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PREVALENCE OF HEPATITIS E VIRUS INFECTION IN ACUTE VIRAL HEPATITIS IN K.T.H A PERIOD BETWEEN OCTOBER 2004 – APRIL 2005

A thesis

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By

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Dedication

To the soul of my father …

Kind mother …

To all whom I love …

Nahid

CONTENTS

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ABSTRACT

Hepatitis E virus (HEV), the major aetiologic agent of enterically transmitted non A, non B hepatitis worldwide. During the period between October 2004 and April 2005 a cross sectional hospital – based study, was conducted in Khartoum Teaching Hospital to investigate the prevalence of acute hepatitis E among Sudanese patients presenting with acute hepatitis.

All patients presented with acute hepatitis were screened for viral hepatitis (A, B, C, E). Eleven out of fifty patients studied patients were found to have hepatitis E IgM antibodies (22%).

In our study no difference was found in the clinical presentation between hepatitis E infection and other viral hepatitis, nevertheless, a high incidence of fulminant hepatic failure was observed in patients with hepatitis E infection (2 out of 11 patients).

الخلاصـــــة

هذه دراسة مقطعية أجريت في مستشفى الخرطوم في الفترة ما بين أكتوبر 2004م إلى ابريل 2005م.

هدفت الدراسة لمعرفة نسبة انتشار التهاب الكبد بالفيروس هـ (E) بالنسبة للالتهاب بأنواع فيروسات الكبد الوبائي الأخرى في السودان.

أخذت 50 حالة مصابة بالتهاب الكبد الحاد ووجد من بينها 11 حالة مصابة بالتهاب الكبد بالفيروس هـ (E) 22%.

اثبتت الدراسة انه ليس هناك فرق واضح في الأعراض السريرية بين التهاب الكبد بالفيروس هـ (E) والفيروسات الأخرى ، ولكن وجد لديهم نسبة عالية من فشل الكبد الحاد الذي أدى إلى الوفاة (مصابين من بين 11 مصاب بالتهاب الكبد بالفيروس E).

ABREVIATIONS

Ab	Antibodies
ALP	Alkaline Phosphatase
ALT	Alanin amino Transferase
AST	Aspartate amino Transferase
FHF	Fulminant Hepatic Failure
HAV	Hepatitis A virus
Hb	Hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
Ig	Immuno globulin
KTH	Khartoum Teaching Hospital
US	Ultrasonography
WBCs	White Blood Cells

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INTRODUCTION

Acute viral hepatitis is a systemic infection affecting the liver predominantly. Almost all cases of acute viral hepatitis are caused by one of five viral agents: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), the HBV-associated delta agent or hepatitis D virus (HDV), and hepatitis E virus (HEV). Other transfusion-transmitted agents, e.g., "hepatitis G" virus and "TT" virus, have been identified but do not cause hepatitis. All these human hepatitis viruses are RNA viruses, except for hepatitis B, which is a DNA virus. Although these agents can be distinguished by their molecular and antigenic properties, all types of viral hepatitis produce clinically similar illnesses. These range from asymptomatic and in apparent to fulminant and fatal acute infections common to all types, on the one hand, and from subclinical persistent infections to rapidly progressive chronic liver disease with cirrhosis and even hepatocellular carcinoma, common to the bloodborne types (HBV, HCV, and HDV), on the other hand[(1)].

LITERATURE REVIEW

ACUTE VIRAL HEPATITIS

VIROLOGY AND ETIOLOGY:-

Hepatitis A

Hepatitis A virus is a non-enveloped 27-nm, heat-, acid-, and ether-resistant RNA virus in the hepatovirus genus of the picornavirus family. Hepatitis A has an incubation period of approximately 4 weeks. Its replication is limited to the liver, but the virus is present in the liver, bile, stools, and blood during the late incubation period and acute preicteric phase of illness. Despite persistence of virus in the liver, viral shedding in feces, viremia, and infectivity diminish rapidly once jaundice becomes apparent. HAV is the only one of the human hepatitis viruses that can be cultivated reproducibly in vitro[2,3].

Antibodies to HAV (anti-HAV) can be detected during acute illness when serum aminotransferase activity is elevated and fecal HAV shedding is still occurring. This early antibody response is predominantly of the IgM class and persists for several months, rarely for 6 to 12 months. During convalescence, however, anti-HAV of the IgG class becomes the predominant antibody . Therefore, the diagnosis of hepatitis A is made during acute illness by demonstrating anti-HAV of the IgM class. After acute illness, anti-HAV of the IgG class remains detectable indefinitely, and patients with serum anti-HAV are immune to reinfection. Neutralizing

antibody activity parallels the appearance of anti-HAV, and the IgG anti-HAV present in immune globulin accounts for the protection it affords against HAV infection[2,3].

Hepatitis B

Hepatitis B virus is a DNA virus with a remarkably compact genomic structure; despite its small, circular, 3200-basepair size[4].

Viral proteins and particles . The envelope protein expressed on the outer surface of the virion and on the smaller spherical and tubular structures is referred to as *hepatitis B surface antigen* (HBsAg),.. The antigen expressed on the surface of the nucleocapsid core is referred to as *hepatitis B core antigen* (HBcAg), and its corresponding antibody is anti-HBc. A third HBV antigen is *hepatitis B e antigen* (HBeAg), a soluble, nonparticulate, nucleocapsid [4].

Serologic and virologic markers After infection with HBV, the first virologic marker detectable in serum is HBsAg). Circulating HBsAg precedes elevations of serum aminotransferase activity and clinical symptoms and remains detectable during the entire icteric or symptomatic phase of acute hepatitis B and beyond. In typical cases, HBsAg becomes undetectable 1 to 2 months after the onset of jaundice and rarely persists beyond 6 months. After HBsAg disappears, antibody to HBsAg (anti-HBs) becomes detectable in serum and remains detectable indefinitely thereafter. Because HBcAg is sequestered within an HBsAg coat, HBcAg is not detectable routinely in the serum of patients with HBV infection. By contrast, anti-HBc is readily demonstrable in serum, beginning within the

first 1 to 2 weeks after the appearance of HBsAg and preceding detectable levels of anti-HBs by weeks to months. Because variability exists in the time of appearance of anti-HBs after HBV infection, occasionally a gap of several weeks or longer may separate the disappearance of HBsAg and the appearance of anti-HBs. During this "gap" or "window" period, anti-HBc may represent serologic evidence of current or recent HBV infection, and blood containing anti-HBc in the absence of HBsAg and anti-HBs has been implicated in the development of transfusion-associated hepatitis B. In part because the sensitivity of immunoassays for HBsAg and anti-HBs has increased, however, this window period is rarely encountered[4-10].

Early during the course of acute hepatitis B, HBeAg appears transiently; its disappearance may be a harbinger of clinical improvement and resolution of infection. Persistence of HBeAg in serum beyond the first 3 months of acute infection may be predictive of the development of chronic infection[5].

Hepatitis D The delta hepatitis agent, or HDV, is a defective RNA virus that coinfects with and requires the helper function of HBV (or other hepadnaviruses) for its replication and expression. Slightly smaller than HBV, delta is a formalin-sensitive, 35- to 37-nm virus with a hybrid structure. The delta core is "encapsidated" by an outer envelope of HBsAg, indistinguishable from that of HBV except in its relative compositions of major, middle, and large HBsAg component proteins. Although complete hepatitis D virions and liver injury require the cooperative helper function of HBV, intracellular replication of HDV RNA can occur without HBV[11,12].

During acute HDV infection, anti-HDV of the IgM class predominates, and 30 to 40 days may elapse after symptoms appear before anti-HDV can be

detected. In self-limited infection, anti-HDV is low titer and transient, rarely remaining detectable beyond the clearance of HBsAg and HDV antigen[11,12].

Hepatitis C

Hepatitis C virus, which, before its identification was labeled "non-A, non-B hepatitis," is a linear, single-stranded, positive-sense, 9400-nucleotide RNA virus,. The HCV genome contains a single large open reading frame (gene) that codes for a virus polyprotein of approximately 3000 amino acids[13].

The most sensitive indicator is the presence of HCV RNA, which requires molecular amplification by polymerase chain reaction (PCR)). In most patients with acute hepatitis C, antibody detected appears between 1 to 3 months after the onset of acute hepatitis but sometimes not for a year or longer[14,16].

PATHOLOGY:

The typical morphologic lesions of all types of viral hepatitis are similar and consist of panlobular infiltration with mononuclear cells, hepatic cell necrosis, hyperplasia of Kupffer cells, and variable degrees of cholestasis. The mononuclear infiltration consists primarily of small lymphocytes, although plasma cells and eosinophils occasionally are present. Liver cell damage consists of hepatic cell degeneration and necrosis, cell dropout, ballooning of cells, and acidophilic degeneration of hepatocytes (forming so-called Councilman bodies. In uncomplicated viral hepatitis, the reticulin framework is preserved[17].

In hepatitis C, the histologic lesion is often remarkable for a relative paucity of inflammation, a marked increase in activation of sinusoidal lining cells, lymphoid aggregates, the presence of fat, and, occasionally, bile duct lesions in which biliary epithelial cells appear to be piled up without interruption of the basement membrane. Occasionally, microvesicular steatosis occurs in hepatitis D. A cholestatic variant of slowly resolving acute hepatitis A also has been described[13-16].

In *massive hepatic necrosis* (fulminant hepatitis, acute yellow atrophy), the striking feature at postmortem examination is the finding of a small, shrunken, soft liver. Histologic examination reveals massive necrosis and dropout of liver cells of most lobules with extensive collapse and condensation of the reticulin framework [18,19].

EPIDEMIOLOGY:

Hepatitis A

This agent is transmitted almost exclusively by the fecal-oral route. Person-to-person spread of HAV is enhanced by poor personal hygiene and overcrowding; large outbreaks as well as sporadic cases have been traced to contaminated food, water, milk, frozen raspberries and strawberries, and shellfish. Intrafamily and intrainstitutional spread are also common. Early epidemiologic observations suggested that there is a predilection for hepatitis A to occur in late fall and early winter. In temperate zones, epidemic waves have been recorded every 5 to 20 years as new segments of nonimmune population appeared; however, in developed countries, the incidence of type A hepatitis has been declining, presumably as a function

of improved sanitation, and these cyclic patterns are no longer being observed. No HAV carrier state has been identified after **acute** type A hepatitis[2,3].

Hepatitis B

Percutaneous inoculation has long been recognized as a major route of hepatitis B transmission, but the outmoded designation "serum hepatitis" is an inaccurate label for the epidemiologic spectrum of HBV infection recognized today. As detailed below, most of the hepatitis transmitted by blood transfusion is not caused by HBV; moreover, in approximately two-thirds of patients with acute type B hepatitis, there is no history of an identifiable percutaneous exposure.. HBsAg has been identified in almost every body fluid from infected persons, and at least some of these body fluidsmost notably semen and salivaare infectious, albeit less so than serum, when administered percutaneously or nonpercutaneously to experimental animals. Among the nonpercutaneous modes of HBV transmission, oral ingestion has been documented as a potential but inefficient route of exposure. By contrast, the two nonpercutaneous routes considered to have the greatest impact are intimate (especially sexual) contact and perinatal transmission[4-6].

