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Review Article

Viral hepatitis, hallmarks and molecular features

Orlando Vargas-Sierra[a1*], Nathalia Beatriz Camara-Medina[a2], Nicole Vincze-Galicia[a3], Camila Uriarte-Figueroa[a4], Javiera Pozo-Montalvo[a5], Perla Yaceli Uc-Uc[a6], Daniela Rebolledo-Solleiro[a7]

[a]Universidad Anáhuac Cancún, Campus Internacional, Cancún Quintana Roo, México.

ID ORCID:
[1]https://orcid.org/0000-0001-8072-919X, [2]https://orcid.org/0000-0003-2286-1357, [3]https://orcid.org/0000-0002-1597-0400, [4]https://orcid.org/0000-0003-1053-9862, [5]https://orcid.org/0000-0001-5716-0054, [6]https://orcid.org/0000-0002-3437-7741, [7]https://orcid.org/0000-0002-6994-7599

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ABSTRACT

Hepatitis is a liver inflammation which has different etiologies, it can be caused pharmacologically or can be associated with fatty liver or alcohol consumption. However, viral infection is the most important cause. Recently, the World Health Organization (WHO) has published reports of outbreaks of hepatitis of unknown etiology in several countries in children less than 16 years old. In this review we describe the general aspects of viral hepatitis, the molecular description of the hepatotropic viruses, laboratory findings, molecular diagnosis, and prevention strategies. In addition, the main characteristics of some viruses that are not hepatotropic but have been previously reported to be related to some types of hepatitis are mentioned. Finally, a brief description of new cases of hepatitis of unknown origin is presented and the adverse effects of SARS-CoV-2 vaccines are briefly discussed.

Key words: hepatitis; virus; liver; unknown etiology.

*_Corresponding Author:_ Orlando Vargas-Sierra. Universidad Anáhuac Cancún, Campus Internacional. Address: Carretera Chetumal-Cancún Mz. 2 SM. 299 Z.8 Lt. 1. Benito Juárez, Cancún, Quintana Roo. C.P. 77565, México. Tel.: (998) 881 7750. Email: ovargas@anahuac.mx

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RESUMEN

La hepatitis es una inflamación del hígado la cual tiene distintas etiologías, ya sea farmacológica, asociada con hígado graso o el consumo de alcohol, siendo la más notable la infección viral. Recientemente la Organización Mundial de la Salud (OMS) ha publicado reportes de brotes de hepatitis de etiología desconocida en varios países en niños menores de 16 años. En esta revisión se describen los aspectos generales de la hepatitis viral, la descripción molecular de los virus hepatotrópicos, los hallazgos de laboratorio, el diagnóstico molecular y las estrategias de prevención; además se hace mención a las características principales de algunos virus que no son hepatrópicos pero en los que previamente se ha reportado su relación con algunos tipos de hepatitis. Por último, se realiza una descripción breve de los casos nuevos de hepatitis de origen desconocido y se abordan brevemente los efectos adversos de las vacunas del SARS-CoV-2.

Palabras clave: hepatitis; virus; hígado; etiología desconocida.

INTRODUCTION

The liver is an organ located in the upper right section of the abdominal cavity, beneath the diaphragm, and above the stomach, the right kidney, and intestines. It weighs about three pounds, and it is cone shaped. Its main functions include bile secretion, bilirubin metabolism, coagulation factors synthesis, nutrient metabolism, mineral and vitamin storage, and xenobiotics metabolism.[1-5]

Liver disease can be acute or chronic; mild or severe; and reversible or irreversible. Hepatitis means liver inflammation, which has different etiologies. Its cause can be associated with fatty liver, alcohol consumption, pharmacological causes or due to a virus. The latter has showed to be the main cause that can damage this organ. There are several different types of hepatitis, which depending on what triggers it, and the duration of the inflammation, are divided into acute (sudden) or chronic (long-lasting) hepatitis. Acute hepatitis (AH) is an inflammatory process causing liver cell death either by necrosis or by triggering apoptosis; lasts for less than six months, and it is characterized by normalization of the liver function tests. It is mainly caused by a viral infection; however, it can also be the result of exposure to drugs (acetaminophen) or ethanol consumption. On the other hand, chronic hepatitis (CH) is defined as an inflammation of the liver that continues for a period of at least 6 months, caused by various pathogenic agents, which leads to inflammatory processes and cellular necrosis of the liver tissue. It is a disease that can progress to cirrhosis, liver cell carcinoma, liver failure and eventually death.[6-12]

Recently the WHO has published reports of outbreaks of hepatitis of unknown etiology in several European and American countries. At least 169 cases, as of April 21st, 2022, all of them in children under 16 years of age. It is important to highlight that the common viruses associated with acute viral hepatitis (hepatitis viruses A to E) have not been detected in any of these cases, so it's important to review the general aspects of this disease.[13]

In this review, we focus on viral hepatitis, we will describe its main characteristics, and review the data available to date on new hepatitis of unknown etiology.

