Local and systemic autoimmune manifestations linked to hepatitis A infection

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Abstract

Hepatitis A virus (HAV) represents a global burdening infectious agent causing in the majority of cases a self-limiting acute icteric syndrome, the outcome is related to the hepatic substrate and the potential pre-existing damage, whereas a plethora of extra-hepatic manifestations has also been reported. Despite the absence of post-HAV chronicity it has been associated with an additional burden on existing chronic liver diseases. Moreover, the induced immune response and the antigenic molecular mimicry are considered as triggering factors of autoimmunity with regional and distal impact. Diseases such as autoimmune hepatitis, Guillain-Barré syndrome, rheumatoid arthritis, Still's syndrome, Henoch-Schönlein purpura, autoimmune hemolytic anemia, antiphospholipid syndrome, systematic lupus erythematosus or cryoglobulinemic vasculitis have been described in patients with HAV infection. Although the exact mechanisms remain unclear, this review aims to accumulate and clarify the pathways related to this linkage. (Acta gastroenterol. belg., **2023,** 86, **429-436**).

Keywords: Hepatitis A, immune response, autoimmune hepatitis, autoimmune diseases.

Introduction

Hepatitis A virus (HAV) is currently a leading cause of acute hepatitis worldwide (1). Despite the existence of effective vaccines against HAV, infection may occasionally result in acute liver failure, and lead to liver transplantation or even to death (2). It is an important pathogen with significant public health impact causing about 200 million infections, and 30 million symptomatic diseases (ranging from mild disorder to fulminant hepatic failure, comprising 0.35% of all cases of fulminant liver failure); according to the World Health Organization, 1.4 million new cases of hepatitis A are reported worldwide annually, with a consequent 90,000 deaths annually. While outbreaks in industrialized regions are relatively infrequent, the most recent outbreak of hepatitis A in the United States started in 2016, involved 35 states, and indicated the re-emergence of hepatitis A. As of October 7th, 2022, there are 44660 publicly reported cases, leading to 27282 (61%) hospitalizations and 417 deaths (3).

Virology and clinical manifestations

HAV is a small non-enveloped RNA virus that belongs to the genus *Hepatovirus*, and is classified within the *Picornaviridae* family. Specifically, the genome of HAV is a positive-sense single stranded non-segmented RNA molecule of around 7500 nucleotides that has a single open reading frame (1). Human HAV have been categorized into three genotypes, HAV I, II, III and subdivided into seven subtypes (IA, IB, IC, IIA, IIB, IIIA and IIIB). Genotype I, followed by III, are the most frequently reported, whereas genotype II is rarely isolated and its genetic diversity is undetermined. HAV is predominantly transmitted through fecal-oral route, whereas blood transfusion-related HAV has occasionally been described. HAV infection follows specific regional patterns relevant to the respective socioeconomic and sanitary conditions, thus reflecting the fecal-oral transmission route (4).

Upon insertion in the alimentary tract, HAV particles escape from the acidic gastric environment and reach quickly the hepatic parenchyma to replicate and further are secreted to the gastrointestinal tract from the liver through the biliary system. Once infected, most adults develop clinical manifestations of self-limiting icteric hepatitis, whereas less than 30% of young children suffer from clinical symptoms. Extra-hepatic manifestations include several organs and can be classified as inflammatory or autoimmune-mediated (Table 1). Infection related inflammatory disorders include acute kidney injury, acute pancreatitis, acalculous cholecystitis, pericardial/pleural effusions, and skin pathologies (scarlatiniform eruption, urticaria, panniculitis, maculopapular prolonged rash evanescent skin rash, serum sickness-like illness rash). On the other hand, triggering the immune response could result in manifestations such as autoimmune hepatitis (AIH), autoimmune hemolytic anemia, immune thrombocytopenic purpura, anterior uveitis, antiphospholipid syndrome, systemic lupus erythematosus (SLE), acute reactive arthritis, rheumatoid

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Table 1. — **Extrahepatic manifestations of Hepatitis A infection**

