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Impact of hepatitis B and C virus on chronic spontaneous urticaria; potential pathogenic triggers and aggravating factors

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ABSTRACT

Chronic urticaria (CU) is a common dermatological condition characterized by persistent wheals lasting more than six weeks. Chronic spontaneous urticaria (CSU), the most prevalent CU subtype, significantly impairs patients' quality of life. Although its precise pathogenesis remains unclear, current evidence implicates multiple factors including immune dysregulation, stress, certain medications, and viral infections in its development and exacerbation. Among infectious triggers, hepatitis B (HBV) and C (HCV) viruses have emerged as potential CSU inducers. These viruses may trigger urticarial symptoms through various mechanisms, particularly immune system activation and cutaneous inflammatory responses. While the exact pathogenic pathways require further elucidation, clinical evidence suggests antiviral therapy may occasionally improve urticarial symptoms. Standard management of virus-associated CSU involves second-generation antihistamines as first-line treatment. For refractory cases, targeted therapies like omalizumab may be considered. Notably, successful HCV eradication has in some cases led to significant CSU improvement, an effect less frequently observed with HBV treatment. This study investigates the association between hepatitis infections and CSU, focusing particularly on elucidating how HBV and HCV could contribute to CSU pathogenesis.

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1. Introduction

Chronic urticaria (CU) is a dermatological condition characterized by the presence of wheals (hives) in superficial dermis, angioedema in lower dermis and subcutis, or both for at least 6 weeks [1-3]. CU can be categorized into two subtypes depending on whether certain causal factors are present or absent as either chronic spontaneous urticaria (CSU), where no external trigger is known, or chronic inducible urticaria, when a definable trigger is known [4,5].

CSU, the most prevalent subtype of CU, accounting for almost two-thirds of all CU cases, has a major and serious effect on the individual's quality of life [6-8]. Autoimmune processes are thought to be the primary pathophysiology that causes cutaneous basophil and mostly mast cell (MCs) activation, which results in degranulation mediators in CSU. However, multiple factors have been associated with CSU pathogenesis including stress, food, pharmacological agents, vaccination, and even various infectious processes [9,10].

Viral infections, including herpes viruses (HHV-4, HHV-6), norovirus, human immunodeficiency virus, Coronavirus disease 2019, viral hepatitis particularly hepatitis C virus (HCV) and hepatitis B virus (HBV), are probable comorbidities and potential causes of CU, particularly CSU [11]. Considerable impact on morbidity and provide significant challenges to global health, particularly regarding HBV and HCV [12,13]. Multiple types of hepatic and extrahepatic tissue damage are caused by chronic HBV and HCV infections, which also have been correlated with CSU comorbidities[14,15].

Clinical management of CSU associated with viral hepatitis demonstrates differential therapeutic responses. While HCV eradication frequently leads to significant urticaria improvement, therapy for HBV typically shows minimal effect on CSU activity [16]. CSU is a prevalent dermatological condition whose underlying causes often remain unknown. Despite recent improvements in identifying several triggering and exacerbating factors, including microorganisms like hepatitis viruses, especially HBV and HCV, the role and mechanistic impact of these pathogens on the development and severity of CSU have seldom been examined. Furthermore, given the lack of definitive treatment for CSU, the detection and eradication of underlying infections and comorbidities play a crucial role in disease progression. The scarcity of data in this field not only poses challenges in disease management and therapy but also contributes to affecting the quality of life for patients. This study aims to achieve a more profound understanding of the mechanisms involved in CSU by examining the role and impact of HBV and HCV in its development and exacerbation. Additionally, the findings may contribute to more accurate diagnosis and the development of effective therapeutic strategies for CSU.

2. Structure and genome of HBV and HCV

2.1 HBV

HBV infection constitutes a persistent worldwide public health concern, generating substantial disease-related morbidity and socioeconomic impacts [17]. HBV is a hepatotropic DNA virus that belongs to the Hepadnaviridae family, which spreads through contact with infectious body fluids, including blood or mucosal contact. Thus, sexual transmission, nosocomial transmission, and vertical transmission (mother-to-child) are common modes of transmission [18,19]. The HBV genome consists of relaxed circular DNA (rcDNA), which is partially double-stranded and replicated via pre-genomic RNA (pgRNA). All HBV transcripts are produced using covalently closed circular DNA (cccDNA), which is formed from rcDNA present in the nucleus of infected hepatocytes [20]. This virus has a compact genome containing four open reading frames (ORFs), including P (Polymerase), S (Surface), C (Core), and X, each of which encodes different proteins essential for the viral life cycle and pathogenesis[21,22]. The ORF's P region encodes HBV polymerase (POL), S region encodes HBV surface antigens (HBsAg), the C region encodes for HBV e Antigen (HBeAg) and HBV core protein (HBc), and the X region encodes for HBV regulatory X protein (HBx) [23]. The viral envelope is made up of multiple proteins and a lipid bilayer. The envelope proteins consist of three distinct HBsAg forms, including small (S), medium (M), and large (L), which enable the virus to enter host cells. The viral capsid, which is made up of the HBc, is the surface of the viral core, and it is necessary for viral replication and genome packing. The core harbors the DNA along with the POL and multiple core-derived proteins, notably the HBeAg [22,24].