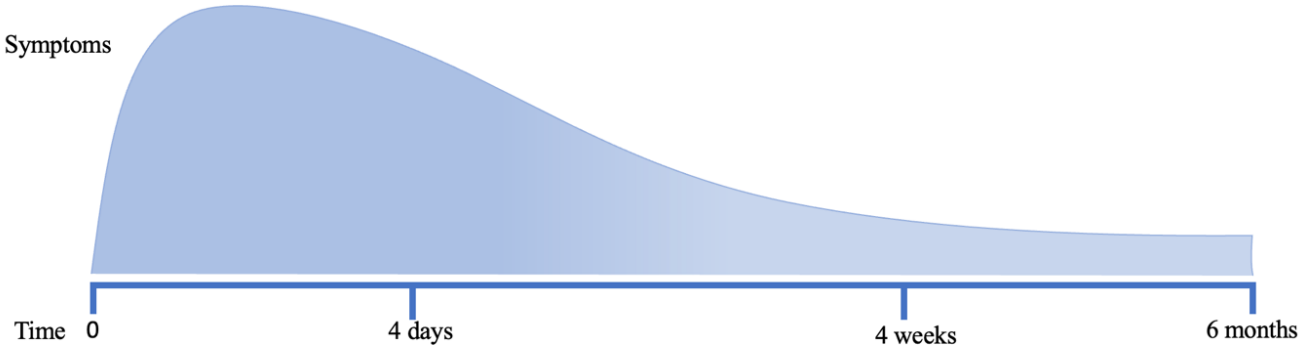
GENERAL ASPECTS OF VIRAL HEPATITIS

ACUTE HEPATITIS

AH may be asyntomatic, nevertheless; it could be frequently accompanied with fever, jaundice, dark urine, lethargy, fatigue, nausea, and gastrointestinal symptoms such as abdominal pain, diarrhea, and vomiting. Viral infections are the most common cause of acute hepatitis, being Hepatitis A virus (HAV) infection the main cause. The transmission occurs from person to person, during fecal-oral route or through the consumption of contaminated food and water. Several other viral infections, for example, Hepatitis E (HEV) and Hepatitis B virus (HBV), are also associated with acute hepatitis, but with a lower prevalence. HEV is transmitted through the same route as HAV, while HBV is transmitted by sexual contact, blood transfusion, and other infected fluids.[11, 14-15]

Viral hepatitis infection is classified into three stages, all presenting different signs, symptoms, and temporality. First, is the prodrome stage, which lasts 3-4 days beginning with the manifestation of general non-specific signs and symptoms of an illness, corresponding to mild fever, fatigue, and general malaise. Afterwards, these evolve into gastrointestinal manifestations such as anorexia, loss of appetite, nausea, discomfort in the right upper quadrant of the abdomen, and alterations of taste and smell. Ultimate-

ly, when cephalalgia, photophobia, cough, coryza, myalgia, cutaneous exanthema, urticaria or arthritis as extrahepatic phenomena appear, patients are highly contagious during this period.[16-17] Subsequently, the stage of emerging jaundice due to increased serum bilirubin causes yellowing of the skin and sclera of the eyes, darkening of the urine, and pale stools. This period lasts 1-4 weeks when symptoms are diminished. Patients may lose weight and pruritus might occur if cholestasis is severe. It is important to mention that patients will present abdominal pain due to the enlargement and hypersensitivity of the liver or as a consequence of splenomegaly.[16] At last comes the convalescence phase, in which the general symptoms disappear, but abnormalities in liver function tests still persist. Generally, AH has a good prognosis with a self-limiting course and resolution lasting less than six months until the patient liver functions' return to its normal state, as in the case of infection with Hepatitis A. Occasionally, acute hepatitis can evolve into liver failure with a critical prognosis as shown in Figure 1.[18]



Prodrome stage

Non-specific signs and symptoms of an illness: mild fever, fatigue, and general malaise.
Gastrointestinal manifestations: anorexia, loss of appetite, nausea, discomfort in the right upper quadrant of the abdomen and alterations of taste and smell.
Finally: cephalalgia, photophobia, cough, coryza, myalgia, cutaneous exanthema, urticaria or arthritis as extrahepatic phenomena.
The patients are highly contagious during this period.

Jaundice stage

Yellowing of the skin and sclera of the eyes, darkening of the urine, and pale stools, lose weight, pruritus.
The patients will present abdominal pain due to the enlargement and hypersensitivity of the liver or as consequence of splenomegaly.

Convalescence stage

The general symptoms disappear.
Abnormalities in liver function tests persist and resolution lasting less than six months until patients liver functions return to its normal state.
Nevertheless, occasionally acute hepatitis can evolve into liver failure with a critical prognosis.

Figure 1. Viral infection stages with signs, symptoms and temporality.