Inflammatory		**Autoimmune**	
Organ – Pathology	*Reference*	*Organ – Pathology*	*Reference*
Acute kidney injury	5	Autoimmune hepatitis	18,19,21-26
Acute pancreatitis	5	Autoimmune hemolytic anemia	35,64,65
Acalculous cholecystitis	5, 6	Immune thrombocytopenic purpura	13
Pericardial/pleural effusions	5	Acute reactive arthritis Rheumatoid arthritis	6 12
		Glomerulonephritis	6, 11,59
Scarlatiniform eruption	7	Mononeuritis multiplex	6
Urticaria	7	Transverse myelitis	6
Panniculitis	7	Guillain-Barré syndrome	33,34
Maculopapular prolonged rash	7	Cryoglobulinemia	7,61
Evanescent skin rash	7	Cutaneous vasculitis	7
Serum sickness-like illness rash	7	Systemic lupus erythematosus	9, 10, 40
		Antiphospholipid syndrome	11
		Acute bilateral granulomatous anterior uveitis	8
		Polymyositis (myoglobinuria)	63
		Henoch-Schönlein purpura	60
		Still's disease	62

Table 2. — **HLA and HAV-related autoimmunity**

HLA	**Clinical relevance**
*HLA DRB1*1301*	Slow HAV clearance and autoantibodies expression among Brazilian and Argentinian children with hepatitis A
*HLA DRB*1301*	Indicator for AIH, is related with persistent liver damage after HAV infection in both pediatric and adult patients
*HLA DRB1*1301* and *HLA DRB1*1401*	Basic AIH susceptibility alleles
*HLA DRB1*0404*	AIH association in areas with high seroprevalence of HAV
*DRB1*1302* of the *DRB1*13*	Mostly expressed in patients of Far East and African Continent

AIH; autoimmune hepatitis, HAV; hepatitis A virus, HLA; human leukocyte antigen.

arthritis, glomerulonephritis, neurological pathologies (mononeuritis multiplex, transverse myelitis, Guillain-Barré syndrome) as well as cryoglobulinemia and vasculitis (5-13).

Currently, due to the increasing incidence of HAV infection among adults, some of the aforementioned complications are frequently detected (14). In a national study, Chen et al (15) recorded a mortality rate of 16.8 per 1000 hospitalizations for HAV infection, with male gender, age greater than 40 years, cirrhosis and long hospitalization predicting worse outcome. Nevertheless, although mild geographical and socioeconomic fluctuations, the global annual deaths by HAV infection were reduced by half during the last twenty years (18.6K in 2017 compared to 33.6K in 1990), and a parallel reduction was calculated considering the resulted disability.

In patients already burdened with chronic hepatopathies or cirrhosis, HAV over-infection can lead to a further deterioration, causing for example acute liver failure. Although no etiological association between HAV infection and liver failure has been identified, there is a significant link between the severity of liver disease and the degree of preexisting damaged liver (2).

Genetic factors potentially involved in HAV-related autoimmune hepatitis

AIH development or worse course of the disease is linked with certain genetic risk factors, albeit without following the Mendelian pathway. Such genetic factors include the following: Human leucocyte antigen (HLA), Single-nucleotide polymorphisms, Monogenetic syndromes, and Epigenetics. The development of AIH may occur in genetically susceptible people exposed to a number of environmental triggering factors such as viruses, including the HAV, xenobiotics, and drugs (16). Interestingly the presence of the *HLA DRB1*1301* allele has been associated with slow HAV clearance and autoantibodies expression among Brazilian and Argentinian children with hepatitis A; *HLA DRB*1301* allele, an indicator for AIH, is related with persistent liver damage after HAV infection in both pediatric and

adult patients. Further studies with adult patients with AIH from North Europe, and America identified both *HLA DRB1*1301* and *HLA DRB1*1401* as the basic susceptibility alleles (17). In Mexico, in spite of the comparatively high seroprevalence of HAV infection, there has been an association with AIH only for individuals with *HLA DRB1*0404* alleles (17). Furthermore, there are striking differences regarding the alleles *DRB1*1301* which are considered as the most frequent among white race individuals, and characterized by a remarkably low frequency in Far East and African Continent. For the latter, the most typical met alleles include *DRB1*1302* of the *DRB1*13* group (17) (Table 2).

Hepatic autoimmune manifestations linked to hepatitis A infection

Patients with acute HAV infection could also develop AIH (18,19) (Figure 1). In this respect, the HAV-related tissue injury is mediated by an intense immune response, rather than a direct HAV-related toxicity, and an uncontrolled latent stimulation of host's defense could be the main mechanism. This possible autoimmune mechanism appears to be common in both human and animal models for *Picornaviridae* (18,19).

