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A review regarding virology, etiology, prevalence and associated risk factors of Hepatitis A.

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Abstract

Hepatitis A is an infectious disorder of the liver prompted by Hepatovirus A virus (HAV). It is a kind of viral hepatitis. It has naked nucleocapsid virus with a single stranded, positive polarity RNA. It is devoid of virion polymerase and has a single serotype. Transmission is via fecal–oral route. In contrast to Hepatitis B virus and Hepatitis C virus, blood borne transmission of HAV is infrequent because viremia is short-term and of low titer. Mostly instances, have few or no signs, specifically in younger ones. The virus replicates in the gastrointestinal tract and then spreads to the liver during a short-term viremic period. HAV is not cytopathic for the hepatocyte. Hepatocellular injury is triggered by immune attack by the cytotoxic T cells. The time among the infection and signs, in patients that progress them, is among two and six weeks. When the signs occur, they commonly last 8 weeks and might encompass nausea, vomiting, diarrhea, jaundice, pain in abdomen and fever. Around 10 to 15 percent of patients undergo a recurrence of signs at some stage in the six months after the preliminary infection. Acute liver failure may also seldom occur, with this being extra regular in elderly. No antiviral medication is available. The most suitable test to diagnose acute infection is IgM antibody. Isolation of the virus from clinical samples is not done. Vaccine consists of killed virus. Administration of immune globulin in the course of the incubation can alleviate the disease.

Keywords: Hepatitis A; Risk factors; Prevalence; Pakistan; Vaccination; Hygiene

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1. INTRODUCTION

Hepatitis A is an important viral disease of humans. It is caused by Hepatitis A which is member of hepatovirus genus and picornavirideae family. Hepatitis A virus infection is considered to be the major health issue all over the world, resulting in an acute inflammation of liver in the worst case[1]. HAV is classified in *Hepatovirus* genus and *Picornaviridae* family. It is also recognized as enterovirus 72. It has one serotype, and there is no antigenic association to Hepatitis B or other hepatitis viruses. Its structure can be

defined as small, non-enveloped *Hepatovirus*. It is linear positive strand RNA virus. Its genotype is studied on the basis of analysis of 168 nucleotide segment of VP1-2A protein. Hepatitis A virus is divided into six genotypes I to VI. Genotype 1, 2 and 3 are divided into subtypes A and B. Studies has shown that genotype I is the most prevalent in worldwide and subtype IA is more reported than IB in central Asia[2]. Symptoms include jaundice, abdominal pain, fever, malaise and anorexia. Symptoms usually disappear within 1-2 months after onset. Virus infection does not reach to chronic stage and its acute infection leads to lifelong immunity. Household and sexual contact are risk factors for infection among adults and other factor for infection may include homosexuality between men who have intercourse with the same gender, commonly using drugs and travelling to various countries where HAV may be endemic[3].

2. GENOME INFORMATION

HAV is considered to be similar to the genome of poliovirus and other viruses of picornaviridae family on the basis of molecular study of RNA genome of HAV. New taxonomic classification of HAV includes only human HAV and other closely related mammalian viruses of picornaviral genus. It is positive sense single stranded RNA virus of 7.5 kb length in which untranslated RNA of a length 50 bases. A giant polyprotein is encoded by open reading frame (ORF) OF RNA. Highly structural internal ribosome entry site (IRES) present within the 50UTR which controls the initiation of translation of ORF. Within the ORF, there is a complex internal stem loop named as CRE that is responsible 2 cis-acting RNA replication element. The genome ends downstream of the ORF in a short 30UTR fragment ending in a 30 poly A tail. In comparison of other positive strand RNA viruses, synthetic genome length RNA is considered to be infectious and produces assembly of viruses when transformation is done in permissive cell culture[4].