CHRONIC HEPATITIS

CH is defined as an inflammation of the liver that continues for a period of at least 6 months, leading to inflammatory processes and cellular necrosis of the liver tissue. It can be developed by fatty liver, alcohol-related liver disease and the use of certain drugs, when these are taken over a long period of time, such as amiodarone, isoniazid, methyldopa, and acetaminophen. CH could also be associated with viral infections; Hepatitis C virus infection is associated in 80% of cases and is characterized by viral persistence in the host hepatocyte. Less cases are related to Hepatitis B with or without Hepatitis D virus. CH is often asymptomatic for decades until chronic complications start to show up as a consequence of advanced liver damage stages when specific symptoms occur. These include, cirrhosis development, which may include liver and spleen enlargement, spider angiomas, telangiectasis, palmar erythema (redness of the

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palms), ascites, coagulopathy, and hepatic encephalopathy. Unlike AH, it is not uncommon for CH to progress to fibrosis. Due to repair with connective tissue, the excessive hepatic necrosis accompanied by an excessive decomposition of the extracellular matrix (ECM) developing cirrhosis -which is the final stage of the fibrotic process characterized by permanent hepatocyte damage, nodular regeneration, aberrant architecture and mostly accompanied by scar tissue formation that impairs hepatocyte function and impaired portal blood flow- CH can progress into liver cancer or death.[19-23]

HEPATOTROPIC VIRUSES

Although there are multiple hepatitis etiological factors, viral hepatitis is the global leading cause of the inflammation of the liver tissue. Hepatitis A and B viruses were discovered in 1960. It was not until 1990 that other hepatitis viruses were no longer classified as non-A, non-B, and up to date there has been four more hepatitis viruses recognized; Hepatitis C, D, E and G, as seen in Table 1.[24-25]

Table 1. Canonical Hepatotropic and Non-canonical Hepatotropic viruses

DISEASE	VIRUS	VIRUS CHARACTERISTICS	TRANSMISSION	SIGNS AND SYMPTOMS	DIAGNOSIS
HEPATOTROPIC VIRUSES					
HEPATITIS	HAV (Hepatitis A Virus)	Family: Picornaviridae Viral symmetry: non-enveloped, Icosahedral capsid Nucleic acid: Single strand (ss) positive (+) RNA (acts directly as a messenger) Genome size: approximately 7.500 kilobase (kb)	Oral-fecal route and it is mainly associated with the lack of access to potable water.	Weakness, fatigue, nausea, vomiting, abdominal pain, arthralgias, myalgias, diarrhea and anorexia.	Molecular biology techniques (RT-PCR); serological tests (surface antigen) or antibody detection (IgM, IgG)
	HBV (Hepatitis B Virus)	Family: Hepadnaviridae Viral symmetry: enveloped, Icosahedral capsid Nucleic acid: Incomplete double-stranded (ds) circular DNA genome virus Genome size: 3.2 kb Others: Eight genotypes (A-H)	From mother to child at birth, body fluids and through sexual contact; sharing needles, syringes, or other drug-injection equipment.	Fatigue, nausea, vomiting and right upper quadrant pain before or during jaundice onset.	
	HCV (Hepatitis C Virus)	Family: Flaviviridae Viral symmetry: enveloped, Icosahedral capsid Nucleic acid: Single-stranded (ss) positive (+) RNA viruses linear double-stranded DNA. Genome size: 9.6 kb Others: It is classified into eight genotypes	Primarily by parental routes including blood transfusions, intravenous drugs injections or by high-risk sexual practice.	Nonspecific, they can include fatigue, sleep disturbances, nausea, diarrhea, abdominal pain, anorexia, myalgia, arthralgia, weakness, depression, anxiety and weight loss.	
	HDV (Hepatitis D Virus)	Family: Kolmioviridae Viral symmetry: enveloped, capsid of unknown symmetry Nucleic acid: circular single strand (ss) negative (-) RNA Genome size: 1.7 kb Others: The only member of the Deltavirus genus, It is classified into eight genotypes, It's enveloped by HBV surface antigens	It only affects patients with this co-infection of the B and D viruses. It is spread by perinatal transmission and through contact with infected body fluids.	The infection may be asymptomatic, and usually progresses to mild self-limited disease or severe acute hepatitis with spontaneous resolution.	