The increasing prevalence of AIH (18,19) is combined with ongoing sporadic HAV epidemics, where HAV infection is considered as trigger of AIH (18,21-26). Reports of post-HAV infection histologically established AIH, signify that lack of normalization of liver tests after HAV should prompt concern for AIH, especially in cases with seroconversion to smooth muscle antibody positivity (19). Likewise, during post-HAV-treatment period, a recurrent increase of liver enzymes arises possibility of AIH development (27).

A perpetuating immune-mediated liver inflammation, may persist after the resolution of viral hepatitis (28). It has been hypothesized that HAV infection triggers the onset of AIH via anti smooth muscle actin- or antinuclear-antibody production. Moreover, AIH /primary biliary cholangitis variant triggered by an acute hepatitis A infection has also been reported (29). AIH can occur following vaccination with inactivated HAV, thereby further strengthening the autoimmunity hypothesis (30,31). Of note, cases of AIH are also described following anti-COVID-19 vaccination (32). Reports of HAV infection triggering other systemic immune related diseases like Guillain-Barre syndrome (33,34) and autoimmune hemolytic anemia (35), support the theory that molecular mimicry between HAV and hepatic epitopes might trigger AIH, though further research is needed to elucidate this field.

Proposed immunological features possibly involved in HAV/AIH-related tumorigenicity

HAV lacks chronicity, which is principally predisposed for progression of hepatopathies to liver cirrhosis and its complications including hepatocellular carcinoma (HCC) (2). Especially, it has to be stressed, that advanced

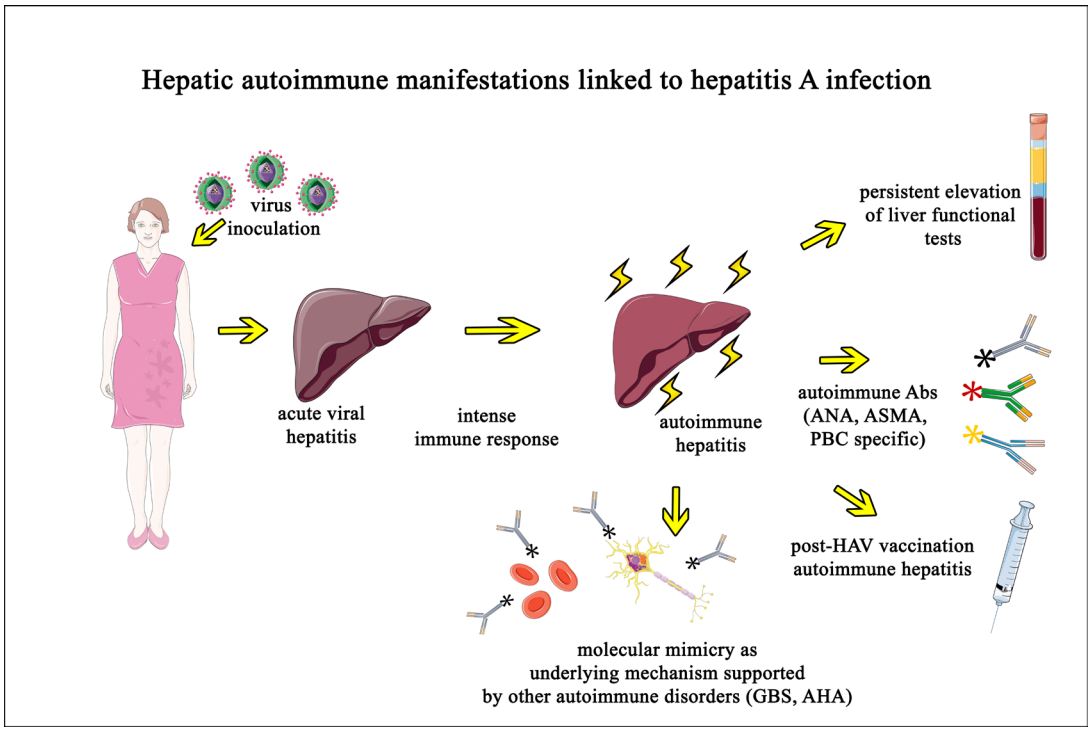

Figure 1. — Potential mechanisms involved in autoimmune hepatitis related with hepatitis A infection. Abs; antibodies, AHA; autoimmune hemolytic anemia, ANA; antinuclear antibodies, ASMA; Anti-smooth muscle actin antibodies, GBS; Guillain-Barré Syndrome, HAV; hepatitis A virus, PBC; primary biliary cholangitis.