2.2 HCV

HCV represents a major global health challenge, impacting significant populations across the world with distinct geographical prevalence patterns [25]. HCV is an enveloped virus belonging to the Flaviviridae family, which spreads through contact with contaminated blood or infected bodily fluids. Vertical transmission (mother-to-child), sexual intercourse, unsafe blood exposure, and injection-related risks are major routes of HCV infection [26, 27]. This virus possesses a positive-sense and single-stranded RNA (ssRNA) genome containing a single ORF, which encodes a large polyprotein consisting of more than 3000 amino acids [28]. Cleavage of the HCV polyprotein results in the production of seven non-structural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B) and three structural proteins (core, E1, and E2 glycoproteins). Polyprotein maturation, genome replication, virion assembly, and the inhibition of host antiviral defenses all depend on these viral components [29]. The RNA

genome and multimeric core proteins, are found in the nucleocapsid that is surrounded by an envelope with a lipid bilayer that contains two envelope glycoproteins (E1 and E2)[30].

3. HBV and HCV in relation to CSU

HBV and HCV infections of liver cells can trigger a spectrum of hepatic diseases, ranging from acute hepatitis (AHB/AHC) to chronic hepatitis (CHB/CHC), which may progress to severe liver complications including fibrosis, cirrhosis, and ultimately hepatocellular carcinoma [31,32]. These viral hepatitis infections may increase susceptibility to diverse extrahepatic complications, notably systemic inflammatory conditions, neurological sequelae, autoimmune dysregulation and even dermatologic manifestations including purpuric eruptions, lichen planus, and CSU [15,33]. The association between CSU and viral hepatitis has been understood for decades [34]. Epidemiological studies indicate that CHB markers are present in fewer than 5% of CSU cases, while CHC markers are found in approximately 2% of patients [35].

4. CSU appearance and aggravation mechanisms

4.1 Biological mechanisms underlying the development of CSU

The pathophysiology of CSU is mostly attributed to the activation and degranulation of basophils and particularly MCs, which increases vascular permeability and irritates nerve endings due to the release of preformed mediators [36,37]. Autoimmunity (mostly), coagulation, inflammation, circulating immune complexes (CICs) that mediate complement activation, intracellular signaling pathways disruption within MCs, and even the existence of the microorganism in the skin can all contribute to degranulation MCs that results in pathogenesis CSU [36,38]. Following processing antigens by dendritic cells (DCs), they are given to CD4+ T cells (cluster of differentiation), which stimulate CD4+ Th2 cells to release cytokines including interleukin (IL)-4, IL-5, and IL-13. When naïve mature B cells that produce IgM and IgD antibodies engage with these cytokines, the antibody class shifts from IgM to IgE [39,40]. There are two main types of MCs degranulating autoimmune signals that are known to exist. Type I autoimmune (Autoallergy, TIaiCSU) is based on the presence of autoantigens in the skin, such as IL-24, thyroid peroxidase (TPO), and thyroglobulin (TG) that can form a complex with IgE and bind to FcεRI, activating MCs. In type IIb autoimmune (TIIbaiCSU) response, IgG also perhaps IgM and IgA activate MCs by binding to FcεRI or IgE cross-linking FcεRI [35,41,42]. FcεRI activation starts a cascade of intracellular signals in MCs, all of which leads to the release of mature mediator granules by an exocytosis process called degranulation [43]. Furthermore, some other significant mechanisms have also been discovered, all of which are implicate in MCs activation and degranulation. Besides Toll-like receptors [40,44], G protein-coupled receptors (GPCRs), such as mas-related G protein-couples receptor member X2 (MRGPCRX2) which is highly expressed in skin MCs of individuals with CSU, binds to neuropeptides such substance P (SP) and cortistatin (CST) [45,46]. Another type of GPCR is protease-activated receptor (PAR), which is triggered by serine proteases including trypsin, tryptase, and active coagulation factors [47]. Additionally, complement component 3a receptor (C3aR) and C5aR are recognized as MCs receptors that bind to anaphylatoxin C3a and C5a that produced in classical pathway of the complement system which may be activated by IgG_1 and IgG_3 [44,47]. Produced mediators such histamine, proteases, prostaglandin D2 (PGD2), cysteinyl leukotriene C4 (LTC4) and platelet-activating factor are released instantly upon MCs degranulation [48,49]. Furthermore, MCs release proinflammatory cytokines/chemokines like IL-4, IL-5, IL-6, IL-8/ CXCL8, IL-13, IL-17, IL-25, IL-31, IL-33, and nerve growth factor (NGF), as well as tumor necrosis factor α (TNFα) and vascular endothelial growth factor (VEGF), all of which may be directly or indirectly linked to the onset of urticarial wheals [50,51]. These mediators trigger the sensory nerve ends, stimulate vascular permeability and vasodilation, infiltrate inflammatory cells such as T lymphocytes (mostly Th2), monocytes, eosinophils, basophils, and neutrophils to the skin's superficial dermis through the veins. These permeabilizing agents cause skin irritation, redness, and swelling that promote the formation of urticarial wheals [52-54].