	HEV (Hepatitis E Virus)	Family: Hepesviridae Viral symmetry: non-enveloped, icosahedral capsid Nucleic acid: single-stranded (ss) positive (+) RNA Genome size: 7.2 kb	By the fecal-oral route, it is also associated with lack of access to drinking water and animals can act as a reservoir of the virus.	Almost all patients with HEV are asymptomatic or may develop a mild HAV-like illness.	
	HGV (Hepatitis G Virus)	Family: Flaviviridae Viral symmetry: Enveloped, capsid of unknown symmetry Nucleic acid: single-stranded (ss) positive (+) RNA Genome size: 9.4 kb Others: Lymphotropic human virus	Through percutaneous injuries, contaminated blood, sexual contact, and vertical mother-to-child transmission.	Typically considered nonpathogenic.	
OTHER NON-CANONICAL HEPATOTROPIC VIRUSES					
Erythema infectiosum	Parvovirus B19	Family: Parvoviridae Viral symmetry: non-enveloped, icosahedral capsid Nucleic acid: linear single-stranded DNA Genome size: 5.6 kb Others: it is the only parvovirus pathogenic for humans, may develop acute hepatitis	Mainly through respiratory droplets, and in some cases by blood transfusions and the placental route.	This infection may be asymptomatic or associated with headache, erythema infectiosum and anemia in children and multiple joint pains and inflammation and general malaise in adults.	Serological tests
Infectious mononucleosis	Epstein-Barr	Family: Herpesviridae Viral symmetry: Enveloped, icosahedral capsid Nucleic acid: Linear double-stranded DNA Genome size: 170 kb Others: Human herpesvirus type 4, infection can affect liver	Body fluids, especially saliva.	Liver involvement, leading to elevation of liver enzymes, cholestatic hepatitis, characterized by obstruction of bile flow.	Serological Testing and Molecular Assays
Infectious mononucleosis	Cytomegalovirus	Family: Hepesviridae Viral symmetry: enveloped icosahedral capsid Nucleic acid: Double-stranded DNA virus Genome size: 236 kb Others: the largest genome of any known human virus, Human herpesvirus 5, it is associated with hepatitis and pancreatitis in immunocompetent patients	Body secretions such as saliva, urine, tears, blood or genital secretions.	Typically cause mononucleosis syndrome or usually presents as asymptomatic infection.	Serological Testing and Molecular Assays
Chickenpox	Varicella -zoster virus	Family: herpesviridae Viral symmetry: enveloped, icosahedral capsid Nucleic acid: Linear double-stranded DNA virus Genome size: 125 kb Others: Human herpesvirus 3, Neurotropic virus, can develop complications, related to the liver	airborne, with viruses coming from the vesicles that form on the skin, as this is where they are found in high viral concentrations.	Persistent radicular pain, this viral infection can develop other complications, related to the liver.	symptoms and signs analysis, RT-PCR from blister

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Yellow Fever	Yellow fever virus	Family: Flaviviridae Viral symmetry: enveloped, icosahedral capsid Nucleic acid: Single-stranded, positive-polarity RNA genome Genome size: 11 kb Others: some reports related with hepatitis	By mosquitoes of the Aedes and Haemagogus species.	High fever, skin hemorrhages and the death of liver and kidney cells are common.	Serological Testing and Molecular Assays
Rubella	Rubella virus	Family: Matonaviridae Viral symmetry: enveloped, icosahedral capsid Nucleic acid: Positive-stranded RNA Genome size: 9.7kb Others: may be playing a role in liver injury	Airborne transmission, mother-to-child transmission.	During pregnancy, miscarriage or stillbirth, serious birth defects such as deafness, eye and heart abnormalities; in adults was associated with elevations of serum aminotransferases, globular degeneration, and focal necrosis of liver cells.	Serological Testing and Molecular Assays
Acute respiratory infection	HADV Human adenovirus	Family: Adenoviridae Viral symmetry: non-enveloped, icosahedral Nucleic acid: Doubled-stranded DNA Genome size: 36kb Others: recently reported in cases of severe acute hepatitis in children	Inhalation of aerosolized droplets, fecal-oral spread, or conjunctival inoculation.	Pharyngitis, coryza or pneumonia, and in children serotypes 40 and 41 have been associated with gastrointestinal symptoms such as diarrhea, abdominal pain and vomiting.	Antigen detection, polymerase chain reaction (PCR), virus isolation, and serology

Hepatitis A Virus (HAV)

HAV belongs to the Picornaviridae family and Hepatoviral genus, which are non-enveloped icosahedral single strand positive RNA non-enveloped small viruses. It is approximately 7,500 nucleotides in length and its RNA acts directly as a messenger. So far, the mechanism of the virus entering the host cell is not very clear. Previously, it was suggested that the virus enters the cell using its phosphatidyl serine residues allowing it to bind to HAV cellular receptor 1 protein (HAVCR1). Recently it has been shown that this receptor is not essential for virus entering into the cell, nonetheless studies to characterize the related molecules are still lacking. Still the process after virus entry into the cell is better understood. Once the virus enters by endocytosis, RNA is directly translated by a cap-independent mechanism using the IRES structures present. Then, by intermediate steps the virus is assembled and released from the cell. It is worth mentioning that HAV replication does not have a cytopathic effect on hepatocytes.[26-28]

According to the World Health Organization (WHO), there are nearly 1.4 million new cases of HAV globally every year, causing just about 7,000 deaths. Hepatitis A is an acute infection that appears in non-vaccinated population or among people that have not been infected before. It is transmitted through an oral-fecal route, and it is mainly associated with the lack of access to potable water as shown in Figure 2.