liver disease/cirrhosis remains the principal risk factor for HCC in the context of AIH regardless of its origin. Estimates of HCC risk among patients with AIH in cohort studies have varied widely. A systematic analysis of 25 published cohorts revealed a 3.1 × 1000 patients/year incidence of HCC in patients with AIH that tripled in those patients with cirrhosis (36). HCC occurred in the same proportion of female and male patients with AIH, and was more frequent in patients who had cirrhosis at presentation or signs of portal hypertension. Other recent meta-analysis, demonstrated a higher HCC prevalence in AIH among males and Asian populations and cirrhosis at present of AIH, was also related with an augmented risk of HCC. Therefore, regular HCC surveillance appears to be recommended for patients with AIH-related cirrhosis, particularly for those in Asia (37).

Some data suggest that HAV infection could trigger antiphospholipid syndrome development and precipitation (10) and this syndrome, beyond AIH (38), is also linked with HCC manifestations (39,40). In addition, SLE, potentially triggering by HAV (11,41), apart from AIH (42), is also associated with an increased risk of tumors including HCC (43). However, the pathophysiological background of HAV-mediated tissue damage cannot be a direct and absolute risk factor for HCC, although it could play a theoretical role at least in some subpopulations possibly implying a potential contribution to HCC (44). HAV could modulate immunity that may be involved in tumor pathophysiology, though without true proof for causality. In this regard, limited data suggest that upregulated CD4(+)CD25(+)FoxP3(+) T regulatory (T-reg) cells may impair the effector function of CD8(+) T cells, promote HCC progression, and represent a potential prognostic marker for viral-related HCC patients (45). The upregulation of T-regs during acute hepatitis A, induced by bilirubin stimulated galectin-9 (GAL-9)/T cell immunoglobulin domain and mucin domain 3 (TIM-3) cascade, suppresses the cytotoxicity of CD4+ T-cells via both antiproliferative and apoptotic signals (46). Nevertheless, the GAL-9/TIM-3 pathway downregulates normal immunity and facilitates the survival of HCC malignant cells, thus consisting a potential target of future treatments (47). Moreover, human hepatitis A virus cellular receptor (HAVCR)-1, known as T-cell immunoglobulin and a mucin domain containing molecule 1 (TIM-1), beyond its role in autoimmune disorders (48,49), is implicated in oncogenic linked actions, such as cell proliferation, differentiation or dissemination events, thereby consisting an additional target for cancer therapy (50); HAVCR-1 may be involved in the pathophysiology of certain malignancies including HCC (51,52); HAVCR-1 overexpression in cancer is linked with disruption of tight junctions and malignant metastasis (53); and loss of cohesion of the tight junction structure can result in invasion and ultimately in metastasis of malignant cells (54). However, the above-mentioned considerations warrant future research to elucidate in depth their hypothetical role in HAV/AIH-related possible oncogenic process.

Extrahepatic autoimmune manifestations attributed to hepatitis A infection

Extrahepatic rheumatologic and other immune mediated disorders can develop owing to contact with the HAV (55-57). In this regard, recent data indicate that, extrahepatic autoimmune manifestations appear to increase the mortality in patients with AIH. Patients with multiple extrahepatic autoimmune manifestations exhibit a higher mortality than those with only one extrahepatic autoimmune manifestation (58).

Hepatitis A-related kidney disorders

Regarding the renal spectrum of autoimmunity, a main mechanism implicated with the pathogenesis is the formation of immune complexes with subsequent glomerulonephritis. The individuals who are more likely to be affected are men older than forty years, with diabetes mellitus, elevated inflammation markers (CRP, leukocytes) and prone to drink alcohol with respective liver biochemical profile (raised bilirubin and AST/ALT or low albumin levels). Hepatitis A may be connected with mesangioproliferative glomerulonephritis with deposits of IgM and complement components accompanied by the development of severe nephrotic syndrome, neutrophilic leukocytosis, and a reduction in the blood complement (components C3 and C4) levels. Likewise, HAV-related human mesangioproliferative glomerulonephritis may lead to deposits of all three types of immunoglobulins and C1q, resulting in the development of acute renal failure (59). Experimental infection of monkey marmosets with HAV resulted in the development of proliferative glomerulonephritis with deposits of IgM, component C3 (less frequently other immunoglobulins), and vasculitis. Moreover, the development of human IgA nephropathy in hepatitis A has also been reported. In case of a non-fulminant HAV infection with acute kidney injury, up to the half patients might necessitate renal replacement treatment (6). In this respect, while two patients with fulminant HAV infection and acute kidney injury died because of fulminant hepatic failure, one more patient required liver transplantation.