Perinatal transmission occurs primarily in infants born to HBsAg carrier mothers or mothers with acute hepatitis B during the third trimester of pregnancy or during the early postpartum period. Perinatal transmission is uncommon in North America and western Europe but occurs with great frequency and is the most important mode of HBV perpetuation in the Far East and developing countries. Although the precise mode of perinatal

transmission is unknown, and although approximately 10% of infections may be acquired in utero, epidemiologic evidence suggests that most infections occur approximately at the time of delivery and are not related to breast feeding. The likelihood of perinatal transmission of HBV correlates with the presence of HBeAg; 90% of HBeAg-positive mothers but only 10 to 15% of anti-HBe-positive mothers transmit HBV infection to their offspring[5].

The more than 350 million HBsAg carriers in the world constitute the main reservoir of hepatitis B in human beings. Serum HBsAg is infrequent (0.1 to 0.5%) in normal populations in the United States and western Europe. However, a prevalence of up to 5 to 20% has been found in the Far East and in some tropical countries; in persons with Down's syndrome, lepromatous leprosy, leukemia, Hodgkin's disease, polyarteritis nodosa; in patients with chronic renal disease on hemodialysis; and in injection drug users[17].

Other groups with high rates of HBV infection include spouses of acutely infected persons, sexually promiscuous persons (especially promiscuous homosexual men), health care workers exposed to blood, persons who require repeated transfusions especially with pooled blood product concentrates (e.g., hemophiliacs), residents and staff of custodial institutions for the mentally retarded, prisoners, and, to a lesser extent, family members of chronically infected patients. In volunteer blood donors, the prevalence of anti-HBs, a reflection of previous HBV infection, ranges from 5 to 10%, but the prevalence is higher in lower socioeconomic strata, older age groups, and persons including those mentioned above exposed to blood products[8,9].

Hepatitis D

Infection with HDV has a worldwide distribution, but two epidemiologic patterns exist. In Mediterranean countries (northern Africa, southern Europe, the Middle East), HDV infection is endemic among those with hepatitis B, and the disease is transmitted predominantly by nonpercutaneous means, especially close personal contact. In nonendemic areas, such as the United States and northern Europe, HDV infection is confined to persons exposed frequently to blood and blood products, primarily injection drug users and hemophiliacs. HDV infection can be introduced into a population through drug users or by migration of persons from endemic to nonendemic areas. Thus, patterns of population migration and human behavior facilitating percutaneous contact play important roles in the introduction and amplification of HDV infection. Occasionally, the migrating epidemiology of hepatitis D is expressed in explosive outbreaks of severe hepatitis, such as those that have occurred in remote South American villages as well as in urban centers in the United States. Ultimately, such outbreaks of hepatitis D either of coinfections with acute hepatitis B or of superinfections in those already infected with HBV may blur the distinctions between endemic and nonendemic areas[9].

Hepatitis C

Routine screening of blood donors for HBsAg and the elimination of commercial blood sources in the early 1970s reduced the frequency of, but did not eliminate, transfusion-associated hepatitis. During the 1970s, the likelihood of acquiring hepatitis after transfusion of voluntarily donated, HBsAg-screened blood was approximately 10% per patient (up to 0.9% per

unit transfused); 90 to 95% of these cases were classified, based on serologic exclusion of hepatitis A and B, as "non-A, non-B" hepatitis. For patients requiring transfusion of pooled products, such as clotting factor concentrates, the risk was even higher, up to 20 to 30%, while for those receiving such products as albumin and immune globulin, because of prior treatment of these materials by heating to 60°C or cold ethanol fractionation, there was no risk of hepatitis[20-22].

In addition to being transmitted by transfusion, hepatitis C can be transmitted by other percutaneous routes, such as self-injection with intravenous drugs. In addition, this virus can be transmitted by occupational exposure to blood, and the likelihood of infection is increased in hemodialysis unit. As a bloodborne infection, HCV potentially can be transmitted sexually and perinatally; however, both of these modes of transmission are inefficient for hepatitis C. Although 10 to 15% of patients with acute hepatitis C report having potential sexual sources of infection, most studies have failed to identify sexual transmission of this agent. The chances of sexual and perinatal transmission have been estimated to be approximately 5%, well below comparable rates for HIV and HBV infections[20-22].

CLINICAL AND LABORATORY FEATURES:

Symptoms and Signs Acute viral hepatitis occurs after an incubation period that varies according to the responsible agent. Generally, incubation periods for hepatitis A range from 15 to 45 days (mean 4 weeks), for hepatitis B and D from 30 to 180 days (mean 4 to 12 weeks), for hepatitis C from 15 to 160 days (mean 7 weeks), and for hepatitis E from 14 to 60 days

(mean 5 to 6 weeks). The *prodromal symptoms* of acute viral hepatitis are systemic and quite variable. Constitutional symptoms of anorexia, nausea and vomiting, fatigue, malaise, arthralgias, myalgias, headache, photophobia, pharyngitis, cough, and coryza may precede the onset of jaundice by 1 to 2 weeks. The nausea, vomiting, and anorexia are frequently associated with alterations in olfaction and taste. A low-grade fever between 38 and 39°C (100 to 102°F) is more often present in hepatitis A and E than in hepatitis B or C, except when hepatitis B is heralded by a serum sicknesslike syndrome; rarely, a fever of 39.5 to 40°C (103 to 104°F) may accompany the constitutional symptoms. Dark urine and clay-colored stools may be noticed by the patient from 1 to 5 days before the onset of clinical jaundice[10,18,19].

With the onset of *clinical jaundice*, the constitutional prodromal symptoms usually diminish, but in some patients mild weight loss (2.5 to 5 kg) is common and may continue during the entire icteric phase. The liver becomes enlarged and tender and may be associated with right upper quadrant pain and discomfort. Infrequently, patients present with a cholestatic picture, suggesting extrahepatic biliary obstruction. Splenomegaly and cervical adenopathy are present in 10 to 20% of patients with acute hepatitis. Rarely, a few spider angiomas appear during the icteric phase and disappear during convalescence. During the *recovery phase*, constitutional symptoms disappear, but usually some liver enlargement and abnormalities in liver biochemical tests are still evident. The duration of the posticteric phase is variable, ranging from 2 to 12 weeks, and usually is more prolonged in acute hepatitis B and C. Complete clinical and biochemical recovery is to be expected 1 to 2 months after all cases of

hepatitis A and E and 3 to 4 months after the onset of jaundice in three-quarters of uncomplicated cases of hepatitis B and C. In the remainder, biochemical recovery may be delayed. A substantial proportion of patients with viral hepatitis never become icteric[5,13,14].

Laboratory Features:

The serum aminotransferases aspartate aminotransferase (AST) and ALT (previously designated SGOT and SGPT) show a variable increase during the prodromal phase of acute viral hepatitis and precede the rise in bilirubin level. The acute level of these enzymes, however, does not correlate well with the degree of liver cell damage. Peak levels vary from 400 to 4000 IU or more; these levels are usually reached at the time the patient is clinically icteric and diminish progressively during the recovery phase of acute hepatitis. The diagnosis of anicteric hepatitis is difficult and requires a high index of suspicion; it is based on clinical features and on aminotransferase elevations, although mild increases in conjugated bilirubin also may be found.Jaundice is usually visible in the sclera or skin when the serum bilirubin value exceeds 43 umol/L (2.5 mg/dL). When jaundice appears, the serum bilirubin typically rises to levels ranging from 85 to 340 umol/L (5 to 20 mg/dL). The serum bilirubin may continue to rise despite falling serum aminotransferase levels. In most instances, the total bilirubin is equally divided between the conjugated and unconjugated fractions. Bilirubin levels above 340 umol/L (20 mg/dL) extending and persisting late into the course of viral hepatitis are more likely to be associated with severe disease. In certain patients with underlying hemolytic anemia, however, such as glucose-6-phosphate dehydrogenase deficiency and sickle cell anemia, a high serum bilirubin level is common, resulting from superimposed

hemolysis. In such patients, bilirubin levels greater than 513 umol/L (30 mg/dL) have been observed and are not necessarily associated with a poor prognosis[6,15,20].

Neutropenia and lymphopenia are transient and are followed by a relative lymphocytosis. Atypical lymphocytes (varying between 2 and 20%) are common during the acute phase. These atypical lymphocytes are indistinguishable from those seen in infectious mononucleosis. Measurement of the prothrombin time (PT) is important in patients with acute viral hepatitis, for a prolonged value may reflect a severe synthetic defect, signify extensive hepatocellular necrosis, and indicate a worse prognosis. Occasionally, a prolonged PT may occur with only mild increases in the serum bilirubin and aminotransferase levels. Prolonged nausea and vomiting, inadequate carbohydrate intake, and poor hepatic glycogen reserves may contribute to hypoglycemia noted occasionally in patients with severe viral hepatitis. Serum alkaline phosphatase may be normal or only mildly elevated, while a fall in serum albumin is uncommon in uncomplicated acute viral hepatitis. In some patients, mild and transient steatorrhea has been noted as well as slight microscopic hematuria and minimal proteinuria[20].

A diffuse but mild elevation of the gamma globulin fraction is common during acute viral hepatitis. Serum IgG and IgM levels are elevated in about one-third of patients during the acute phase of viral hepatitis, but the serum IgM level is elevated more characteristically during acute hepatitis A. During the acute phase of viral hepatitis, antibodies to smooth muscle and other cell constituents may be present, and low titers of rheumatoid factor, nuclear antibody, and heterophil antibody also can be found occasionally. In

contrast, virus-specific antibodies, which appear during and after hepatitis virus infection, are serologic markers of diagnostic importance[1-3,8].

As described above, serologic tests are available with which to establish a diagnosis of hepatitis A, B, D, and C. Tests for fecal or serum HAV are not routinely available. Therefore, a diagnosis of type A hepatitis is based on detection of IgM anti-HAV during acute illness. Rheumatoid factor can give rise to false-positive results in this test.

A diagnosis of HBV infection can usually be made by detection of HBsAg in serum. Infrequently, levels of HBsAg are too low to be detected during acute HBV infection, even with the current generation of highly sensitive immunoassays. In such cases, the diagnosis can be established by the presence of IgM anti-HBc[6,7].

In patients with hepatitis B surface antigenemia of unknown duration, e.g., blood donors found to be HBsAg-positive and referred to a physician for evaluation, testing for IgM anti-HBc may be useful to distinguish between acute or recent infection (IgM anti-HBc-positive) and chronic HBV infection (IgM anti-HBc-negative, IgG anti-HBc-positive). A false-positive test for IgM anti-HBc may be encountered in patients with high-titer rheumatoid factor. Tests for the detection of HBV DNA in liver and serum are now available.

In patients with hepatitis C, an episodic pattern of aminotransferase elevation is common. A specific serologic diagnosis of hepatitis C can be made by demonstrating the presence in serum of anti-HCV. When a second- or third-generation immunoassay (that detects antibodies to nonstructural

and nucleocapsid proteins) is used, anti-HCV can be detected in acute hepatitis C during the initial phase of elevated aminotransferase activity. This antibody may never become detectable in 5 to 10% of patients with acute hepatitis C, and levels of anti-HCV may become undetectable after recovery from acute hepatitis C[7-9, 15,17].