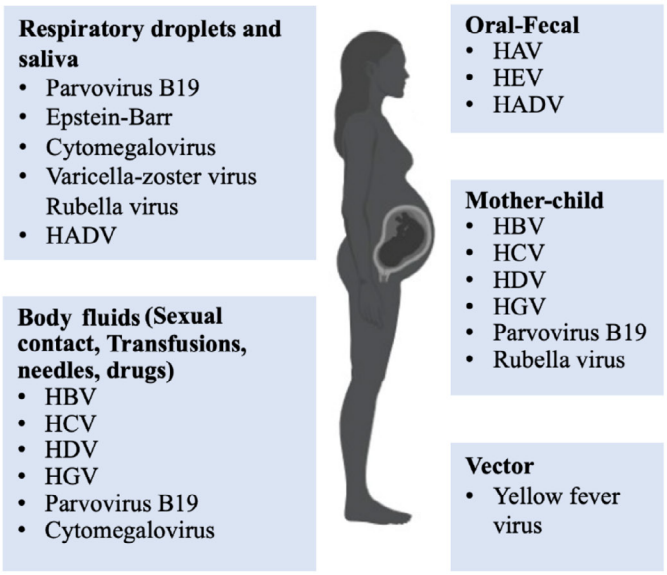

Figure 2. Transmission routes.

HAV has regularly an incubation period of 2-4 weeks, usually causing fever, malaise, and jaundice, being the most common symptoms. Weakness, fatigue, nausea, vomiting, abdominal pain, arthralgias, myalgias, diarrhea and anorexia can also be related with this infection.[24-25, 29]

Hepatitis B Virus (HBV)

The HBV a member of the Hepadnaviridae family, is enveloped and has an icosahedral symmetry. It is an incomplete double-stranded circular DNA with a genome virus of 3.2 kb in length, with a lipopeptide layer and an internal nucleocapsid. At least 8 different genotypes (A-H) have been identified. Once the virus is in the perisinusoidal space, it utilizes its surface antigens binding to the sodium taurocholate co-transporting polypeptide (NTCP) receptor on the hepatocytes membrane and enters via endocytosis. Since the virus is without cover, the nucleocapsid is maintained until the viral DNA reaches the nucleus. Once in the nucleus, the double helix is completed and covalently locked. Thus, it can remain in the nucleus for a long time. Nevertheless, it can also integrate into the genome of the infected cell. Genome integration is a mechanism by which HBV causes neoplastic transformation and the development of cancer.[30-32]

This virus can be transmitted either from mother to child at birth. Figure 2 shows that the incubation period is variable between 28-180 days, producing an acute or chronic hepatitis infection. Acute HBV infection can be presented as a subclinical disease, which is the most common way, to an icteric hepatitis. Patients could experience fatigue, nausea, vomiting and right upper quadrant abdominal pain before or during jaundice onset. During the acute phase, there is an elevation of the HBV viral load and total bilirubin. Although a great portion of acute HBV infections can resolve with liver enzyme normalization, a chronic HBV phase will begin if the ALT remains elevated after six months from its initial presentation.

Chronic HBV may be developed in younger patients with genetic predisposition or in those who did not develop symptoms when acute HBV infection occurred. Regularly, these patients are asymptomatic for years until there is an HBV exacerbation or complication. The worse disease progression of HBV infection can be related to several host factors, such as male gender, alcohol intake and obesity. Patients with chronic HBV could develop liver cirrhosis or hepatocellular carcinoma (HCC), as a complication due to the parenchymal inflammation and fibrosis of a long-term infection.[12, 21, 25, 29, 32]

Hepatitis C Virus (HCV)

This is an enveloped virus belonging to the Flaviviridae family. It is classified into eight genotypes, positive-sense single-stranded (ss) RNA viruses with an Icosahedral capsid. Its genome is approximately 9.6 kb in length. HCV is transmitted primarily by parental routes including blood transfusions, intravenous drugs injections or by high-risk sexual practice.

As Figure 2 shows, HCV is estimated to infect more than 1% of the global population, and nearly 80% develop a slowly evolving, asymptomatic chronic liver disease which is characterized by cell damage, inflammation and fibrosis that can later develop into cirrhosis or Hepatic carcinoma after a few decades. Chronic HCV infections can occur in nearly all patients with an HCV infection, while 15%-45% of patients may present spontaneous clearance of the virus or an acute HCV infection. Nearly all cases of acute HCV infections are asymptomatic. Some patients present similar symptoms as other acute hepatitis, like jaundice, nausea, dark urine, and others. Such symptoms may appear or develop from 2-26 weeks after exposure, and they usually last two to twelve weeks. Although symptoms of an HCV infection are nonspecific, they can include fatigue, sleep disturbances, nausea, diarrhea, abdominal pain, anorexia, myalgia, arthralgia, weakness, depression, anxiety, and weight loss. It is also important to note that patients who develop cirrhosis may also develop ascites and other stigmata of cirrhosis.[23-24, 28-29, 33]

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Hepatitis D Virus (HDV)

This virus belongs to the Kolmioviridae family and is the only member of the Delta virus genus. It is distinct from other types of hepatitis viruses because requires of HBV for its replication and is therefore, referred to as HBV satellite virus. It's a single-stranded negative-sense RNA virus, it's the only animal virus having a circular RNA and it's enveloped by the HBV surface antigens. Its genome is very small (~1700 nucleotides) and has a capsid of unknown symmetry. HDV does not encode for an RNA-dependent RNA polymerase (RdRp) like other RNA viruses but relies on host DNA-dependent RNA polymerases (DdRp) for RNA synthesis and replication of its genome in the cell nucleus. Therefore, it only affects patients with this co-infection of the B and D viruses. HDV is spread by perinatal transmission and through contact with infected body fluids. The infection may be asymptomatic, and usually progresses to mild self-limited disease or severe acute hepatitis with spontaneous resolution. On the other hand, HDV superinfection in chronic HBV carriers often results in a prolonged clinical course.[25, 29, 34-35]

