

Comorbidity of viral hepatitis and chronic spontaneous urticaria: A systematic review

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Abstract

Chronic viral infections including those by hepatitis B (CHB) virus and hepatitis C (CHC) virus have been reported to be comorbidities of chronic spontaneous urticaria (CSU). Here, we performed the first comprehensive review of the peer-reviewed literature (PubMed, Web of Science and Google Scholar) on the prevalence of CHB and CHC in patients with CSU and vice versa. The prevalence of CHB and CHC in CSU does not appear to be increased. Less than 5% and 2% of patients with CSU have markers of CHB and CHC, respectively, according to most of the 32 studies reviewed. Urticarial rash including CSU occurs in $\leq 3\%$ of patients with CHC as reported by most of 20 studies analysed. Very few patients have been assessed for the effects of antiviral hepatitis treatment on their CSU, and two but not all reportedly showed improvement. Hepatitis B/C infections appear unlikely to be linked to CSU. We suggest that routine screening for these infections in patients with CSU is not relevant or cost-effective and should not be performed unless liver function tests are abnormal, risk factors or symptoms of viral hepatitis are present, or urticarial vasculitis is suspected.

KEYWORDS

chronic spontaneous urticaria, HBV, HCV, review, viral hepatitis

1 | INTRODUCTION

Chronic spontaneous urticaria (CSU), a mast cell-driven disease that lasts for >6 weeks and several years on average, occurs in 0.5%–1% of the population, especially in middle-aged female patients.^{1–3} Autoimmune and infectious diseases including viral hepatitis have been reported to be relevant comorbidities of CSU.^{4–7} Hepatitis A, B, C, D and E viruses (HAV, HBV, HCV, HDV and HEV) are responsible for most cases of viral hepatitis, whereas most of the morbidity and mortality is caused by chronic hepatitis B (CHB) and C (CHC).⁸ According to a recent WHO report, the worldwide prevalence of CHB and CHC is 0.5%–6.2%.⁸ Unlike hepatitis A, CHB and CHC can result in chronic disease, long-term liver damage and cutaneous manifestations.^{9,10}

Abbreviations: CHB, chronic hepatitis B; CHC, chronic hepatitis C; CICs, circulating immune complexes; CSU, chronic spontaneous urticaria; GBV-C, hepatitis G virus; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus.

Kolkhir and Pereverzina equally contributed to this study.

It is now more than 150 years since Graves for the first time described urticaria in a patient with viral hepatitis.^{11,12} In 1983, Vaida and coworkers reportedly observed markers of CHB in 17.6% of patients with chronic urticaria. They suggested that the frequency of current and previous HBV infection is several times higher than reported in the general population and that HBV may be causally related to urticaria.⁶ Since then, several studies have linked CHB and CHC to CSU. Here, we performed the first comprehensive review of the peer-reviewed literature summarizing the prevalence of hepatitis, primarily CHB and CHC, in patients with CSU and vice versa. We also discuss possible mechanisms for a causal and pathogenic association between viral hepatitis and CSU.

2 | MATERIALS AND METHODS

2.1 | Search strategy

A PubMed, Web of Science and Google Scholar search were performed with the keywords “urticaria” and “hepatitis”, “HBsAg”, “HAV”,

"HBV", "HCV", "HDV", "HEV", "HGV" and "GBV-C" to find studies that addressed the following questions: (i) What is the prevalence of CHB and CHC in CSU patients? (ii) What is the prevalence of urticarial rash in patients with viral hepatitis? (iii) Does the treatment of viral hepatitis lead to CSU improvement or remission? (iv) What is a possible pathogenic relationship between viral hepatitis and CSU?

2.2 | Study selection criteria

A study was considered eligible for the systematic review if: (i) it included ≥ 10 CSU patients. In our analyses, we excluded cases of acute and inducible urticaria as well as urticarial vasculitis whenever possible. However, not all studies clearly differentiate between acute and chronic urticaria (the term "urticarial rash" was used) or between chronic spontaneous urticaria, chronic inducible urticaria and/or urticarial vasculitis (the term "chronic urticarial rash" was used). Therefore, we did not exclude these studies, but included this information in the tables' legends; (ii) it was prospective or retrospective study; and (iii) it reported a number of CSU patients with hepatitis or number of patients with urticarial rash in hepatitis patients.