3. ETIOLOGY

Viral hepatitis is an extreme worldwide public health issue in the world. Currently six different types of hepatitis viruses have been diagnosed and referred to as hepatitis A, B, C, D, E and G. The main supply of infection for HAV and hepatitis E virus (HEV) is the faces with the most prevalent path of transmission. Hepatitis B virus, hepatitis C virus and hepatitis D, are blood borne viruses and are spread mainly by skin (percutaneous) or mucosal breakdown. Hepatitis B, C and D cause highly severe infection while all other hepatitis infections are not severe[5]. Trend of HAV disease arise in three awesome ways based on disease endemicity. In growing nations with the terrible sanitary facilities, excessive contamination quotes arise among youngsters who develop immunity without symptoms, and outbreaks are rare. Countries suffering intermediate tiers of disease experience accelerated number of vulnerable adults and occasional big outbreaks. Countries with sufficient sanitation system have low charges of contamination and rare outbreaks unless the disease is not always added into the population from an outside supply[6]. The history and physical examination findings are not enough to distinguish in patients with viral hepatitis but may indicate various risk factors such as for hepatitis A (e.g travel to an endemic area, intake of contaminated food or shellfish), hepatitis B (e.g use of drugs intravenously, homosexuality, occupational exposure), or hepatitis C (e.g multiple transfusion of blood or intravenous drug abuse). Clinically it is very difficult to differentiate between HepA and HepB from one another. Hepatitis A, however has a sudden onset of symptoms whereas hepatitis B has deceptive start. Hepatitis C has insidious onset but in most cases it is asymptomatic and has a subclinical lengthy course[7]. The effect on societies and international locations is pretty linked to the average age at contamination. In high endemicity countries, when asymptomatic infection is possible, almost all youngsters emerge as inflamed eye at an early age. As the frequency declines, the infections, the infections average age increases slowly. The incidence rate could be very low in low endemicity countries and few individuals end up inflamed in childhood, so most kids and plenty of adults remain at risk of infection. Because the hazard of developing symptomatic HAV contamination will

increase with age, as a rustic or subpopulation studies an epidemiological transition to a disease endemicity, people who are inflamed are at an increased threat of symptomatic HAV contamination, inclusive of acute liver failure and death[8].

Conventional techniques were used in separation of IgM and IgG by using a method of sucrose gradient centrifugation and then further confirmed by another method testing for anti-HAV has been used previously but the process is quite time consuming[9]. Various other molecular techniques used in diagnosis of hepatitis A virus as to maintain the stability of HAV RNA. Reverse transcriptase PCR is used with human plasma. It is studied that sensitivity and specificity of serological assays were 100 % irrespective of temperature and storage duration[10]. Polymerase chain reaction (PCR) is used in identification in genome of virus. PCR is rapid method and expensive method used in serology as this can detect minute quantity of antigen present in the sample[11]. Investigation of outbreaks done for epidemiological and serological studies, but only molecular investigations can join seemingly random or obvious cases[12].

4. RISK FACTORS

Various factors such as environmental sanitation, prevailing socioeconomic and hygiene conditions etc are involved in prevalence of viral infection. The rate of Hepatitis A virus infection is higher in developing countries due to poor conditions of sanitation. By improving sanitation conditions in recent decades, the rate of HAV endemicity in several of these countries has lowered from high to intermediary level[13]. Hospital acquired infections of Hepatitis are not common but there are some factors that can be cause outbreaks of nosocomial infections such as blood transfusion between healthy and symptomatic donor. Sometimes cases have been recorded in which there is contact of healthy subject with an older child or adult that suffering from vomiting and diarrhea or involuntary urination. Cases of HAV infection have been reported in new born babies in neonatal ICU wards. Extensive studies failed to find main sources of transmission of virus in neonatal ICU wards. In the study of Rosenblum and his colleagues there is mention involvement of neonatal case of HAV infection[14]. The prevalence of hepatitis A is related to socioeconomic status, sanitation and lack of get right of entry to secure drinking water. High earning countries with top sanitation and hygienic conditions are low endemicity regions (infection rates are poor, i.e 50% via age 30 years). Because of inadequate sanitary situations and get right of entry to clean water, majority of population in growing countries is contaminated in early childhood (i.e seroprevalence in children up to about 90 percent), classifying the areas as enormously endemic[15]. Transmission of hepatitis A is related to oral, anal intercourse and an increased number of different sexual partners[16]. Potential risk factors studied are: shellfish consumption, drinking spring water, contact with an infected case, intravenous drugs use or family contact with child in day care unit[17]. Most cases of hepatitis A occur during community wide outbreaks, during which the highest rates of infection reported among children, adolescents, and young adults[18].