Hepatitis E Virus (HEV)

HEV is a non-enveloped virus, from the Hepeviridae family, classified into four genotypes. Positive-sense single-stranded (ss) RNA viruses, with an icosahedral capsid and a genome 7.2 kb in length, currently HEV life cycle and pathogenesis remain unknown. HEV infection is one of the biggest struggles for the global public health system as it is a causative agent of endemic and epidemic hepatitis worldwide. According to WHO, there are nearly 20 million international new infections annually, with an estimate of nearly 3.3 million acutely symptomatic patients and more than 4,400 deaths during 2015. HEV is usually transmitted by the fecal-oral route.

It is also associated with lack of access to drinking water, and animals can act as a reservoir of the virus. Almost all patients with HEV are asymptomatic or may develop a mild HAV-like illness. Genotypes one and two have an incubation period of 2-10 weeks, and genotypes three and four become a chronic infection which is unique to the immunocompromised population. It is worth to mention that those patients with liver disease who are pregnant or malnourished are more likely to present a progression from acute infection to liver failure due to their immunosuppressive condition.[23-25, 29, 36]

Hepatitis G Virus (HGV)

It is a single-stranded RNA virus with positive polarity, which is related to HCV, also known as human pegivirus 1. Its genome is approximately 9.4 kb in length, it is enveloped, and it has capsid of unknown symmetry. In contrast to other hepatitis viruses it is found primarily in lymphocytes and not hepatocyte. Therefore, it is considered a lymphotropic human virus. It is transmitted through percutaneous injuries, contaminated blood, sexual contact, and vertical mother-to-child transmission. Surprisingly, co-infection of human lymphocytes with HGV and HIV inhibits HIV replication, as a consequence this virus is typically considered nonpathogenic.[37-41]

OTHER NON-CANONICAL HEPATOTROPIC VIRUSES

Parvovirus B19

Parvovirus 19 is a non-enveloped linear single-stranded DNA virus that belongs to the Parvoviridae family, with 5.6 kb genome in length, it is the only parvovirus pathogenic for humans. This infection may be asymptomatic or associated with headache, erythema infectiosum and anemia in children, and multiple joint pains and inflammation and general malaise in adults. Aplastic anemia is mentioned as a complication of this infection in young adults. The infection may develop acute hepatitis, manifested by yellowing of the skin (jaundice) and hepatosplenomegaly or maintained even for years in immunocompetent individuals. Parvoviruses are transmitted mainly through respiratory droplets, although they can also be spread through blood transfusions and the placental route.[42-45]

Epstein-Barr Virus

The Epstein-Barr virus genome is linear double-stranded DNA, it's enveloped with icosahedral capsid and a genome size of around 170 kb. This virus is a member of the Herpesviridae family, it is transmitted mainly by body fluids, especially saliva. It is one of the most common viruses in humans, it's the main cause of infectious mononucleosis and it's also linked to the development of several human cancers. EBV infection can cause liver involvement, leading to elevation of liver enzymes, but it usually resolves on its own. However, in some less common cases, cholestatic hepatitis, which is a rare form of acute hepatitis characterized by obstruction of bile flow, may occur sporadically.[46-50]

Cytomegalovirus

Cytomegalovirus (CMV) is a double-stranded DNA virus, has an icosahedral capsid and it is enveloped, it has the largest genome of any known human virus, and it is a member of the Herpesviridae family. Like EBV, to which it is related, it is transmitted through bodily secretions such as saliva, urine, tears, blood, or genital secretions. Typically causes mononucleosis syndrome or is usually present as an asymptomatic infection. Chang et al. and other authors have previously reported cases of CMV associated with hepatitis and pancreatitis in immunocompetent patients, in which elevated lipase levels, elevated aminotransferases and epigastric pain after an acute viral prodrome are present.[48, 51-52]

Varicella-Zoster Virus

Varicella-zoster virus belongs to the Herpesviridae family, it is an enveloped linear double-stranded DNA virus with an icosahedral capsid and a genome of 125 kb in length. It is the etiologic agent of chickenpox and herpes zoster. It is very easily transmitted by airborne, with viruses coming from the vesicles that form on the skin, as this is where they are found in high viral concentrations. Although it is a neurotropic virus, which can cause persistent radicular pain, this viral infection can develop other complications, related to other organs such as the liver.[53-55]