Hepatitis A-related Henoch-Schönlein purpura

Cases of hepatitis A-related vasculitis include Henoch-Schönlein purpura (60) cryoglobulinemic vasculitis, and isolated cutaneous necrotizing vasculitis. This disorder can be triggered by several factors, such as infections, medications, circulating immune complexes and environmental insults. The pathological process of Henoch-Schönlein purpura involves the skin, joints, gut and kidneys. Vasculitis develops about five weeks after the onset of the disease accompanied with a second wave of hepatitis and a protracted course (more than one month) of hepatitis.

Hepatitis A-related Cryoglobulinemia

Cryoglobulinemia, a blood dyscrasia also linked with HAV, is classified into two main subgroups: type I, which is seen in clonal hematologic diseases, and type II/III, which is called mixed cryoglobulinemia; many lymphoproliferative, infectious and autoimmune disorders have been associated with mixed cryoglobulinemia. The manifestations of type I cryoglobulinemia are often related to intravascular obstruction, whereas those seen in the mixed cryoglobulinemias often originate in true immune complex-mediated vasculitis. Cryoglobulin-associated diseases are heterogeneous, include various syndromic presentations (vasculitis is the most common), and can be associated with acute clinical syndromes with high mortality. Although it is mainly described in patients with hepatitis C and B, cryoglobulinemia is detected in high proportion of patients with hepatitis A, too (61). Cryoprecipitate is represented by IgM, including antibodies against HAV. IgA and/or IgG are also represented in the cryoprecipitate of patients. Sporadic cases with cryoglobulinemic vasculitis, in both adults or children, have been observed during acute HAV infection. These patients display biopsy-proven cutaneous leukocytoclastic vasculitis with arthritis or glomerulonephritis. Cryoglobulinemic vasculitis is induced by immune complexes-mediated inflammatory process of small-sized blood vessels and is accompanied by the activation of complements. Regarding the above-mentioned subgroups of cryoglobulinemia and based on the composition of immunoglobulins (Ig), cryoglobulinemia can be categorized into type I with monoclonal Ig (usually IgM), type II with polyclonal IgG and monoclonal IgM Rheumatoid factor (RF), and type III with polyclonal IgG and polyclonal IgM RF. Mixed types II and III can be associated by HAV infection though infrequently.

Hepatitis A-related rheumatoid arthritis

Regarding the rheumatologic issues and autoimmunity, real arthritis in hepatitis A develops within vasculitis; RF is observed in patients with relapsing hepatitis A who exhibit cryoglobulinemic vasculitis (61).

Recent studies show that several exposures of wastewater treatment plant workers to HAV could be an etiological trigger of rheumatoid arthritis; excluding infections of hepatitis B and C viruses in these workers indicates that their constant exposure to HAV owing to their recurrent contact with contaminated water could be one of the main etiological issues causing the development of rheumatoid arthritis accompanied with their constant disturbed liver function test (12).

Hepatitis A-related adult-onset Still's disease

Hepatitis A may be also linked with adult-onset Still's disease development, a multi-genic systemic auto-inflammatory disorder characterized by fever, maculopapular rash on the trunk and legs, generalized arthralgia, severe neutrophilic leukocytosis, and hyperferritinemia, effectively controlled by steroids (62). Of note, recent data indicate that new-onset adult-onset Still's syndrome can develop following COVID-19 vaccination 10.2169/internalmedicine.0590-22 (63).

Hepatitis A-related autoimmune parotitis

Unilateral autoimmune parotitis with pain and swelling in the face, generalized arthralgia, rash, and histopathological mononuclear infiltration of the affected parotid gland may develop as an extrahepatic manifestation of hepatitis A, also effectively controlled by steroids but resistant to antibiotics (63).