5. PREVALENCE

Another study has revealed that Hepatitis A virus is more prevalent in rural areas than in urban areas. It is studied that women population are at high risk for adopting blood borne infections because they usually suffer from severe anemia or postpartum hemorrhage, they may experience blood transfusion which might be not done according to international rules[19]. Hepatitis A is commonly named as traveler's infection. Vaccination status should be checked of migrating people[20]. Following influenza virus, hepatitis A virus has been most common inside the beyond few decades. The basic difference between two viruses is of age. Since Hep A virus specially affects kids in industrialized countries compensate for an asymptomatic or oligo symptomatic path. The infection specially exists in people who are not immune journeying to growing countries[21]. Seroprevalence of hepatitis A was low among the street youth, except as expected, among youth born in virus endemic countries. Gay community or the use of injection drugs played an significant

role in prevalence of virus[22]. Geographic distribution of HAV infection is shown in Figure 1.[23]

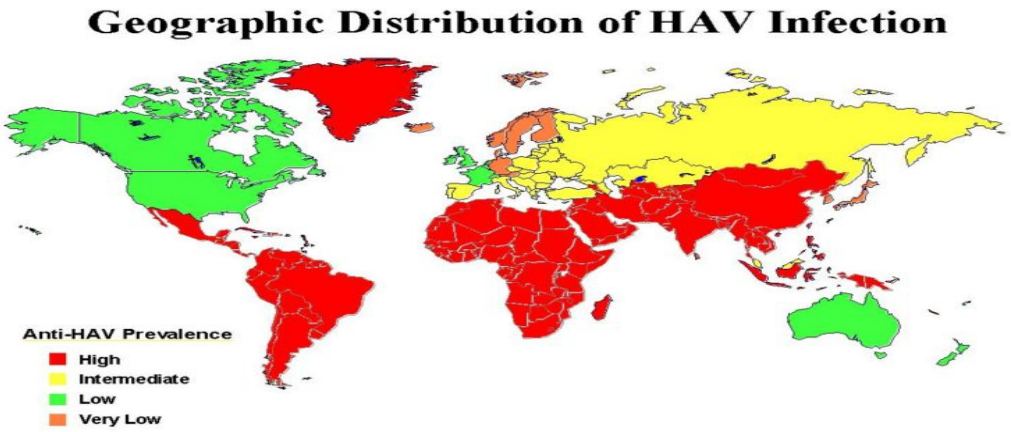

Fig. 1. Geographic distribution of HAV Infection

6. TRANSMISSION

Fecal oral route is the main route of the transmission. Infection transfers via individual to individual or intake of contaminated food and water. The other source of spread is bivalve mollusks that filter large volume of water from their body when they receive human sewage and thus may increase amount of contaminants from polluted water and store in their edible tissue. Drinking water should be properly treated to make virus free but unfortunately current water treatment strategies are unable to deliver virus free effluents[24]. Hospital acquired infections of Hepatitis are not common but there are some factors that can cause outbreaks of nosocomial infections such as blood transfusion between healthy and symptomatic donor. Sometimes cases have been recorded in which there is contact of healthy subject with an older child or adult that suffering from vomiting and diarrhea or involuntary urination[25]. New born babies show cases of infection in ICU. Vast studies are not able to find main sources of transmission of virus in neonatal ICU wards. In the study of Rosenblum and his colleagues there is mention of neonatal case of HAV infection[26]. HAV transmission is usually individual to individual via the fecal oral route and happens among high risk organizations and communities in all likelihood to create extreme disease including vacationers to tropical countries, MSM, people using illicit drugs and individuals with continual liver disease. Foodborne, waterborne, and transfusion of blood- and transplantation of organs related outbreaks are uncommon however perceive to occur. There is also excessive frequency of HAV contamination among individuals who use illicit drugs. There is no proof that injection of medicines leads drastically to the high spread of HAV contamination in this population, however, and its miles theorized that transfer is not always blood borne however takes place by using direct man or women to person contact related to crowding and bad hygiene[27]. HAV can enter into our nourishment once they were collected or cooked by their consequent contact with sullied hands and natural surfaces. Because this is vital issue in know-how the origin of numerous food borne episodes of hepatitis A, as well as for hazard analysis and development of environmental manage measures, the creators have tried to cope this angle by quantitative exploratory approaches. HAV has contaminated each floor, and the inoculum permitted to dry for shifting lengths beneath encompassing situations[28]. Institutional flare ups of HAV have been suggested and in day care facilities, child wards, eating institutions in well known the infection may additionally may give rise to secondary instances in reputed networks. Recent researches have shown that HAV can survive on stay on

nonporous lifeless surfaces for many days. It has been reported that efficacy of many disinfectants of HAV is missing. Many classes of chemicals used for both institutional and domestic aims do not kill HAV, so cannot be taken as control measures[29]. In non-epidemic durations, individual to individual transmission of hepatitis A has always accounted for the general public instances. Common sources (water borne or water borne) outbreaks of HAV has typically impact on specific communities[30].