Yellow Fever Virus

Yellow fever virus has a single-stranded positive-polarity RNA genome, with 11kb of length, is enveloped and has an icosahedral capsid, belongs to the Flaviviridae family and is an arbovirus transmitted by mosquitoes of the Aedes and Haemogogus species. High fever, skin hemorrhages and the death of liver and kidney cells are common in this viral infection and has a high case fatality rate. Evidence of the relationship of this virus with the development of hepatitis is pointed out in some reports such as the one published by Rezende et al. in which they present a patient who showed hyporexia, asthenia, adynamia and jaundice two months after the onset of acute yellow fever; accompanied by an increase in transaminases and direct bilirubin levels. It is also accompanied by weakness and fatigue that may last for several weeks, while slightly abnormal liver function may persist for 60 days or more.[56-58]

Rubella Virus

Rubella virus is an enveloped positive-stranded RNA virus with icosahedral capsid that belongs to the Matonaviridae family, it is highly contagious and transmitted through airborne transmission. It is well documented that infection during pregnancy can cause miscarriage or stillbirth, and can cause serious birth defects such as deafness, eye and heart abnormalities. Several years ago, two independent reports on a 24-year-old and a 28-year-old man with rubella infection were associated with elevations of serum aminotransferases, globular degeneration, and focal necrosis of liver cells, and it was suggested that cytotoxic T cells may be playing a role in liver injury in acute rubella infections in adults.[59-62]

Human Adenovirus (HAdV)

HAdV are doubled-stranded DNA non-enveloped viruses from the Adenoviridae family, with a incosahedral capsid, and a genome of 36 kb in length. The typical route of transmission is through inhalation of aerosolized droplets, fecal-oral spread, or conjunctival inoculation. These viruses usually cause self-limited infections in the non-immunocompromised population and after an incubation period of 2 to 14 days, symptoms of this respiratory tract infection may be observed including pharyngitis, coryza or pneumonia, and in children serotypes 40 and 41 have been associated with gastrointestinal symptoms such as diarrhea, abdominal pain and vomiting.[63-64] Its relationship to the development of hepatitis is discussed further on.

DIAGNOSIS

The diagnosis of acute hepatitis is based on laboratory findings as elevated levels of Aspartate Transaminase (AST), Alanine Aminotransferase (ALT) above 500 IU/L, total bilirubin elevated levels, serological markers like virus surface antigens and serum antibodies detection. In the case of chronic hepatitis, the serological detection is persistent for more than six months; after this period the virus should have been cleared of serum. On the other hand, hepatitis viruses could be detected by molecular techniques as real-time polymerase chain reaction (RT-PCR), for viral nucleic acid present in relatively small amounts in body fluids of infected patients. Diagnosis for CH includes blood tests followed by a liver biopsy to confirm or reject the diagnosis of hepatitis. The blood test as in AH, measures the levels of liver

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enzymes (transaminases) and other substances produced by the liver, which will appear elevated, helping the medical practitioner to identify the main cause and determine the severity of liver damage. As mentioned before, a liver biopsy will be also necessary to confirm the diagnosis, as it determines how severe the inflammation is, if any fibrosis has been developed on the tissue, and allowing to specify the stage of necroinflammatory activity (mild, moderate, severe, and very severe), helping to identify the cause of hepatitis. Depending on the results, the medical practitioner may ask for complementary tests like markers (in case of fibrosis), abdominal ultrasound to verify if the liver is enlarged, if it has nodular appearance, and when performing with doppler it can even show signs of portal hypertension. An endoscopy will evaluate the presence of gastroesophageal varices due to portal hypertension that is associated with liver cirrhosis. Finally, the progression of the initial fibrosis to advanced cirrhosis can culminate in hepatic cellular carcinoma. Quantification of alpha-fetoprotein (AFP) is commonly used as a biomarker for early detection and follow-up of hepatic cell carcinoma.[8, 21, 65-68]

PREVENTION STRATEGIES

Viral Hepatitis remains as a problem for the global public health system due to the high non-vaccinated population. According to WHO, in its latest update of June 2022, in 2019 chronic HBV infection had an estimated prevalence of 296 million infected people which represents an increase of 15.18% (compared to the 2017 report). Furthermore, the annual incidence has been estimated at 1.5 million new cases and 820,000 deaths associated with HBV infection, mainly due to cirrhosis and hepatocellular carcinoma. The biggest risk factor for chronic HBV is perinatal transmission, which can be prevented with a birth and three-dose vaccination, administration of Hepatitis B immunoglobulin (HBIG) to infants, and antiviral treatment of high-viral-load mothers. However, it should be noted that HBV vaccination has resulted in a decrease in the incidence of HBV infection; also important is the screening of blood bank donors with HBV serologic markers, which has virtually eliminated post-transfusion Hepatitis B. The protective effect of the Hepatitis B vaccine is related to the formation of antibodies against HBs Ag induced by the vaccine. Currently due to the vaccine introduction in childhood, young adults are now becoming more susceptible to HAV infections, therefore one of the greatest challenges for HAV is to increase vaccination coverage globally, still implementing the single-dose schedule, to decrease the new infections, and, in the long term, to achieve its eradication. Although vaccines are particularly effective in pre-exposure situations, administration of Hepatitis A vaccine to those who live with a child who develops Hepatitis A has been shown to be effective in preventing secondary cases, and also induces a permanent immunity that protects against further contact with the virus. On the other hand, there is still no vaccine available against Hepatitis C, so its prevention requires the application of health measures.[12, 24, 29, 69-70]