Hepatitis A-related autoimmune polymyositis

Hepatitis A might also associate with the development of polymyositis, an autoimmune connective tissue disease, characterized by myoglobinuria, increased creatine kinase activity and electromyographic alterations demonstrated by muscle biopsy (64).

Hepatitis A-related SLE

HAV-related cryoglobulinemia might also trigger the development of SLE (11,41) an autoimmune connective tissue disease, connected with AIH (42). Hepatitis A-related lupus-like syndrome development is characterized by symmetrical arthralgia in the wrists, metacarpophalangeal and proximal interphalangeal joints, left-sided pleurisy, Lupus cells, and antinuclear antibodies, antibodies against double-stranded deoxy-ribonucleic acid, and cardiolipin (41). However, beyond others disorders, such a loose connection with SLE warrants further investigation for clarification.

Hepatitis A-related antiphospholipid syndrome

Hepatitis A appears to induce secondary antiphospholipid syndrome accompanied by neurological plus ophthalmological manifestations (10). Antiphospholipid syndrome is a multisystemic autoimmune hypercoagulable disorder characterized by the appearance of thrombosis (principally deep vein thrombosis and stroke) and obstetric morbidity (clinical criteria) in patients with persistently high levels of antiphospholipid antibodies (aPL). Antiphospholipid syndrome is divided into 3 forms: primary antiphospholipid syndrome, linked with another autoimmune disease (such as SLE), and catastrophic antiphospholipid syndrome, characterized by the induction of thrombosis in diverse locations in a short period of time, leading to a systemic coagulopathy with a high mortality rate, a condition quite similar to coagulopathy owing to COVID-19. In this respect, relative data indicate that patients with cryoglobulinemic

vasculitis display concomitantly clinical characters of antiphospholipid syndrome. Moreover, the association of severe or catastrophic antiphospholipid syndrome with cryoglobulinemia should be evaluated by clinicians who treat patients with multi-organ ischemia or necrosis. It is recommended to ruling out the occurrence of antiphospholipid syndrome in patients with cryoglobulinemic vasculitis recalcitrant to the regular treatment and vice versa. Remarkably, primary biliary cholangitis – AIH overlap syndrome may be associated with antiphospholipid syndrome. A relative meta-analysis showed that primary biliary cholangitis, AIH, and primary sclerosing cholangitis are significantly associated with aPL positivity with a trend of a higher prevalence of thrombotic complications in AIH patients with aPL than in those with AIH alone (38).

Hepatitis A-related hematological manifestations

Regarding the hematological manifestations, beyond aplastic anemia, and red cell aplasia, autoimmune hemolytic anemia has also been attributed to HAV infection. For the diagnosis, a proof of autoantibodies against red blood cells by utilizing a direct antiglobulin test, is necessitated. A common accompanying finding is the reactive reticulocytosis. The patients respond usually well under glucocorticoids (65,66). Moreover, immune-mediated thrombocytopenia in HAV infection is a further known hematological manifestation. Likewise, the mechanism is yet to be unraveled; it is thought, however, to be either a consequence of bone marrow depression, or of immune-mediated peripheral destruction of thrombocytes due to anti-platelet antibodies existence or even circulating immune complexes or their raised consumption (13). Furthermore, HAV may be complicated by both autoimmune hemolytic anemia and pancytopenia.

Hepatitis A-related ophthalmological disorders

Concerning the ophthalmological pathologies associated with HAV infection, uveitis is an acknowledged manifestation which is depended upon gender, age as well as histopathological/anatomical particularities. Uveitis may be appeared before the symptoms of hepatitis A and bilateral granulomatous anterior uveitis following hepatitis A infection may occur in immunocompetent setting. The anterior uveitis is believed to be immune-mediated by deposition of immune complexes (conjugated antigen-antibody) and activation of complement pathway secondary to systemic viremia. The course after topical steroid therapy is usually favorable. A further relevant known association between HAV and ocular anatomy is the post-vaccination (simultaneously injected formalin inactivated HAV and live attenuated yellow fever virus) onset of the so-called multiple evanescent white dot syndrome (classified as an inflammatory chorio-retinal disorder). It is hypothesized that the action is mediated also via a not well elucidated autoimmune mechanism (8).