7. PATHOGENESIS

Pathogenesis of HAV includes gastrointestinal tract and liver. Virus first goes to intestine then moves towards liver where replication occurs, from where virus secreted in bile. High concentrations are fond in stool specimens. Primates are natural host of HAV. Incubation period (i.e period from exposure to start of symptoms) of HAV is 28 days. Severity of infection increases during the 2nd week period that leads to onset of jaundice. If jaundice does not occur in peak infectivity then may be level of serum alanine aminotransferase (ALT) increases. Before the increase in concentration of ALT, viremia (virus in blood) can be observed and virus remains in blood and can be detected even if ALT level has dropped to normal value and symptoms have resolved[31] (Acheson and Fiore 2004). Previous researches confirmed that HAV-related RNA and antigen are primarily present in liver cells and the disease pattern of these abnormalities continue to be unknown to lesser extent in kupffer cells[32]. Hepatitis cases were categorized by several aspects as date of onset of infection, its outbreak and transmission in community[33]. Clinical features of Hepatitis viruses are shown in Table 1 [34].

Table 1. Clinical features of Hepatitis viruses[33]

Virus	Transmission mode	Carriers (Chronic)	Diagnosis	Vaccine available	Citation
HAV	feco oral	No	IgM, IgG	Yes	33
HBV	sexual, blood, during birth	Yes	HBsAg, HBsAb, IgM HBc Ab	Yes	
HCV	sexual*, blood	Yes	HCV Ab	No	
HDV	sexual*, blood	Yes	Antibodies to delta Antigen	No	
HEV	feco oral	No	None	No	

*Transmission via sex is poorly documented.

8. STUDIES IN PAKISTAN

Acute viral hepatitis is distributed over a large area infection among kids in Pakistan and money owed for 50-60% of all instances of acute viral hepatitis in kids. By means of age of 5 years and 98- 100 percent at maturity, nearly 96 percent of the population is exposed to HAV. Almost all hepatitis A reflected excessive incidence of hepatitis A contamination in youngsters particularly individuals who are have been admitted to hospital with acute hepatitis. Most of the kids have been uncovered to the virus all through formative years and remain immune for existence long immunity[35]. Highly affected by personal and public hygiene is the epidemiology of hepatitis a virus. In developed and industrialized countries in Northern and Western Europe and North America, the disorder has nearly disapperaed. While hepatitis A is a pandemic in Pakistan

with mini epidemics happening all through the summer and wet seasons. Nevertheless, this cohort of patients had a low frequency of hepatitis Abecause of the pattern length being mainly of growing populace[36]. There is growing trouble in nations with intermediate endemicity, where infection is rare due to improved water remedy and hygiene, however where in adults without preceding exposure turn out to be infected all through sporadic, outbreaks commonly with clinically evident disorder[37]. While hepatitis A is generally self-limited, it usually causes substantial morbidity in adults, with jaundice ranging from 40% to 70 percent. Following preliminary recovery, signs may additionally relapse in upto 10% of individuals prolonging disease for a few weeks to months. There is catastrophic hepatic failure, but in less than 1 % of instances[38]. The results of HBV infection are determined by the age of acquisition. There is a chance of a child being diagnosed with over 90 percent and emerge as a long run carrier of HAV. This probability falls from about 90% within the first six months of existence, to approximately 25% by way of the age of 5 years, and to 10% by means of the age 15 years. It is rare (2-5%) to become continual carrier for adults inflamed later in life[39]. In developing countries HAV can cause infection in new born babies easily. So, vaccination should be done to produce immunity to prevent infection. When vaccine is applied in 2 years old children, protective antibodies are produced in 97 to 100% of cases 1month after the first injection. The children those are younger than twelwe months, acquired the maternal antibodies interact with the immune response trigger by HAV vaccines. In these cases, Ig is an option, but is not routinely recommended. An adequate immunity is produced in healthy people younger than 40 years by injecting one dose of the monovalent HAV vaccine. Pregnancy is not currently a clashing for using Ig treatment. Thus, all people having doubt for infection journeying for any purpose, frequency or duration to countries with high or intermediate HAV endemicity should be vaccinated or retain Ig before going. When suspected person is going to countries with high or intermediate endemicity is confirmed then first dose of hepatitis A vaccine should be injected[40].