The presence of HDV infection can be identified by demonstrating intrahepatic HDV antigen or, more practically, an anti-HDV seroconversion (a rise in titer of anti-HDV or de novo appearance of anti-HDV). Circulating HDV antigen, also diagnostic of acute infection, is detectable only briefly, if at all. Because anti-HDV is often undetectable once HBsAg disappears, retrospective serodiagnosis of acute self-limited, simultaneous HBV and HDV infection is difficult. Early diagnosis of acute infection may be hampered by a delay of up to 30 to 40 days in the appearance of anti-HDV[11].

PROGNOSIS:

Virtually all previously healthy patients with hepatitis A recover completely from their illness with no clinical sequelae. Similarly, in acute hepatitis B, 95 to 99% of previously healthy adults have a favorable course and recover completely. There are, however, certain clinical and laboratory features that suggest a more complicated and protracted course. Patients of advanced age and with serious underlying medical disorders may have a prolonged course and are more likely to experience severe hepatitis. Initial presenting features such as ascites, peripheral edema, and symptoms of hepatic encephalopathy suggest a poorer prognosis. In addition, a prolonged PT, low serum albumin level, hypoglycemia, and very high serum bilirubin values suggest severe

hepatocellular disease. Patients with these clinical and laboratory features deserve prompt hospital admission. The case-fatality rate in hepatitis A and B is very low (approximately 0.1%) but is increased by advanced age and underlying debilitating disorders. Among patients ill enough to be hospitalized for acute hepatitis B, the fatality rate is 1%. Hepatitis C occurring after transfusion is less severe during the acute phase than hepatitis B and is more likely to be anicteric; fatalities are rare, but the precise case-fatality rate is not known. Patients with simultaneous acute hepatitis B and hepatitis D do not necessarily experience a higher mortality rate than do patients with acute hepatitis B alone; however, in several recent outbreaks of acute simultaneous HBV and HDV infection among injection drug users, the case-fatality rate has been approximately 5%. In the case of HDV superinfection of a person with chronic hepatitis B, the likelihood of fulminant hepatitis and death is increased substantially. Although the case-fatality rate for hepatitis D has not been defined adequately, in outbreaks of severe HDV superinfection in isolated populations with a high hepatitis B carrier rate, the mortality rate has been recorded in excess of 20%[1-3,8,9,11,15].

COMPLICATIONS AND SEQUELAE:

A small proportion of patients with hepatitis A experience *relapsing hepatitis* weeks to months after apparent recovery from acute hepatitis. Relapses are characterized by recurrence of symptoms, aminotransferase elevations, occasionally jaundice, and fecal excretion of HAV. Another unusual variant of acute hepatitis A is *cholestatic hepatitis*, characterized by protracted cholestatic jaundice and pruritus. Rarely, liver test abnormalities persist for many months, even up to a year. Even when these complications occur, hepatitis A remains self-limited and does not progress to chronic liver

disease. During the prodromal phase of acute hepatitis B, a serum sickness-like syndrome characterized by arthralgia or arthritis, rash, angioedema, and rarely hematuria and proteinuria may develop in 5 to 10% of patients. This syndrome occurs before the onset of clinical jaundice, and these patients are often erroneously diagnosed as having rheumatologic diseases. The diagnosis can be established by measuring serum aminotransferase levels, which are almost invariably elevated, and serum HBsAg[4-6].

The most feared complication of viral hepatitis is *fulminant hepatitis* (massive hepatic necrosis); fortunately, this is a rare event. Fulminant hepatitis is primarily seen in hepatitis B and D, as well as hepatitis E, but rare fulminant cases of hepatitis A occur primarily in older adults and in persons with underlying chronic liver disease. Hepatitis B accounts for more than 50% of fulminant hepatitis cases, a sizable proportion of which are associated with HDV infection. Participation of HDV can be documented in approximately one-third of patients with acute fulminant hepatitis B and two-thirds of patients with fulminant hepatitis superimposed on chronic hepatitis B. Fulminant hepatitis is seen rarely in hepatitis C, but hepatitis E, can be complicated by fatal fulminant hepatitis in 1 to 2% of all cases and in up to 20% of cases occurring in pregnant women. Patients usually present with signs and symptoms of encephalopathy that may evolve to deep coma. The liver is usually small and the PT excessively prolonged. The combination of rapidly shrinking liver size, rapidly rising bilirubin level, and marked prolongation of the PT, even as aminotransferase levels fall, together with clinical signs of confusion, disorientation, somnolence, ascites, and edema, indicates that the patient has hepatic failure with encephalopathy. Cerebral edema is common; brainstem compression,

gastrointestinal bleeding, sepsis, respiratory failure, cardiovascular collapse, and renal failure are terminal events. The mortality rate is exceedingly high (greater than 80% in patients with deep coma), but patients who survive may have a complete biochemical and histologic recovery. If a donor liver can be located in time, liver transplantation may be life-saving in patients with fulminant hepatitis[9,19].

It is particularly important to document the disappearance of HBsAg after apparent clinical recovery from acute hepatitis B. Before laboratory methods were available to distinguish between acute hepatitis and acute hepatitis-like exacerbations (*spontaneous reactivations*) of chronic hepatitis B, observations suggested that approximately 10% of patients remained HBsAg-positive for longer than 6 months after the onset of clinically apparent acute hepatitis B. Half these persons cleared the antigen from their circulations during the next several years, but the other 5% remained chronically HBsAg-positive. More recent observations suggest that the true rate of chronic infection after clinically apparent acute hepatitis B is as low as 1% in normal, immunocompetent, young adults. Earlier, higher estimates may have been biased by inadvertent inclusion of acute exacerbations in chronically infected patients; these patients, chronically HBsAg-positive before exacerbation, were unlikely to seroconvert to HBsAg-negative thereafter. Whether the rate of chronicity is 10 or 1%, such patients have anti-HBc in serum; anti-HBs is either undetected or detected at low titer against the opposite subtype specificity of the antigen. These patients may (1) be asymptomatic carriers, (2) have low-grade, mild chronic hepatitis, or (3) have moderate to severe chronic hepatitis with or without cirrhosis. The likelihood of becoming an HBsAg carrier after acute HBV infection is

especially high among neonates, persons with Down's syndrome, chronically hemodialyzed patients, and immunosuppressed patients, including persons with HIV infection.*Chronic hepatitis* is an important late complication of acute hepatitis B[4-7].

After transfusion-associated acute hepatitis C, at least 50% of patients have abnormal biochemical liver tests for more than a year. In some experiences, the frequency of progression to chronicity after acute hepatitis C is as high as 70%. In most of these patients, liver histology is consistent with moderate to severe chronic hepatitis. Thus, after acute HCV infection, the likelihood of remaining chronically *infected* approaches 85 to 90%. Although many patients with chronic hepatitis C have no symptoms, cirrhosis may develop in as many as 20% within 10 to 20 years of acute illness; in some series of cases, cirrhosis has been reported in as many as 50% of patients with chronic hepatitis C. In contrast, neither HAV nor HEV causes chronic liver disease[1,2,12-14,20-22].

Rare complications of viral hepatitis include pancreatitis, myocarditis, atypical pneumonia, aplastic anemia, transverse myelitis, and peripheral neuropathy. *Carriers* of HBsAg, particularly those infected in infancy or early childhood, have an enhanced risk of hepatocellular carcinoma. The risk of hepatocellular carcinoma is increased as well in patients with chronic hepatitis C, almost exclusively in patients with cirrhosis, and almost always after at least several decades, usually after three decades of disease). In children, hepatitis B may present rarely with anicteric hepatitis, a nonpruritic papular rash of the face, buttocks, and limbs, and lymphadenopathy[18,19,23].

TREATMENT:

Treatment of Acute Attack Although therapy has been developed for chronic hepatitis B and C, opportunities for treating acute hepatitis caused by HBV or HCV are limited. In hepatitis B, among previously healthy adults who present with clinically apparent acute hepatitis, recovery occurs in approximately 99%; therefore, antiviral therapy is not likely to improve the rate of recovery and is not required. In rare instances of severe acute hepatitis B, treatment with a nucleoside analogue, such as lamivudine, at the 100-mg/d oral dose used to treat chronic hepatitis B. has been attempted successfully. However, clinical trials have not been done to establish the efficacy of this approach, severe acute hepatitis B is not an approved indication for therapy, and the duration of therapy has not been determined. In typical cases of acute hepatitis C, recovery is rare, progression to chronic hepatitis is the rule, occurring in 85 to 90% of patients, and meta-analyses of small clinical trials suggest that antiviral therapy with interferon alpha (3 million units subcutaneously three times a week) is beneficial, reducing the rate of chronicity considerably by inducing sustained responses in 40% of patients. The duration of therapy and whether to add the nucleoside analogue ribavirin remain to be determined, but the most reasonable approach is to follow recommendations for treatment of chronic hepatitis C. Because of the marked reduction over the last two decades in the frequency of acute hepatitis C, opportunities to identify and treat patients with acute hepatitis C are rare indeed. Hospital epidemiologists, however, will encounter health workers who sustain hepatitis C-contaminated needle sticks; when monitoring for ALT elevations and HCV RNA after these accidents identifies acute hepatitis C, therapy should be initiated[20,24,25].

Notwithstanding these specific therapeutic considerations, in most cases of typical acute viral hepatitis, specific treatment generally is not necessary. Although hospitalization may be required for clinically severe illness, most patients do not require hospital care. Forced and prolonged bed rest is not essential for full recovery, but many patients will feel better with restricted physical activity. A high-calorie diet is desirable, and because many patients may experience nausea late in the day, the major caloric intake is best tolerated in the morning. Intravenous feeding is necessary in the acute stage if the patient has persistent vomiting and cannot maintain oral intake. Drugs capable of producing adverse reactions such as cholestasis and drugs metabolized by the liver should be avoided. If severe pruritus is present, the use of the bile salt-sequestering resin cholestyramine will usually alleviate this symptom. Glucocorticoid therapy has no value in acute viral hepatitis. Even in severe cases associated with *bridging necrosis*, controlled trials have failed to demonstrate the efficacy of steroids. In fact, such therapy may be hazardous[20,25].

In *fulminant hepatitis*, the goal of therapy is to support the patient by maintenance of fluid balance, support of circulation and respiration, control of bleeding, correction of hypoglycemia, and treatment of other complications of the comatose state in anticipation of liver regeneration and repair. Protein intake should be restricted, and oral lactulose or neomycin administered. Glucocorticoid therapy has been shown in controlled trials to be ineffective. Likewise, exchange transfusion, plasmapheresis, human cross-circulation, porcine liver cross-perfusion, and hemoperfusion have not been proven to enhance survival. Meticulous intensive care is the one factor that does appear to improve survival. Orthotopic liver transplantation is

resorted to with increasing frequency, with excellent results, in patients with fulminant hepatitis[19].

PROPHYLAXIS:

Because application of therapy for acute viral hepatitis is limited, and because antiviral therapy for chronic viral hepatitis is effective in only a proportion of patients emphasis is placed on prevention through immunization. The prophylactic approach differs for each of the types of viral hepatitis. In the past, immunoprophylaxis relied exclusively on passive immunization with antibody-containing globulin preparations purified by cold ethanol fractionation from the plasma of hundreds of normal donors. Currently, for hepatitis A and B, active immunization with vaccines is available as well[23].

