in HIV co-infected patients, the efficacy of anti-HCV therapy is reduced and the incidence of cirrhosis and HCC is higher.

Major Advances And Discoveries

Laboratory diagnosis is carried out by ELISA. False results can occur in ELISA, a recombinant immunoblot assay (RIBA) should be performed as a confirmatory test. If the results of RIBA are positive a polymerase chain reaction-based test that detects the presence of viral RNA(Viral load)in serum should be performed to determine whether active disease exists. Reduction of the viral load in patients with hepatitis C is used to monitor the success of drug therapy. 85% of cases of acute hepatitis C may develop chronic hepatitis. Clinically it can't be differentiated from chronic hepatitis. SGPT level is normal in about 40% cases. It can be tested by enzyme immunoassay.(EIA)In suspected cases where EIA is negative HCV RNA can be detected by PCR. In about 20% of cases, cirrhosis develops after 20 years particularly in men who acquire the infection after 40 years and alcoholics and immunosuppressant(38)

Screening

Screening should be done who injected or inhaled illicit drugs, liver function test results with higher results, Babies born to mothers with hepatitis C, Health care and emergency workers who have been exposed to blood or accidental needle sticks, People who undergone long-term hem dialysis treatments, blood transfusions or organ transplants, people with HIV infection and born from 1945 to 1965.

Diagnosis

A number of immunoassays have been developed to detect anti-HCV IgG in serum or plasma specimens. Virology diagnosis of HCV infection is based on two categories of laboratory tests, namely serologic assays detecting specific antibody to HCV (anti-HCV) (indirect tests) and assays that can detect, quantify, or characterize the components of

HCV viral particles, such as HCV RNA and core antigen (direct tests). Direct and indirect virology tests play a key role in the diagnosis of infection, therapeutic decision-making, and assessment of virology response to therapy (39)

Recombinant immunoblot assays (RIBA) were used in the past as supplemental assays to confirm serological reactivity by ELISA, but are now clinically obsolete with the availability of molecular tests. Confirmation of serological reactive tests may be done by a nucleic acid test (NAT) for detection of HCV RNA. Recent studies have also suggested that higher the anti-HCV antibody titer in the patient's serum; more are the chances of it being true positive than false positive (40)

Treatment

Ribavirin (Copegus and Rebetol) is one of the older drugs that doctors prescribe for hepatitis infections. Daclatasvir is one of the newer drugs for hepatitis C. Treatment for HCV infection is available. The role of treatment in acute infection is being evaluated and currently 6 months of standard therapy with interferon (IFN) in terms of absence of HCV RNA from serum is excellent and progression to chronicity is reduced. The recommended treatment for chronic HCV infection is a combination of a pegylated IFN alpha and ribavirin. The treatment duration depends on the genotype of the virus and it has two goals. The first is to achieve sustained eradication of HCV, that is, sustained virology response (SVR), which is defined as the persistent absence of HCV RNA in serum for 6 months or more after completing antiviral treatment. The second goal is to prevent progression to cirrhosis, HCC, and decompensate liver disease requiring liver transplantation (41)

New types of improved antiviral drugs were discovered. Telaprevir, boceprevir are the protease inhibitors. These are antiviral drugs. PEG-ING and ribavirin improve virological response. Polymerase inhibitors are also shown good response. Currently, Polymerase inhibitors, protease inhibitors, and ribavirin are found fit to cure hepatitis C infection. HCV treatments provide cure rates that are more than 90% highlighting the importance of diagnosis. Current US preventive service task force include routine 1-time testing of persons born between 1945-1965 referred to as the birth cohort and targeted testing to high risk persons (42)

Current Debate

Interferon alpha therapy of acute hepatitis C is well-established. Response rate is high. Some of the serological markers in Hepatitis are platelet counts, ALT, GGT, Bilirubin, Cholesterol. The most common markers used in current assays involve measuring products of extracellular matrix synthesis or degradation and the enzyme that regulate their production and modification. In addition to liver biomarkers, the new technological advances MRI, Magnetic resonance elastography are also highly useful in the assessment of liver fibrosis. HCC remains the common cause of cancer mortality worldwide. The new antiviral agents are likely to decrease the incidence of HCC in parts of the world. Recent evidence has shown that HCV infection has a detrimental effect on patient and graft survival in patients with CKD (Chronic kidney disease). New therapies for CHC are now available in clinical practice. The primary route of HCV entry is percutaneous although per mucosal infection has also been described. (43)