Hepatitis A-related Guillain-Barré syndrome

Regarding the neurological pathologies associated with HAV infection, Guillain-Barré syndrome is connected with HAV infection (33,34), as a post-infection immune-mediated disorder. The causative infectious agent is usually bacterial or viral with the most common causes being *Campylobacter jejuni*, influenza virus, Ebstein-Barr virus or cytomegalovirus infections. Guillain-Barré syndrome may also be caused by *Helicobacter pylori* infection and hepatitis A; it is preceded by an acute hepatitis A infection; and acute inflammatory demyelinating polyneuropathy, the most common variant of Guillain-Barré syndrome in the United States and Europe, also seems to follow acute hepatitis A infection.

The clinical characters of Guillain-Barré syndrome following hepatitis A include: a) less than 14 days interval between the onset of hepatitis and the development of neuropathic symptoms, b) frequent association with facial nerve palsy, c) frequent impairment of joint position and vibratory sense along with superficial sensation, and d) appropriate outcome of the neuropathic symptoms, which is independent of alanine aminotransferase concentration linked with hepatic dysfunction severity.

The pathogenesis HAV-related Guillain-Barré syndrome is unidentified. Although the exact trigger of Guillain-Barré syndrome is unknown and a specific immunological explanation has not been noticed, it is possible that immune responses directed towards the infecting organisms are involved in the pathogenesis of Guillain-Barré syndrome by cross-reaction with neural tissues. The infecting microorganism induces humoral and cellular immune responses that, because of the sharing of homologous epitopes (molecular mimicry), cross-react with ganglioside surface components of peripheral nerves. Molecular mimicry of host structures by the saccharide portion of lipopolysaccharides of the gastrointestinal pathogens *Campylobacter jejuni* and *Helicobacter pylori* are thought to be connected with the development of autoimmune sequelae observed in Guillain-Barré syndrome. Specifically, *Helicobacter pylori* infection may contribute to the pathophysiology of both acute inflammatory demyelinating polyradiculoneuropathy and axonal types of Guillain-Barré syndrome (66). *Helicobacter pylori* might also induce humoral and cellular immune responses that, because of the sharing of homologous epitopes with host antigens (ie, molecular mimicry), cross-react with the mentioned ganglioside surface components of peripheral nerves; it may connected with involvement of the proximal parts of peripheral nerves and advanced clinical status in acute inflammatory demyelinating polyneuropathy; and *Helicobacter pylori* infection might influence the pathophysiology of Guillain-Barré syndrome via several other mechanisms, including the release

of proinflammatory and vasoactive substances (eg, cytokines or eicosanoids), induction of oxidative stress and/or apoptotic processes. Likewise, hepatitis A, similar to other infections preceding acute inflammatory demyelinating polyneuropathy, is thought to induce a dysregulated immune response against myelin, a result of cross-reactivity and molecular mimicry; while it is required to conduct precise epidemiological evaluations to distinguish the correlation between hepatitis A and Guillain-Barré syndrome, it is suggested that this infection displays a molecular mimicry as shares cross reactive epitopes, which in turn cross reacts with Schwann cells, myelin, or other peripheral nerve antigens (67).

Hepatitis A-related cardiovascular disorders

Regarding cardiovascular pathologies, there are confined case reports describing an association between HAV infection and acute myocarditis. Although the mechanism remains still unknown, an immune response to infiltration of myocardial cells through the virus, of which distinct viruses may have a more potent cardiotropic behavior (57). In addition, subacute infective endocarditis could occur following dengue and hepatitis A coinfection, particularly between patients with rheumatic heart disease. Hepatitis A may be also associated with child's Kawasaki disease. Moreover, an association of the mentioned hepatitis A virus cellular receptor 1 gene (*HAVCR1*; also known as *TIMD1*) and lipid metabolism might represent a risk for coronary heart disease and ischemic stroke (68).

Conclusion

Hepatitis A infection is a generally self-limited infection without systematic impact. Nevertheless, in a subgroup of patients with immune system vulnerability and genetic predisposition, it could trigger an autoimmune cascade of perpetual systematic or intrahepatic inflammation, thus generating autoimmune disorders. Recognizing those patients and decrypting the exact pathophysiology is the mainstay for a clinical interpretation of those findings, to guide additional prophylactic measures, raise awareness and suggest any post-infection follow up.

Conflict of interest

The authors declare no conflict of interest.

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