Hepatitis A

Both passive immunization with immune globulin (IG) and active immunization with a killed vaccine are available. All preparations of IG contain anti-HAV concentrations sufficient to be protective. When administered before exposure or during the early incubation period, IG is effective in preventing clinically apparent hepatitis A. For postexposure prophylaxis of intimate contacts (household, institutional) of persons with hepatitis A, the administration of 0.02 mL/kg is recommended as early after exposure as possible; it may be effective even when administered as late as 2 weeks after exposure.

Hepatitis A vaccines are approved for use in persons who are at least 2 years old and appear to provide adequate protection 4 weeks after a primary

inoculation. If it can be given within 4 weeks of an expected exposure, such as by travel to an endemic area, hepatitis A vaccine is the preferred approach to *preexposure* immunoprophylaxis. If travel is more imminent, IG (0.02 mL/kg) should be administered at a different injection site, along with the first dose of vaccine. Because vaccination provides long-lasting protection (protective levels of anti-HAV should last 20 years after vaccination), persons whose risk will be sustained (e.g., frequent travelers or those remaining in endemic areas for prolonged periods) should be vaccinated, and vaccine should supplant the need for repeated IG injections[23,26,28].

Hepatitis B

For *preexposure* prophylaxis against hepatitis B in settings of frequent exposure (health workers exposed to blood, hemodialysis patients and staff, residents and staff of custodial institutions for the developmentally handicapped, injection drug users, inmates of long-term correctional facilities, promiscuous homosexual men as well as promiscuous heterosexual individuals, persons such as hemophiliacs who require long-term, high-volume therapy with blood derivatives, household and sexual contacts of HBsAg carriers, persons living in or traveling extensively in endemic areas, unvaccinated children under the age of 18, and unvaccinated children who are Alaskan natives, Pacific Islanders, or residents in households of first-generation immigrants from endemic countries), three intramuscular (deltoid, not gluteal) injections of hepatitis B vaccine are recommended at 0, 1, and 6 months. Pregnancy is *not* a contraindication to vaccination. *postexposure* prophylaxis with a combination of HBIG (for rapid achievement of high-titer circulating anti-HBs) and hepatitis B vaccine (for achievement of long-lasting immunity as well as its apparent efficacy in

attenuating clinical illness after exposure) is recommended. The precise duration of protection afforded by hepatitis B vaccine is unknown; however, approximately 80 to 90% of immunocompetent vaccinees retain protective levels of anti-HBs for at least 5 years, and 60 to 80% for 10 years. Currently, *booster* immunizations are not recommended routinely, except in immunosuppressed persons who have lost detectable anti-HBs or immunocompetent persons who sustain percutaneous HBsAg-positive inoculations after losing detectable antibody. Specifically, for hemodialysis patients, annual anti-HBs testing is recommended after vaccination; booster doses are recommended when anti-HBs levels fall below 10 mIU/mL[23,29-32].

Hepatitis D

Infection with hepatitis D can be prevented by vaccinating susceptible persons with hepatitis B vaccine. No product is available for immunoprophylaxis to prevent HDV superinfection in HBsAg carriers; for them, avoidance of percutaneous exposures and limitation of intimate contact with persons who have HDV infection are recommended[23].

Hepatitis C

IG is ineffective in preventing hepatitis C and is no longer recommended for postexposure prophylaxis in cases of perinatal, needle stick, or sexual exposure. Although a prototype vaccine that induces antibodies to HCV envelope protein has been developed, currently, hepatitis C vaccination is not feasible practically. Genotype and quasispecies viral heterogeneity, as well as rapid evasion of neutralizing antibodies by this rapidly mutating

virus, conspire to render HCV a difficult target for immunoprophylaxis with a vaccine.

For stable, monogamous sexual partners, sexual transmission of hepatitis C is unlikely, and sexual barrier precautions are not recommended. For persons with multiple sexual partners or with sexually transmitted diseases, the risk of sexual transmission of hepatitis C is increased, and barrier precautions (latex condoms) are recommended. A person with hepatitis C should avoid sharing such items as razors, toothbrushes, and nail clippers with sexual partners and family members. No special precautions are recommended for babies born to mothers with hepatitis C, and breast feeding does not have to be restricted[23,24,31, 33-37].

HEPATITIS E VIRUS INECTION

Hepatitis E virus (HEV) is self limited virus , enterically_ transmitted acute viral hepatitis . In the winter of 1955-56, a large epidemic of acute viral hepatitis, affecting 29 000 people, followed an incident of sewage contamination of drinking water in New Delhi, India. Although it was originally considered to be an epidemic of hepatitis A, retrospective testing of stored sera from these patients suggested that a novel infectious agent was responsible for the epidemic. This disease, which was initially described from the Indian subcontinent, was first called enteric non-A, non-B hepatitis (ET-NANBH). Since the early 1990s, following the identification and sequencing of its aetiological agent, the disease became known as hepatitis E and its agent as hepatitis E virus (HEV) [20,38].

THE VIRUS:-

HEV is a spherical non-enveloped, RNA virus that is approximately 32-34 nm in diameter (Fig1). Structurally similar to virus of the Caliciviradae family. The viral genome has been cloned and sequenced from several geographically distinct HEV isolates and shows a high degree of sequence conservation, both of nucleotides and of amino acids[2,3]. The HEV genome is an +RNA of ~7.5 kb, spanning a coding region that includes three open reading frames (ORFs) [39-44].

1 The largest ORF consist of 1693 codons, it codes for nonstructural proteins that are responsible for the processing and replication of the virus.

2 The second ORF is composed of 660 codons, cods for structural proteins.

3 The third ORF consist of 123 codons, its function remains undetermined.

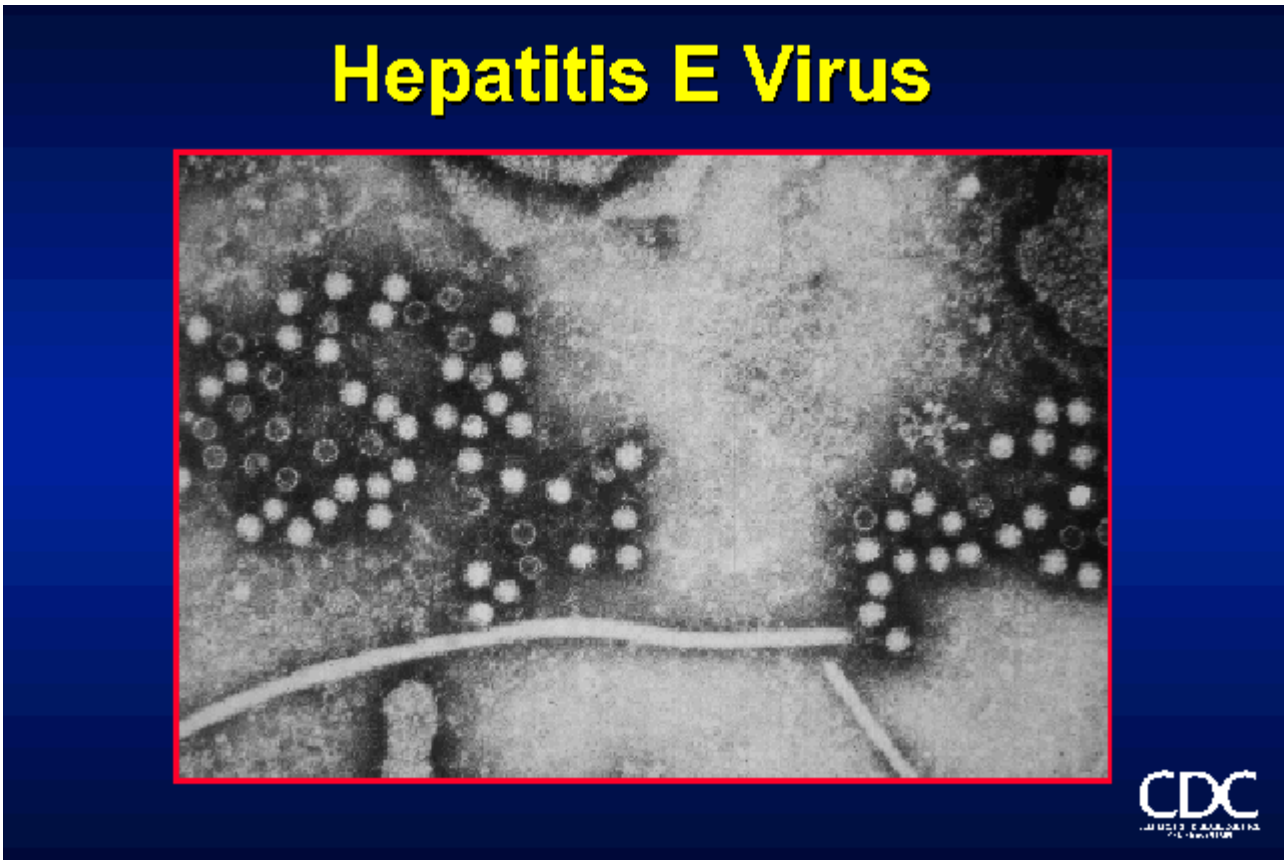

Figure A. Hepatitis E virus. An immunoelectron micrograph of hepatitis E virus (HEV) from the stool of a patient acutely infected with the Burmese isolate. The picture shows 27–34 nm particles aggregated with antibodies present in the serum of a patient infected with HEV. Obtained from the viral hepatitis slide set published by the US Centers of Disease Control and Prevention, Atlanta, GA, USA

Epidemiology of hepatitis E:-

HEV causes epidemics of viral hepatitis, often involving very large numbers of patients. Such epidemics have been reported from several countries on all continents, although most are in tropical and subtropical areas of the world (Ref. 8). Apart from the 1955-56 New Delhi epidemics, other notable epidemics have occurred: Kirgiz Republic, Soviet Union (1955-56, 10 000 cases); Kathmandu Valley, Nepal (1973-74, 10 000 cases); Mandalay, Myanmar (1976-77, 20 000 cases); Kashmir, India (1978-82, 52 000 cases); Xinjiang, China (1986-88, 120 000 cases); and Kanpur, India (1991, 79 000 cases). In addition to epidemic hepatitis, HEV causes rampant sporadic infections in endemic areas of more than 25% of sporadic non-ABC hepatitis cases are due to HEV infection. In India, for example, ~30% of all sporadic viral hepatitis is due to infection by HEV[45].

HEV is transmitted primarily through the faecal-oral route in contaminated drinking water [45]. The disease is found most frequently in geographical regions and situations, such as refugee camps, where faecal contamination of the drinking water supply is frequent. Although they have only minor contributions, other routes of transmission cannot be ruled out. For example, vertical transmission in uterus of HEV from infected mothers to their newborn has been documented [46]. The possibility of parenteral transmission has also been suggested, especially in endemic areas. However, person-to-person transfer is minimal because household contacts of HEV-infected patients do not appear to be at an increased risk[47].

As expected, the seroprevalence of anti-HEV antibodies in endemic areas is significantly higher than in areas where HEV infection is rare. Acute

hepatitis E has been reported in patients residing in developed countries such as Australia, France, Israel, The Netherlands, Spain, UK and USA. These are mainly associated with travel to endemic areas [45]; however, rare cases of acute hepatitis E have also been reported from these regions in the absence of travel to risk areas. HEV infection is also probably more prevalent in industrialized nations than previously appreciated; for example, fulminant HEV-associated hepatitis is found in Europe, where ~1.5% of healthy adults have anti-HEV antibodies [48]. In addition, in the USA, domesticated swine have been found to be infected with HEV, and sequence analysis has shown that swine-derived HEV is similar to a human-derived HEV from a USA isolate [49].