9. VACCINATION

Immunization is very efficient in the control of hepatitis A virus. Decrease in the prevalence of infection is directly associated to vaccination or pre exposure to virus in life after that immunity is produced that persist for long time. Hepatitis A vaccine is made from formalin inactivated virus that grown in cell culture. There are 60 copies of each of three polypeptides in complete virion and empty capsid. After vaccination serum neutralizing antibodies produced that directly target surface epitopes within gathered particles. Inactivated hepatitis A vaccine is useful for both personal protection and systematic immunization. Infected children play significant role in spread of HAV infection. Studies have shown that immunization and improved hygiene conditions play an important role in prevention and control of hepatitis A in communities. Researches have studied that immunoglobulins are effective in preventing infection in pre exposed individuals[41]. Almost all individuals are asymptomatically infected with HAV in their childhood, which significantly stops the clinical hepatitis A infection when they are adults[42]. First tool identified to prevent HAV infection when effective hepatitis a vaccine introduced in the mid 1990s. It is estimated that 1.5 million cases of hepatitis A occur annually[43]. An inactivated vaccine produced in 1995 of hepatitis A virus whose immunogenicity and protective efficacy are sure[44,45]. Although virus is defecated in feces towards the end of incubation period, specific diagnosis is done by recognition of HAV specific IgM antibodies present in blood. IgM antibody is only present in blood after an acute hepatitis A infection. It is evident from 1 to 2 weeks after initial infection and it continues for up to 14 weeks. The existence of IgG antibodies in blood means the acute stage of illness has passed and patient is immune to the further infection. IgG antibodies to Hepatitis A are also found in blood after the vaccination and tests for the immunity to virus are based on the recognition of these antibodies. During acute phase of infection, the liver enzyme alanine transferase is existing in blood at levels much greater than is normal. The enzyme

comes from liver cells injured by virus. Hepatitis A virus is present in feces and blood of the infected people up to 1 days before the clinical infection progresses[46]. Figure 2 shows serum IgM, IgG, and alanine transferase after Hepatovirus A infection[46].

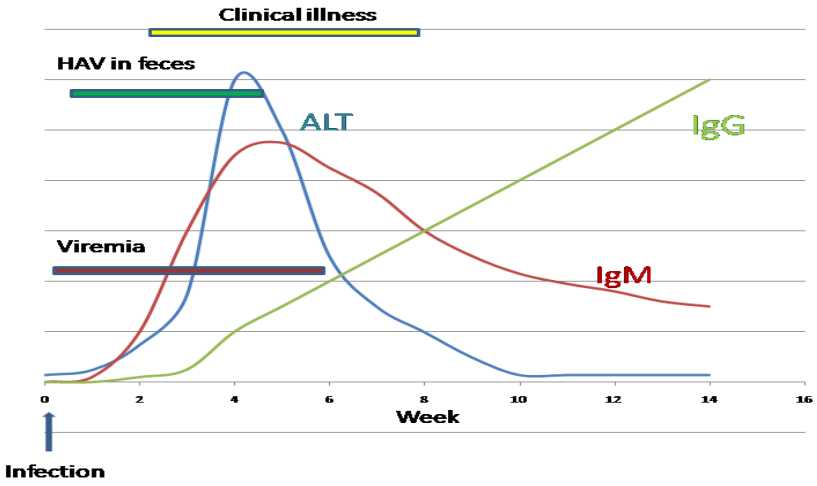

Fig. 2. Serum IgM, IgC, and Alanine transferase after hepatovirus A infection [45]

10. CONCLUSIONS

Hepatitis A is the most common type of acute viral hepatitis globally. The disease is closely linked with unsafe water or food, improper sanitation, poor hygiene and sex. The boiled water should be used and under cooked food or contaminated food should be avoided because feacal-oral route is involved in transmission of HAV so we should take care about use of poor-quality water and contaminated item from carts. Vaccination should be done at early life to every person against HAV. Vaccination should be made locally on the basis of home or community's ability to sustain adequate standard of cleanliness.

CONFLICT OF INTEREST

No conflict of interest

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