UNKNOWN ETIOLOGY HEPATITIS

In general, despite the great variety of viruses that exist and that can cause liver infection, the reality is that the vast majority of viral hepatitis is due to one of the hepatitis viruses discussed above. Recently alerts have been activated due to outbreaks of acute hepatitis in children where the liver damage has not been attributable to one of these hepatitis viruses (Hepatitis A-G). This outbreak has been observed in children under 16 years of age in more than 40 countries in which serum transaminases were seen to rise above 500 IU/L and causing acute liver failure in approximately 10% of the cases, and which, as of early April of this year had already resulted in at least 21 deaths and 38 liver transplants. In these reports, the patients had no history of travel to any hepatitis epidemic area or hepatitis due to drugs or any other non-infectious cause was ruled out. The most common symptoms have been gastrointestinal or systemic, and commonly associated with hepatitis such as yellowing of the eyes or skin, dark urine. Interestingly, respiratory symptoms were also reported in the weeks prior to hospital admissions. It is worth mentioning that most of the patients had no history of vaccination against COVID-19 due to their age range. Previously it has been noted the association of rubella virus with liver damage, this due to the activation of the immune system, specifically the cytotoxic T cells, widely involved in containing viral infection. Important to remember as well is the fact that in front of the SARS-CoV-2 infection the deregulation of the immune system has been reported; leaving aside the protection against infectious agents causes an adverse effect when overactivated.[60, 71]

Since these outbreaks are not related to infection with classical hepatitis viruses, as has been demonstrated and confirmed by various molecular tests, it is worthwhile analyzing the timeline of the development of these cases. So far, the sequence of these events have been as follows: from October 2021 to February 2022, nine cases of hepatitis of unknown origin were reported in Alabama, United States; all were positive for Adenovirus 41, however they also presented coinfection with other viruses such as EBV, only 2

patients required liver transplantation.[72] In early April, 10 cases of severe acute hepatitis of unknown origin were reported in children in central Scotland. On April 21st, 2022, the WHO published at least 169 case reports of outbreaks of hepatitis of unknown etiology in several European and American countries.[13] On May, reports already included 15 countries worldwide, most of them in Europe, reaching 191 cases, where at least 50% were positive for adenovirus -of which 10% reported a co-infection with SARS-CoV-2- 17 liver transplants were required and one death was reported.[63] At the end of May, the number of cases reached 600 patients.[73] By early June, these outbreaks had already affected more than 800 children and had spread to 40 countries.[71] More recently, on July, the WHO reported 1010 cases of this type of hepatitis and 22 deaths.[74]

DISCUSSION AND CONCLUSION

It is important to highlight that currently 12.8 billion doses of the different presentations of the vaccine against COVID-19 have been administered, nearly 3.65 million doses per day- which represents almost 70% of the world's population.[75] We should keep in mind that these vaccines have a safety profile and quality control, no drug therapy is exempt from adverse effects. In the case of COVID-19 vaccines, some distinct adverse effects have been reported, with malaise, fatigue and headache being the most common.[76] In addition, there have been reports of adverse effects related to liver damage by COVID-19 vaccines. Mann et al. have reported a case of hepatoxicity caused by the Pfizer vaccine, a messenger RNA vaccine, which presented jaundice data, abdominal pain that appeared 9 days after the second dose of the vaccine, increased values of various metabolites such as ALP, bilirubin and aspartate transaminase, as well as a considerable increase in white blood cells.[77] Likewise, Ghorbani et al. report a case with hepatitis data after the Sinopharm vaccine, an attenuated virus vaccine.[78] However, as we have mentioned, most of these cases of hepatitis have been in patients that, because of their age range at the time of the development of the disease, had not yet been administered a dose of COVID-19 vaccine, so it is very unlikely that they are part of the adverse effects due to vaccination. Nevertheless, it should not be underestimated that we could be facing cases of hepatitis due to the sequelae of a previous infection with SARS-CoV-2, remembering that during the development of this disease a series of disorders occur at different levels as in the case of the cytokine storm.

In conclusion, there is not enough information about the etiology of these types of hepatitis of unknown origin, and more studies and reports are needed to reinforce the analysis of the relationship of viral infections, such as adenovirus or EBV. We must recall that the approach of the study considers the analysis of the risks of developing hepatitis against viral coinfections by SARS-CoV-2 co-infections. It should also be considered necessary that the analysis of other etiologic factors that may trigger the disease, such as those due to the use of drugs or those of autoimmune component, could involve the production of super antigens and the relationship with other pathologies. Finally, it is necessary to be aware of the different side effects that the COVID-19 vaccine could cause in patients under 16 years of age, because they are still in the early stages of vaccination, keeping in mind that vaccination is a successful and safe strategy that prevents complications due to SARS-CoV-2 infection.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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