The age-specific prevalence of anti-HEV antibodies has also been studied in endemic areas and compared with antibodies to HAV. Whereas anti-HAV seroprevalence reaches >95% by 10 years of age in endemic areas, anti-HEV seroprevalence in an identical population slowly increases until the third decade of life. This pattern suggests a sporadic transmission of the virus that, the short periods of infectious viraemia (virus in the bloodstream), and the consequently limited accumulates over age; this is consistent with the predominantly sub clinical nature of infections pool of HEV infection in the community. Lower prevalence rates of anti-HEV versus anti-HAV antibodies in the same population also suggests that, following infection, antibodies to HEV might disappear from circulation faster than antibodies to HAV, and that children might not mount such a brisk anti-HEV antibody response compared with that mounted by adults.

However, these issues remain unresolved, owing mainly to the lack of sensitive and specific diagnostic systems that are suitable for use in endemic areas[50].

Time course of hepatitis E virus infection:

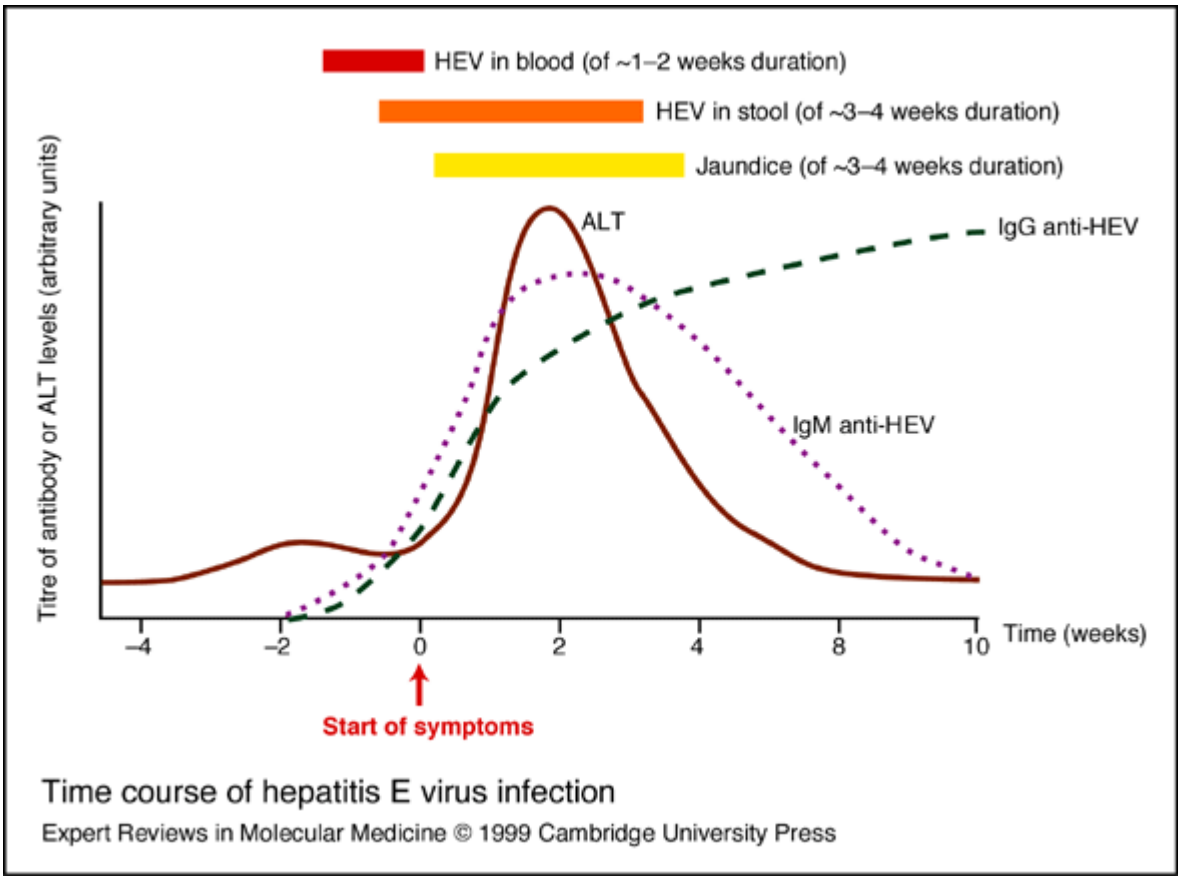

Figure B. Time course of hepatitis E virus infection. Biochemical markers (e.g. serum ALT levels) and symptomatic markers (e.g. jaundice) of viral hepatitis are correlated with detection of HEV RNA by RT-PCR in the bloodstream, or shedding of virus in stools, and the immune response is measured as anti-HEV IgM or IgG levels, detected by enzyme immunoassay on serum samples. Four to eight weeks after exposure to HEV, there is a rise in ALT and the appearance of jaundice. Immediately prior to the onset of clinical symptoms, HEV can be detected in the bloodstream for ~1–2 weeks and is shed in the stools for ~3–4 At the onset of clinical symptoms, HEV is lost from the

bloodstream, but continues to be shed in stools. Anti-HEV IgM and IgG titres continue to increase in the asymptomatic phase. The anti-HEV IgM titre peaks during the symptomatic phase and declines thereafter to baseline values within 3–6 months of symptomatic disease. The anti-HEV IgG titre remains detectable for 2–13 years as determined in various studies (published by the US Centers of Disease Control and Prevention, Atlanta, GA, USA)

Hepatitis Pathogenesis and clinical spectrum of E:-

Although the hepatitis viruses cause liver damage, none is directly cytopathic to hepatocytes (liver cells). Following acute liver injury, the clinical manifestations and outcome of viral hepatitis are actually determined by the host immune response. Because serological (antibody-based) assays for HEV have only recently become available, the pathogenesis of hepatitis E is not well understood. Following the entry of HEV into the host via the oral route, the primary site of replication is probably in the intestinal tract. It is still not clear how the virus reaches the liver, but it is presumably via the portal vein serving the liver. HEV replicates in the cytoplasm of hepatocytes and is released into the bile and bloodstream by mechanisms that are not understood[51].

The symptoms of hepatitis E are typical of acute viral hepatitis and the infection follows a natural history that is similar to that of hepatitis A. Jaundice is usually accompanied by malaise , nausea . vomiting, abdominal pain ,fever, and hepatomegaly. Other less common feature include diarrhea , artharalgia , pruritus and urticarial rash[51].

The incubation period (the time from infection to clinical symptoms) has been measured accurately only in a single case of transmission of HEV to a

human volunteer, and was found to be 32 days[52].

Infectious viral particles are present in the bile and faeces during the late incubation phase of hepatitis E and they persist for a week or two following the onset of clinical disease. The virus is also present transiently in the bloodstream in the late incubation phase of hepatitis E, but it disappears just before the onset of clinical symptoms[52] Anti-HEV antibodies of the IgA, IgG and IgM types appear during the course of disease. IgM antibodies are detectable in the acute phase and disappear in 3-6 months whereas, in various studies, IgG antibodies have been shown to persist for 2-13 years [45].

In ~10% of patients with HEV infection, protracted viraemia has been observed in the absence of anti-HEV antibodies (seroconversion). Seroconversion might be a critical marker for early clearance of the virus from the bloodstream, but this requires more extensive analysis. In most hepatitis E outbreaks, the highest rates of clinically evident disease have been reported in young to middle-age adults; the lower disease rates in younger age groups might be the result of anicteric (i.e. without the elevation of serum bilirubin that is used as a marker of clinical jaundice) and/or sub clinical HEV infection [53].

Hepatitis E in pregnancy :-

One distinctive clinical feature of hepatitis E, compared with other forms of viral hepatitis, is its increased incidence and severity in pregnant women[54] which results in up to 20% mortality. By contrast, none of the other recognized hepatitis viruses causes such severe hepatitis in pregnancy. Though the mechanism(s) is not known, a hypothesis has been put forward to explain the pathogenesis of fulminant hepatitis E in pregnancy[55].

This suggests that the liver sinusoidal cells, particularly the Kupffer cells, are damaged by HEV, which diminishes the ability of these cells to protect hepatocytes against endotoxins that originate from Gram-negative bacteria found in the intestinal tract. Hepatocytes can be injured directly by endotoxins or indirectly by eicosanoids, which are 20-carbon chain (C_{20}) polyunsaturated fatty acids that cause platelet aggregation, inflammation, and other effects. Release of prostaglandins (a type of eicosanoid) can lead to chemotactic attraction of inflammatory neutrophils. This can result in swelling of the tissue by water accumulation (oedema) and arrest of bile flow (cholestasis). The enhanced sensitivity of pregnant women to such an endotoxin-mediated effect is well recognised and might explain the strikingly high mortality of hepatitis E in pregnancy. However, the validity of this hypothesis and the precise cellular/molecular mechanisms underlying it have not been confirmed[55].

The kidneys of cynomolgus monkeys (*Macaca fascicularis*) infected intravenously with HEV were shown to develop acute tubular necrosis with focal haemorrhages, suggesting that HEV can replicate in monkey (and possibly also human) kidneys. By affecting this tissue, HEV might

precipitate pregnancy-associated eclampsia, leading to increased mortality in pregnant women. One feature observed in patients with eclampsia is disseminated intravascular coagulation affecting the liver and kidneys. In pregnant women, a high incidence of disseminated intravascular coagulation associated with hepatitis E is well recognised. However, in experimental HEV infection of pregnant monkeys, no increased mortality has been observed, casting doubt on whether this is a good model for this aspect of human hepatitis E[56].

Liver histology of patients with hepatitis E reveals portal triaditis, cholestasis, lobular inflammation and degeneration of the liver to varying degrees, which are all suggestive of acute viral hepatitis. However, nearly half of the patients have distinctive morphological changes designated as cholestatic viral hepatitis. The discrepancy between the time of appearance of viral replication in the liver with the histopathological and biochemical changes suggests that HEV might not be directly cytopathic and its pathogenesis might be immunologically mediated[57].

Other study shows existence of a Th2 bias in pregnant women with acute hepatitis E, but The role of this Th2 bias in the greater severity of hepatitis E among pregnant women needs further investigation[58].

It is not known whether HEV causes other sequelae or extrahepatic manifestations. None has been recognised apart from the increased incidence of miscarriage, which has been reported in some, but not all, studies on fulminant hepatitis E during pregnancy[56].