4.2 Impact of HBV and HCV in stimulation and aggravation of CSU

Hepatitis B and C hepatotropic viruses may influence urticaria onset and symptom progression through several potential mechanisms, including direct viral induction of MCs mediator release. One other potential effects of viral hepatitis on development of CSU has also been identified as the release of antigens from infected hepatocytes [34]. The endogenous protein Factor V (protein FV), which is produced by the human liver, could be increased during viral hepatitis and activate human MCs and basophils [55]. The FV protein exhibits super allergenic properties through two interconnected immunopathological pathways. First, it directly binds the VH3 (variable domain of heavy chain) domain of IgE, facilitating FcεRI receptor cross-linking on MCs and basophils, which triggers immediate degranulation and histamine release. Second, FV stimulates basophils to produce IL-4 and other cytokines, thereby promoting IgE class-switching in B lymphocytes and establishing a positive feedback loop that perpetuates allergic sensitization through elevated

serum IgE titers [55-57]. Beyond direct viral effects, liver-derived components in chronic hepatitis infections, particularly CICs containing HBV/HCV antigens, represent significant contributors to CSU pathophysiology. These antigen-antibody complexes initiate a cascade of complement activation through the classical pathway, resulting in anaphylatoxin C3a and C5a generation. These inflammatory compounds trigger MCs activation by binding to specific surface receptors, causing the release of histamine and other mediators [58]. Viral hepatitis may contribute to CSU pathogenesis through macrophage functional impairment, which disrupts physiological immune complex clearance, resulting in vascular deposition and subsequent complement activation through the classical pathway. This process generates anaphylatoxins that bind cognate receptors on MCs and leads to degranulation[34,59]. Furthermore, elevated bile acid levels in viral hepatitis patients may exacerbate urticarial symptoms through activation of MCs [60,61]. Moreover, hyperbilirubinemia due to HBV and HCV may contribute to urticarial pathogenesis [62] (Figure 1).

5. Therapeutic strategies for hepatitis-induced CSU

CSU imposes a significant burden on quality of life and economic impact, necessitating prompt and effective treatment strategies [63]. The diagnosis of CSU primarily relies on detailed history-taking and physical examination, as most cases are autoimmune-driven rather than triggered by external factors, and extensive laboratory testing is typically unnecessary. Consequently, routine screening for viral hepatitis in CSU patients is not advised, given its low diagnostic yield and poor cost-effectiveness. However, in rare instances where clinical symptoms such as abnormal liver function tests, signs of viral hepatitis infection, or other relevant features are present, targeted testing may be warranted based on physician judgment [15,64]. However, effectively treating CSU remains clinically challenging, with the ultimate goal being complete symptom relief, whether through targeting the underlying cause or managing symptomatic manifestations [65,66]. Furthermore, concurrent infections and other comorbidities complicate disease management and worsen prognosis. Thus, therapeutic management becomes particularly challenging, as these interrelated conditions may influence each other [35]. Therefore, initial therapeutic focus should target identification and elimination of pathogenic triggers, followed by comprehensive disease and symptom control in subsequent phases [34,67]. Standard treatment of CSU involves three routine steps, first-line therapy begins with standard-dose of second-generation H1 antihistamine monotherapy. For inadequate responders, the second step involves increasing the dose of antihistamines up to four-fold higher, while the third step incorporates add-on therapies including leukotriene receptor antagonists, corticosteroids, omalizumab (anti-IgE), cyclosporine, or other immunomodulators, following evidence-based stepwise protocols for optimal disease control [68,69].