The field of HIV therapeutics is rapidly advancing and it is expected that efficacious and safe directly acting anti-HCV agents will revolutionize the HCV treatment. The initial use of such agents will involve their combination with peginterferon and ribavirin (44)

In 1990 and related years, the measurement of HCV RNA levels is made available. It is now widely used to tailor pigmented INF-alfa and ribavirin, treatment duration and will still be useful for that purpose when telaprevir and boceprevir are prescribed in combination with these two drugs in patients infected with HCV genotype-1. It is likely that virologic response-guided therapy will remain essential in the future, especially in an era of INF-free regimens. (45)

Currently, HCV is responsible for about 8000 deaths annually in the USA. Furthermore, HCV is the leading reason for liver transplantation in the USA. Treatment with ribavirin and pegylated polyethylene glycol recombination therapy can rid the virus in 50% of those infected with genotype 1 and in the 80% of those infected with genotype 2 or 3 (46)

All pregnant women and people born 1945-1965 have to be screened. Natural killer (NK) cells are important for maintenance of innate immune system stability and serve as a first line of defense against tumors and virus infections; they can act either directly or indirectly and are regulated via co-operation between inhibitory and

stimulatory surface receptors. The recently reported inhibitory receptor, TIGIT, can be expressed on the NK cell surface; however, the expression level and function of TIGIT on NK cells during HIV infection is unknown. Recently, the expression and function of TIGIT in NK cells from HIV-infected individuals. Currently, it is observed that the level of TIGIT is higher on NK cells from patients infected with human immunodeficiency virus (HIV) compared with HIV-negative healthy controls. TIGIT expression is inversely correlated with CD4+ T cell counts and positively correlated with plasma viral loads (47)

Challenges

The advanced discovery of direct-acting antivirals (DAAs) is highly useful in the treatment of chronic hepatitis C infection. Direct acting antivirals are now useful in the elimination of HCV scrupulously. In spite of the recent modern drugs still, HCV threat remains challenging. No doubt the direct-acting antiviral drugs have completely changed the treatment scenarios. It is an exciting but challenging opportunity. It is estimated that nearly 40,000 HCV related deaths occurring annually. Discoveries in the areas of molecular biology, immunology, and microbiology is required to face the challenge.

Summary

Patients who have been diagnosed with chronic infection, however often complain of fatigue or depression, and they consistently score lower than HCV negative persons in all aspects of health-related quality of life. It reverts when using antiviral therapy. A number of extrahepatic complications have been associated with hepatitis C infection, including cryoglobulinemia, glomerulonephritis, porphyria, cutaneous tarda, polyarteritis nodosa, Sjogren's syndrome, and lichen planus

HCC remains a common cause of cancer mortality worldwide, with a significant contribution due to chronic hepatitis C infection. The new direct-acting antiviral agents are likely to decrease the incidence of HCC in parts of the world that can afford them. The field of HCV therapeutics is rapidly advancing and it is expected that efficacious and safe direct-acting anti-HCV agents will revolutionize the HCV treatment. Nevertheless, a number of studies need to be performed with highly sensitive and accurate assays based on real-time PCR in order to establish the best use of viral kinetic monitoring.

Conclusion:-

Acute HCV infection is observed for 3-4 months after the onset of symptoms. Antiviral therapy has to be started. The main stay of treatment is the combination of INF and ribavirin. Later pegylated IFN., which consists of polyethylene glycol(48)

Reducing the spread of infection, by raising awareness, screening of blood products, Hygiene/disinfection, post, and pre-exposure prophylaxis and vaccination. Genomic screening for this the infectious agent became possible with the development of various nucleic acid amplification techniques (NAT), such as polymerase chain reaction (PCR), Ligase-chain reaction (LCR), Nucleic acid sequence based amplification (NASBA) and transcriptions (mediated amplification (TMA) techniques are now available. Recent evidence has univocally shown that HCV has a detrimental effect on the patient. Care and develop strategies in the elimination of HCV is mandatory. Identifying those people infected with HCV and to be screened. Risk group, people have to be screened one time. Drug cost is a problem in underdeveloped and even developed countries.

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