Diagnostic tests for HEV:-

Only one serological test to diagnose HEV infection is commercially available (Genelabs Technologies, Singapore). They do a comparison of a new immunochromatographic test to enzyme-linked immunosorbent assay for rapid detection of immunoglobulin m antibodies to hepatitis e virus in human. This study showed that this test was able to detect anti-HEV IgM antibodies in 96.7% of the patient samples tested (n = 151) while maintaining an excellent rapid test gave a good specificity of 90.9% when tested with rheumatoid factor (RF)-positive sera (RF value of < or =850 IU/ml; n = 11) although a higher concentration of RF in samples might cause cross-reactivity. The new test has a good agreement of 97.2% with a kappa value of 0.943 when compared with a reference enzyme-linked immunosorbent assay. The positive predictive value and the negative predictive value for the rapid test thus reached 98.0 and 97.6%, respectively. This is the first rapid, point-of-care test for hepatitis E and will be especially useful for the diagnosis of acute hepatitis E virus infection in field and emergency settings and in resource-poor countries[58]. However, several diagnostic tests are available in research laboratories, including:

(1) EIAs and western blot assays to detect anti-HEV IgM and IgG in serum[59].

(2) PCR tests to detect HEV RNA in sera and stools

(3) immunofluorescent antibody-blocking assays to detect antibody to HEV antigen in the serum and in liver biopsies. However, the sensitivity and

specificity of these tests have not been determined independently using a good panel of anti-HEV positive and negative sera[60].

Prevention:-

No products are currently available to prevent hepatitis E. Passive immunization using immunoglobulins prepared from plasma collected from HEV-infected persons in non-HEV-endemic areas is not effective in preventing clinical disease during hepatitis E outbreaks, and the efficacy of immunoglobulins prepared from plasma collected in HEV-endemic areas is also unclear. In studies with prototype anti-HEV vaccines in animals, vaccine-induced antibody could attenuate HEV infection but did not prevent virus excretion in the stools of infected immunised animals[61].

For viral pathogens that are difficult to culture and therefore not easily amenable to the development of live attenuated strains, a promising approach is to develop subunit vaccines. A subunit vaccine consists of a part of the virus, typically a protein capable of generating a protective immune response in immunised persons. Recombinant DNA technology is now routinely used to generate large amounts of purified viral proteins to be used as subunit vaccines. For HEV, the most promising subunit vaccine candidate so far appears to be the *ORF2*-encoded protein when expressed in insect cells using recombinant baculoviruses [60].. Recently, the products of N-terminally truncated *ORF2* were shown to form empty virus-like particles (VLPs) [61]. These VLPs retain native virus epitopes and appear to be a good vaccine candidate[62].

Alternative strategies for developing anti-HEV vaccines are also being tried in research laboratories. A naked DNA immunisation approach in which *ORF2* was injected as an expression plasmid directly into muscle resulted in moderate anti-pORF2 titres in mice. Within days of *ORF2* plasmid DNA injection, the subsequent injection of genes encoding either of the immunomodulatory cytokines interleukin 2 (IL-2) or granulocyte–monocyte colony-stimulating factor (GM-CSF) resulted in higher anti-pORF2 titres in mice (R. Tuteja and S. Jameel, unpublished). Naked DNA immunization with ORF2 expression vectors has also been tried in macaques, with promising results (S. Kamili and K. Krawczynski, unpublished). Other strategies such as the expression of *ORF2* in bacille Calmette–Guérin (BCG) recombinant mycobacteria or in transgenic plant expression systems are also being tried. If successful, these might lead to oral or edible vaccines to prevent enteric infection by HEV[60].

Therapeutic approaches to hepatitis E infection:-

No therapeutic compounds against hepatitis E are currently available; the only treatments are supportive in nature. Possible drug targets include the HEV Pr and RdRp enzymes, on which even the basic biochemical information is not yet available. Such information will be critical for developing assays to screen libraries of natural or synthetic molecules to search for compounds with anti-HEV activity. The HEV RNA 5' and 3' ends appear to interact with viral and cellular proteins and are crucial for its replication; strategies designed to block these interactions, for example with antisense oligonucleotides, ribozymes or small molecules, might be of therapeutic value. No information is available as to whether any of these approaches are currently being employed[61].

STUDY OBJECTIVES

Main objective:

- To determine the prevalence of hepatitis E in acute hepatitis in Sudanese patient presenting to Khartoum Teaching Hospital.

Specific objective:

- To identify the clinical presentation and complication of hepatitis E.

MATERIALS AND METHODS

Study design:

This is a hospital based cross-sectional study, carried out in Khartoum teaching hospital in the period between October 2004 to April 2005.

Study population were male and females aged >15 years with acute hepatitis, proved by investigations.

Inclusion criteria:

- Patient with acute hepatitis.
- Patients age > 15 years.

Exclusion criteria:

- Patients with chronic liver disease.
- Patients with obstructive jaundice.
- Patients with haemolytic jaundice.

Data collection:

Coded, standard questionnaires we used for interview and was filled by researcher and other medical personnel (House officer, medical officer, medical registrar). History was taken from the patients or their relatives.

A blood sample was drown for analysis, all patient who agree to be included in the study underwent the following tests.

1- Hb%.
2- Reticulocytes count.
3- TWBC.
4- S. billirubin.
5- S. ALP.
6- S. ALT.
7- S. AST.
8- U/S abdomen.

When patients proved to have acute hepatitis, further investigation then were carried out:-

1- HEV IgM.
2- HEV IgG.
3- HBAg.
4- HCV Ab.
5- HAV IgM.

Technical data:

Genlabs diagnostic (GLD) HEV IgM Elisa which is an enzyme linked immunosurbant assay intended for detection of IgM antibodies to hepatitis E virus, this kits were used in the study.

Serum sample was taken and stored below – 20ºC .10 microgram then taken and diluted 1:21 with sample buffer; then incubated for 30 minute at 37ºC. This test has sensitivity of 93% and specifity of 97.5%.

Data entry and analysis:

Were done using SPSS and conducted by four independent persons results will be express in the form of figure, table and graft.

RESULTS

This is a cross-sectional study conducted over 6 months in Khartoum Teaching Hospital, 50 patients with acute hepatitis were studied, 11 of them were found to have hepatitis E IgM antibodies (22%), 9 of them have hepatitis E virus IgG antibodies. 11 patients have hepatitis B sAg (22%),4 patients have hepatitis c virus antibodies (8%) and 2 patents have hepatitis A IgM antibodies(4%). (Figure 1).

Males are found to be more affected than females (63%). (Figure 2)

In this study hepatitis E is found to affect all age groups but more common between 26 -45 year old (54%).(Table 1).

Most patients in the study came from central Sudan (63%), no patient from the north or south (Figure 3).

Educational level of the studied patients revealed that 54% of them have primary school level, 27% have secondary school level and 8% have university degree (Figure 4).

Most of studied patients were of low socioeconomic status (54.5%) (Figure 5).

In our study all patients were jaundiced and had nausea & vomiting (100%), (90.9%) had fever (pv= 0.148), (81%) had abdominal pain (pv= 0.986 not statistically significant).(Figure 6)

4 patients in the study have past history of jaundice (36.4% pv= o.oo6), no patients has history of blood transfusion (Table 2)

Physical examination of the studied patients revealed that 5 patients have enlarged liver (45.5%), 1 patient have enlarged spleen (9.1%) and 2 patients have enlarge liver & spleen (18.2%) and 3 patients have normal liver & spleen (27.3%) pv=0.07.(Table 3)

Two patients presented with fulminant hepatic failure and they died (18%) pv=0.126not statistically significant (Figure 7).

All patents have high billurbin (Table 4), have a high transaminase specially those presented with fulminant hepatic failure (Table 5,6,7).

Table (1):

The age distribution of 11 patients with H.E.V presenting to K.T.H in a period between October 2004 to April 2005

Age group	Frequency	Percentage
15 – 25	1	9.1%
26 – 35	1	9.1%
36 – 45	6	54.5%
> 45	3	27.3%

Table (2):

Past history of jaundice and blood transfusion in 11 patients with hepatitis E in presenting to K.T.H in a period between October 2004 to April 2005

	Frequency	**Percentage**
Blood transfusion	0	0%
Jaundice	4	36.4%

Table (3):

Distribution of enlarged liver and spleen in 11 patients with hepatitis E in presenting to K.T.H in a period between October 2004 to April 2005

	Frequency	Percentage
Enlarged live	5	45.5%
Enlarged spleen	1	9.1%
Enlarged liver & spleen	2	18.2%
Normal liver & spleen	3	27.3%

Table (4):

The levels of bilirubin in 11 patients with hepatitis E in presenting to K.T.H in a period between October 2004 to April 2005

Bilirubin mg/dl	Frequency	Percentage
5.20	1	9.1%
5.24	1	9.1%
7.80	1	9.1%
9.70	1	9.1%
10.00	1	9.1%
11.00	1	9.1%
11.50	1	9.1%
12.00	1	9.1%
15.00	1	9.1%
15.50	1	9.1%
27.80	1	9.1%

Table (5):

The levels of AST in 11 patients with hepatitis E in presenting to K.T.H in a period between October 2004 to April 2005

AST U/L	Frequency	Percentage
60.00	1	9.1%
76.00	1	9.1%
104.00	1	9.1%
150.00	1	9.1%
320.00	1	9.1%
330.00	2	18.2%
494.00	1	9.1%
570.00	1	9.1%
600.00	1	9.1%
655.00	1	9.1%

Table (6):

The levels of ALT in 11 patients with hepatitis E in presenting to K.T.H in a period between October 2004 to April 2005

ALT U/L	Frequency	Percentage
55.00	1	9.1%
70.00	1	9.1%
88.00	1	9.1%
110.00	1	9.1%
228.00	1	9.1%
277.00	1	9.1%
532.00	1	9.1%
597.00	1	9.1%
660.00	1	9.1%
750.00	1	9.1%
787.00	1	9.1%

Table (7):

The relationship between acute fulminant hepatic failure and transaminase level and bilirubin in 11 patients with hepatitis E in presenting to K.T.H in a period between October 2004 to April 2005

	AST U/L	**ALT U/L**	**Bilirubin mg/dl**
Patient 1	600	750	15.5
Patient 2	655	787	27.8

Figure (1): Prevalence of hepatitis E in 50 patients with acute hepatitis presenting of K.T.H between October 2004 - April 2005

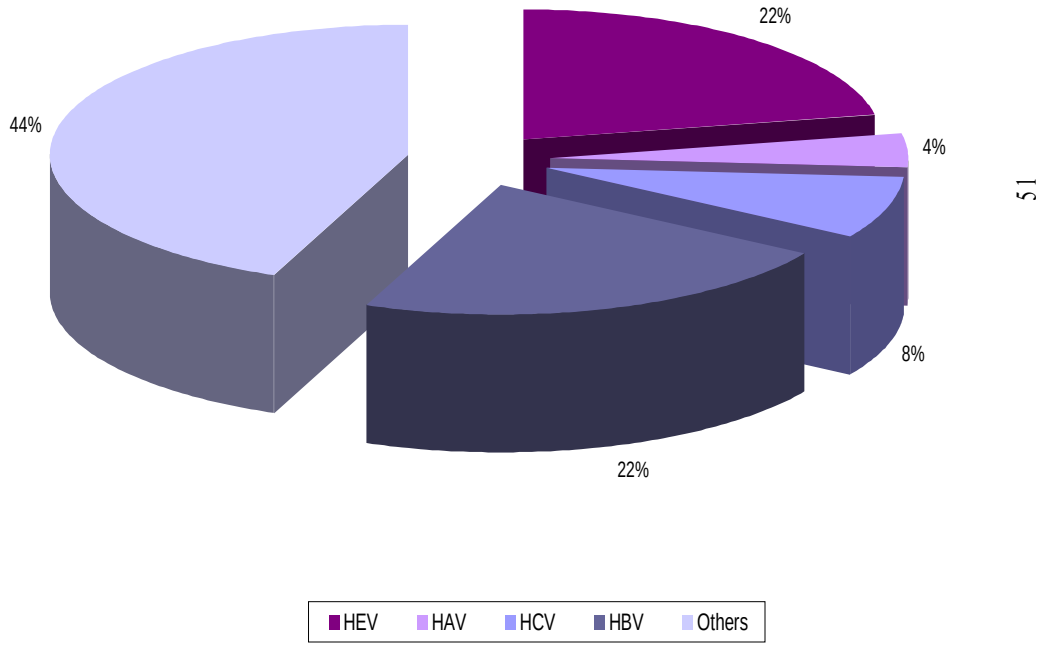

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Figure (2): Distribution of sex in 11 patients with hepatitis E presenting to K.T.H between October 2004 - April 2005