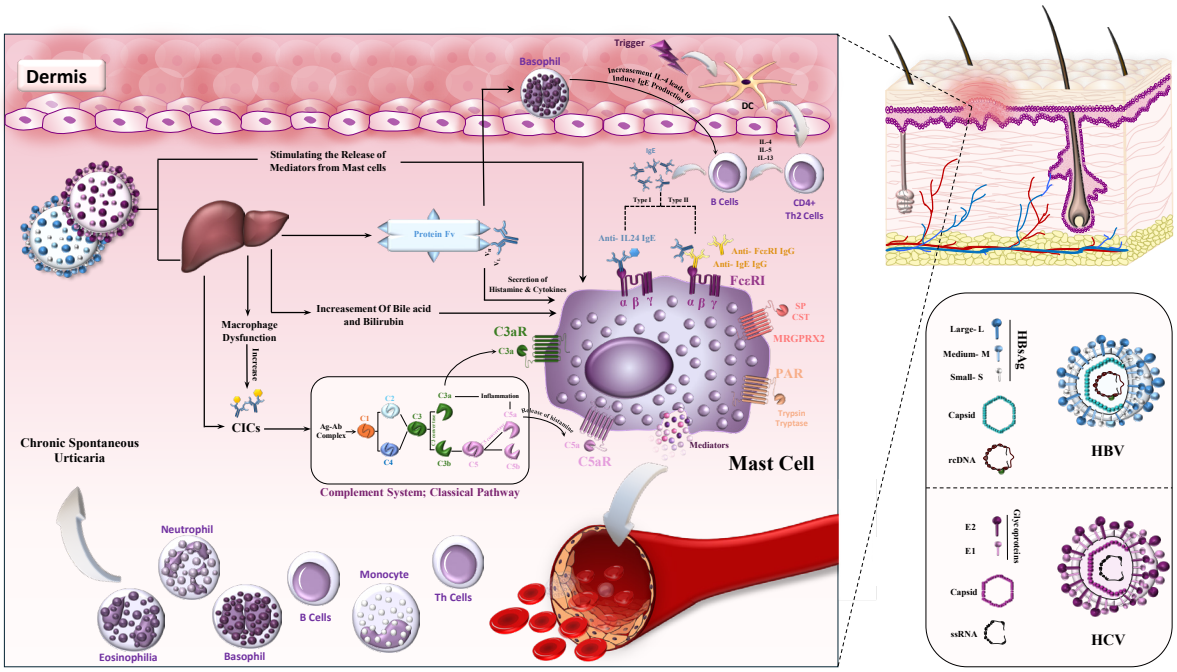

Figure 1. Biological mechanisms in CSU pathogenesis and exacerbation highlighting the immunomodulatory role of HBV and HCV on MCs activation. The pathogenesis of CSU primarily occurs through cutaneous MCs degranulation and subsequent release of inflammatory mediators into the dermal vasculature. This process can be triggered through various mechanisms, ultimately exacerbating CSU symptoms. HBV and HCV represent potential contributing factors that may influence CSU severity through multiple pathways, including direct viral effects, complement system activation via CICs leading to anaphylatoxin accumulation, superantigen production, and alterations in bile acid and bilirubin metabolism.

Research shows limited effectiveness of antiviral hepatitis treatment for CSU, with only occasional cases showing improvement [15]. According to the published report, in a patient with a history of HCV infection who developed CU following HCV reactivation after antiviral treatment, the use of antihistamines along with omalizumab resulted in significant improvement without adverse effects or worsening of the infection and both the urticaria and the patient's quality of life improved dramatically. Therefore, omalizumab appears to be an appropriate therapeutic option for treatment-resistant CU cases comorbid with HCV infection [63]. However, there are limited documented cases of CSU resolving following HBV treatment, unlike HCV, where antiviral therapy has shown clearer associations with CSU remission in some patients [70]. Given its efficacy, omalizumab represents a promising therapeutic option for CSU patients with concurrent hepatitis B or C infection, particularly in cases refractory to conventional treatments [71].

6. Conclusion

Although current scientific evidence has not yet fully elucidated the precise relationship between HBV, HCV and CSU, multiple studies indicate the potential role of these viruses in both the onset and exacerbation of disease symptoms. The probable mechanisms of this effect include direct MCs stimulation through viral superantigen secretion, immune complex formation with subsequent complement system activation, and pathological alterations in bile acid and bilirubin levels. Given the significant negative impact of CSU on patients' quality of life, timely diagnosis and comprehensive disease management are of critical importance. Particularly for patients showing inadequate response to standard therapies, screening for hepatitis infections appears essential. When such infections are confirmed, antiviral treatment and viral eradication may lead to alleviation of cutaneous symptoms and improvement in disease courses. However, to achieve a more thorough understanding of the pathophysiological relationships between these viruses and CSU, as well as to establish optimal treatment protocols, more extensive and precise research efforts remain imperative.

Authors' contributions

Conceptualization and Idea: AJS, MP; Data collection or Processing: AJS, SKZ, SMM; Writing-Review and Editing: SKZ, SMM, MP; Figure design: SKZ, SMM; Supervision and Resource: AJS, MP. All authors read and approved the final version of manuscript.

Conflict of interest

The authors declare that they have no conflicts of interest.

Ethical declarations

Not applicable.

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