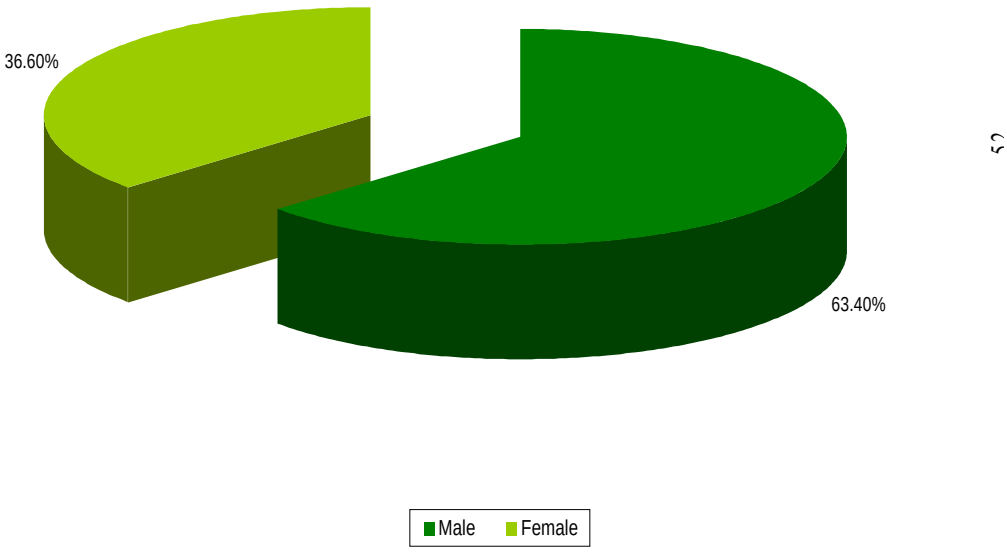
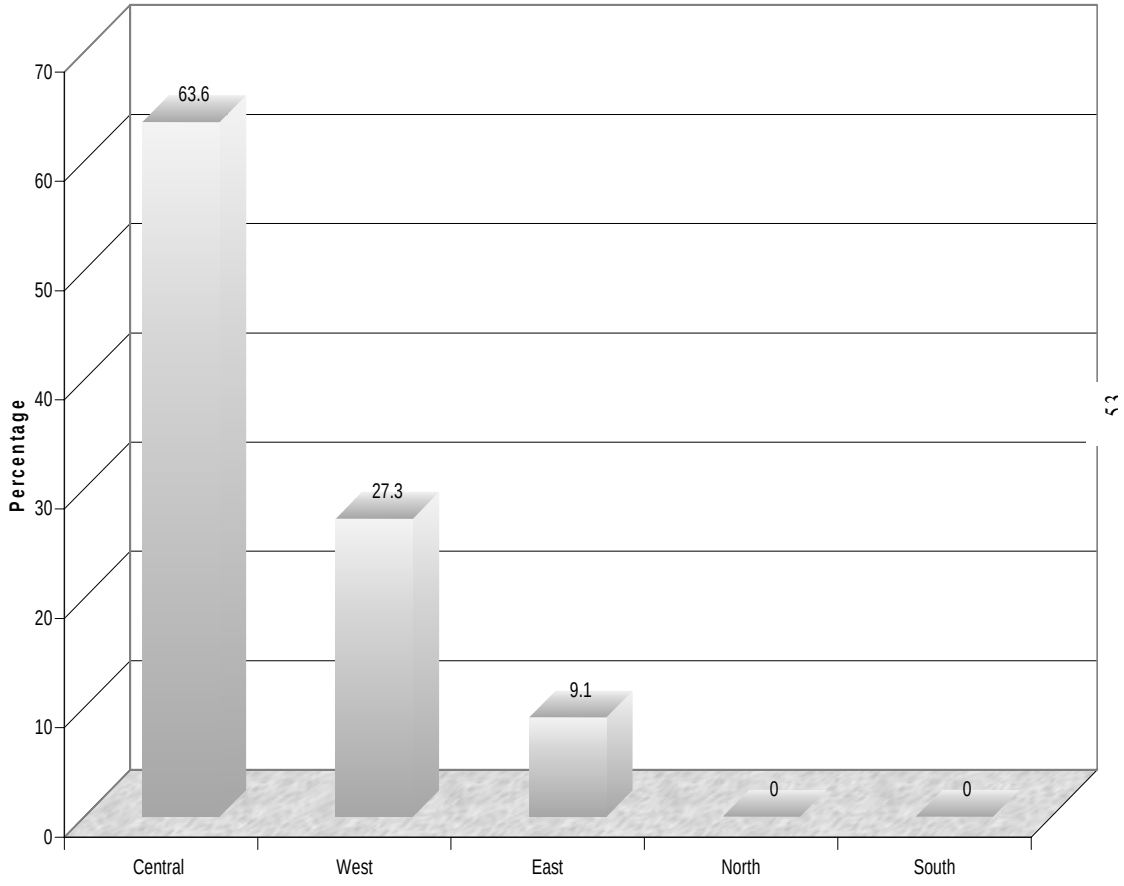


Figure (3): Resident distribution of 11 patients with hepatitis E presenting K.T.H between October 2004 - April



Fgure (4): Distribution of educational level of 11 patients with hepatitis E presenting K.T.H between October 2004 - April 2005

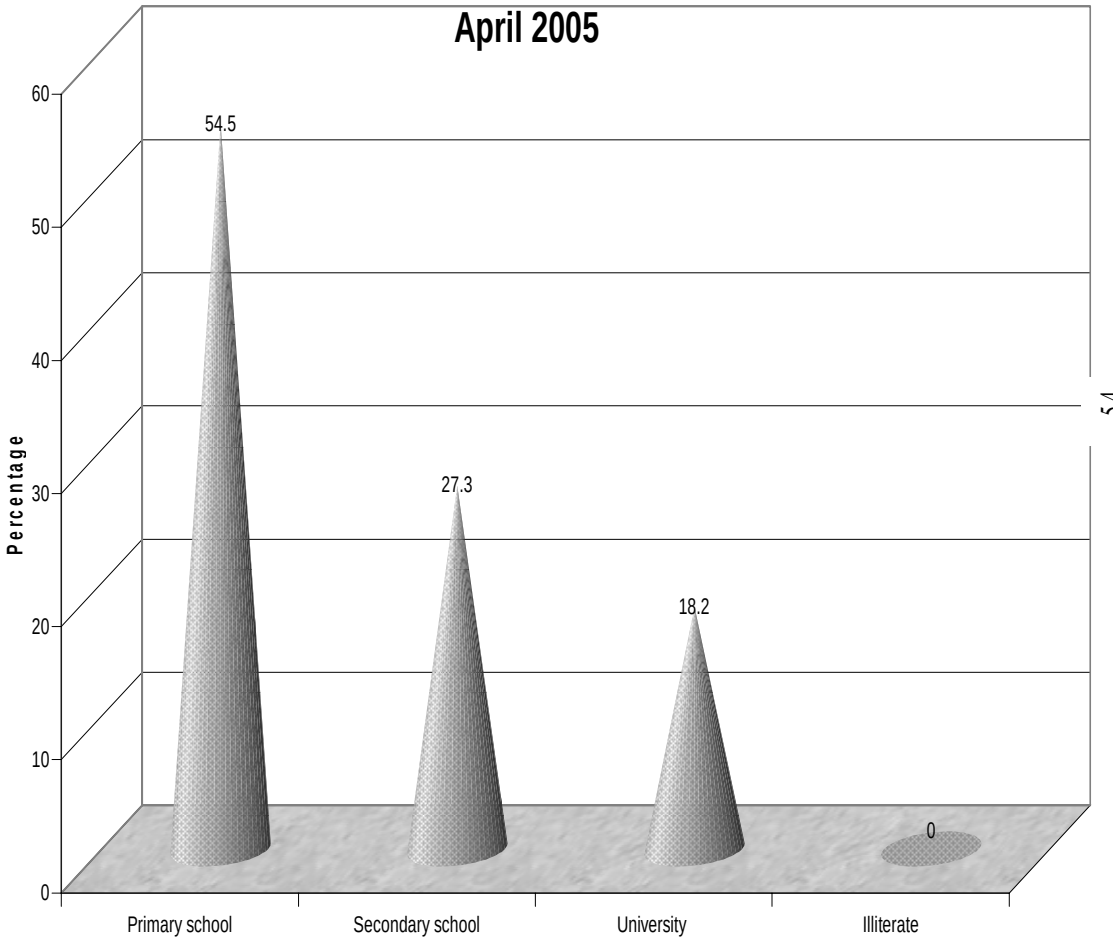


Figure (5): Distribution of socioeconomic status of 11 patients with hepatitis E presenting K.T.H between October 2004 - April 2005

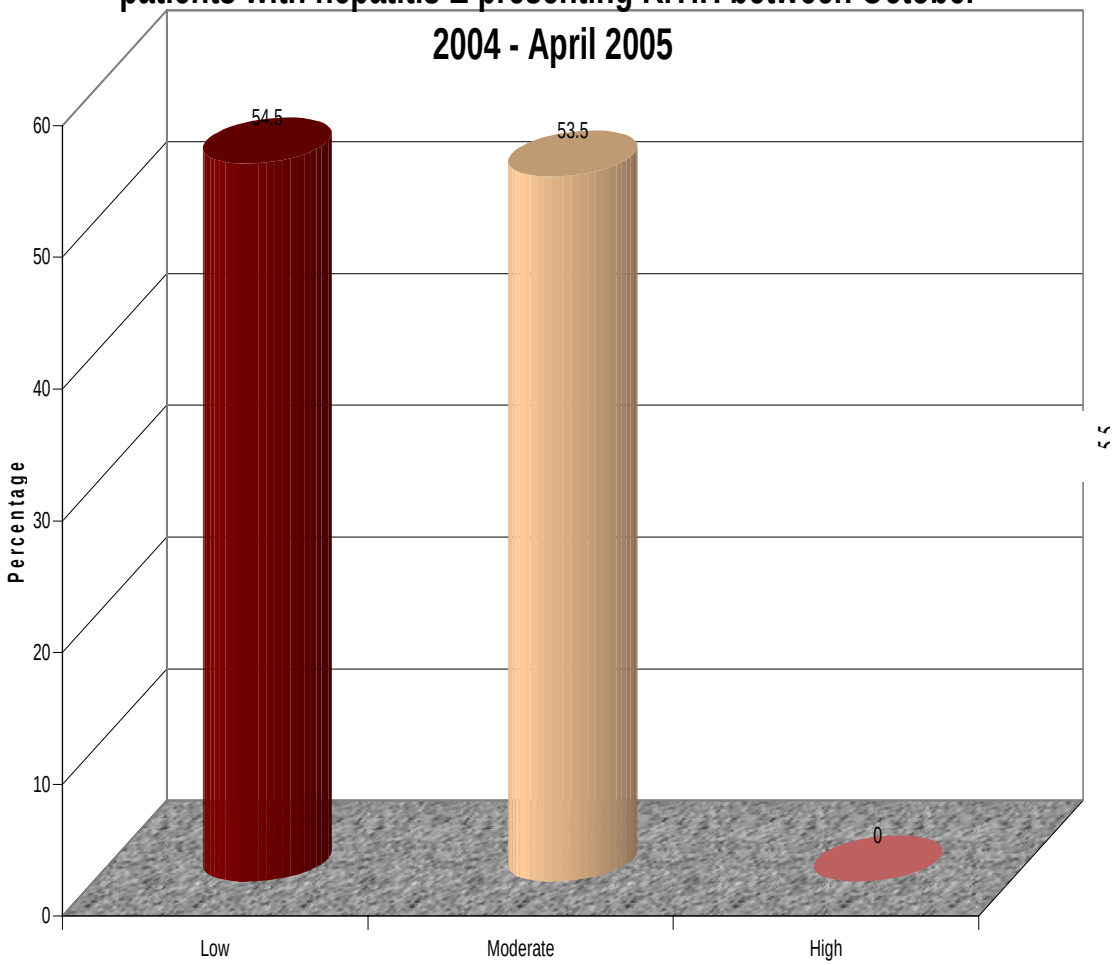


Figure (6): Distribution of presenting symptoms of 11 patients with hepatitis E presenting K.T.H between October 2004 - April 2005

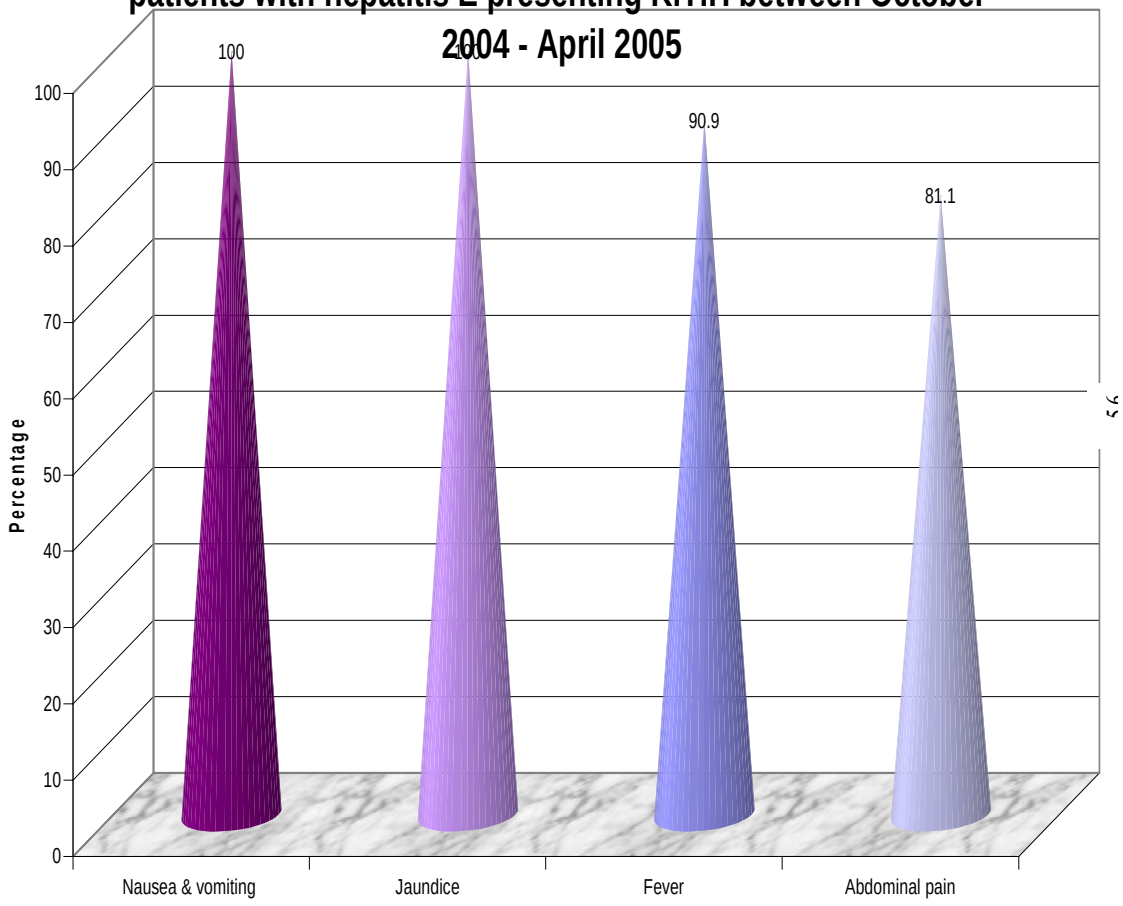
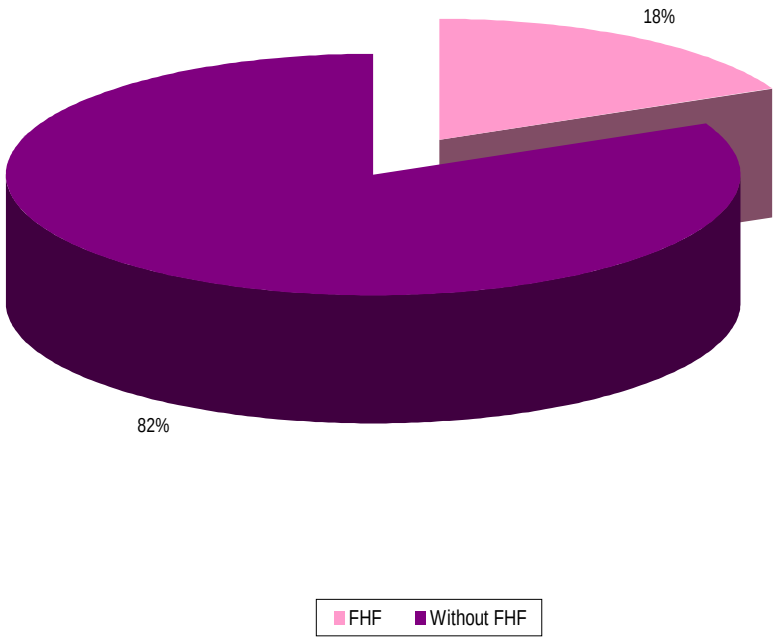


Figure (7): Distribution of fulminant hepatic failure of 11 patients with hepatitis E presenting K.T.H between October 2004 - April 2005



DISCUSSION

Hepatitis E infection is self-limited disease. The virus is entrically transmitted. It is a major cause of viral hepatitis in many of the developing countries, where it causes sporadic and epidemic infection.

This study show the prevalence of hepatitis E in 50 patients with acute hepatitis is 22%, it is different from study done in Khartoum during the 1988 shows when there was epidemic of acute hepatitis, 55 patients were screened for hepatitis E virus IgM and hepatitis E virus IgG, 58% found to have IgM positive and 29 patients found to have IgG [(63)]. Other study done in 1991 – 1992 in acute sporadic hepatitis E in Sudanese children was found that the prevalence was 59% [(64)].

Male are found to be more affected than females (1.8 : 1), the commonest age group between 26-45, this result is similar to that obtained in Kathmandu, Vally, Nepal during 1981 – 1982, which revealed that 75% of patient were male and the age affect between 15 – 36 (ref 62), and also similar to the result of the study done during 1988 floods in Khartoum – Sudan which revealed male patient is 85% in the average age between 3-48 [(63)].

Most of the affected patients were of low socioeconomic status and not educated, this is in keeping with literature where the diseases is found in refuge camps, with bad hygiene and over crowded [(43)].

The study show there is no difference in clinical presentation of hepatitis E and other hepatitis [65].

There is a high incidence of fulminant hepatic failure in hepatitis E which lead to all case fertility (18%). This is different from reported study from East Africa and Asia which revealed mortality rate of 0.5 – 3% and high mortality in pregnant lady 20% [66]. This may be due to small number of patients in the study.

Hepatitis E is commoner than hepatitis A in the studied group. There is no co-infection with hepatitis B or hepatitis C. This is similar to the previous study [63].

The serological provide of hepatitis E in these found in the study suggest that the IgG antibody response appears early in this infection, this is similar to previous study [63].

CONCLUSION

- The study show high prevalence of hepatitis E infection among patient presented with acute hepatitis.
- There is high incidence of fulminant hepatic failure and death in patient with hepatitis E in studied group.
- Hepatitis E is more common in males.
- Hepatitis E is more common in age group 26 – 45.

RECOMMENDATIONS

- Further larger study is needed to know more about hepatitis E in Sudan.
- Increase doctor awareness of the existence of hepatitis E in Sudan and it's possible sequences.
- Improve sanitation, personal hygiene, avoiding drinking water of unknown purity to prevent hepatitis E infection.
- HEV IgM Elisa test should be made available in local laboratories.

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Questionnaire

On prevalence of HEV in acute hepatitis in Sudanese patients in period between October 2004 – April 2005

1- Demographic data:

1.1. Name……

1.2. Sex: Male ☐ Female ☐

1.3. Age: 15-25yrs ☐ 25-35yrs ☐ 35-45yrs ☐ >45yrs ☐

1.4. Residence: East ☐ West ☐ Central ☐ North ☐ South ☐

1.5. Occupation: Laborer ☐ Professional ☐ Government employee ☐
Military ☐ Business ☐ Others ☐

1.6. Educational level: Illiterate ☐ Primary ☐ Secondary ☐
University ☐ Higher level ☐

1.7. Socioeconomic level: Low ☐ Moderate ☐ High ☐

2- History:

present symptom:

2.1. Yellowish discoloration of the sclera: Yes ☐ No ☐ Duration ☐

2.2. Fever: Yes ☐ No ☐ Duration ☐

2.3. Nausea & vomiting: Yes ☐ No ☐ Duration ☐

2.4. Abdominal pain: Yes ☐ No ☐ Duration ☐

Past history: ☐ Blood transfusion ☐ Jaundice ☐

3- Physical examination:

3.1. Pale : Yes ☐ No ☐

3.2. Jaundice: Yes ☐ No ☐

3.3. Abdomen

Liver Normal ☐ Abnormal ☐ Specify…….

Spleen Normal ☐ Abnormal ☐ Specify…….

3.4. Other systems Normal ☐ Abnormal ☐

Specify……

……

4- Investigation:

Haematology:

Hb%……..

Retics…….

TWBCs……..

Liver function test:

Billirubin……

ALP……U/L

AST……U/L

ALT……U/L

Abdominal U/S:

……

……

HEV IgM ……

HCV Ab……

HBV sAg……..

HAV IgM……..

Diagnosis:

HEV Yes ☐ No ☐