The following exclusion criteria were applied: (i) nonrelevant studies, for example, studies which did not include patients with CSU (Table 1) or patients with urticarial rash (Table 2) and (ii) case reports and studies with < 10 patients. However, we included case reports where treatment of viral hepatitis can lead to CSU remission in Table 3.

2.3 | Data extraction

Two reviewers (PK and NP) independently identified and evaluated 554 reports published prior to December 2017, of which 516 were excluded from further analysis after review of titles and/or abstracts including four duplicate studies from the same authors in the same patient groups (Figure S1). Reference lists were searched, and 15 additional studies were included in the review. In total, 53 reports were used for analyses and included in Table 1 ($n = 32$, prevalence of CHB and CHC in patients with CSU), Table 2 ($n = 20$, prevalence of urticarial rash in CHC) and Table 3 ($n = 4$, efficacy of antiviral hepatitis treatment on CSU).

The following information was extracted from each study: the first author, published year, region of study population, and age and number of patients. The heterogeneity of the data in different studies may be due to differences in study design and patient populations, as well as the duration of the follow-up period.

Chronic hepatitis B was diagnosed if the patient was HBsAg-positive. The diagnosis of CHC was made if anti-HCV and/or HCV RNA were detected. Very few studies reported the numbers of HBsAg- and anti-HCV-positive CSU patients without indicating if patients had chronic and/or active hepatitis at the time of the study.

2.4 | Data analysis

We could and did not conduct a meta-analysis and use the statistical methods because of the heterogeneity of the data. Data were

analysed using a descriptive approach. We evaluated the prevalence of hepatitis in patients with CSU and the prevalence of urticarial rash in hepatitis patients based on values as reported. The term "remission" was used when the CSU disappeared completely during and/or after ≤ 3 months after the initiation of antiviral treatment. Antiviral therapy was regarded as not effective if no improvement in CSU symptoms was seen during or after the treatment.

3 | RESULTS

3.1 | Less than 5% and 2% of patients with CSU have hepatitis B and C, respectively, as reported by most studies

A total of 32 independent studies on a total of 5014 patients with CSU in 16 different countries reported on the prevalence of CHB and/or CHC, most of them investigated both (Table 1). CHB was reportedly found in 0%-30% of patients with CSU ($\leq 5\%$ in 17 of 21 studies). CHC was reported in 0%-25.8% of patients with CSU ($\leq 2\%$ in 21 of 28 studies). CHB or CHC was detected in at least one patient with CSU in 18 and 16 studies, respectively. Three and 12 studies found none of the patients with CSU investigated to have CHB and CHC, respectively. Most studies on the rate of CHB and/or CHC in CSU were performed in Turkey ($n = 9$), Thailand ($n = 3$), France ($n = 3$) or Pakistan ($n = 3$). CHB serological markers were similar in patients with chronic urticaria compared to rates observed in the general Turkish population.¹³⁻¹⁵ CSU was not significantly associated with HBsAg positivity as compared to a control group in some,^{16,17} but not all studies.¹⁸

In three studies, the prevalence of HAV ranged from 0% (two studies) to 8.3% (one study).^{16,19,20} The prevalence of hepatitis G virus (GBV-C), in one study, was 1.8%.²¹ We did not find any reports on the prevalence of hepatitis D and E in patients with CSU.

3.2 | Less than 3% of patients with hepatitis C have urticarial rash including CSU as reported by most studies

In 20 independent studies, the prevalence of urticarial rash in patients with CHC ranged from 0% to 14.8% (Table 2). Thirteen of these studies reported urticarial rash rates of 3% or less. Most studies came from Pakistan ($n = 6$), Italy ($n = 4$) and France ($n = 3$).

The prevalence of urticaria in patients with acute hepatitis A was 1.5% as evaluated by one study.²² We did not find any reports on the prevalence of urticaria in patients with HBV, HDV, HEV or GBV-C infection.

3.3 | Treatment of hepatitis C might lead to CSU remission in individual patients

In two of nine patients from different studies, the treatment of hepatitis C likely improved CSU or lead to urticaria remission associated with a negative viral load. In three studies, therapy of HBV (16

TABLE 1 Prevalence of chronic hepatitis B and C in patients with CSU

First author	Year	Age of patients, years	n, patients with CSU	% (n), patients with CHC	% (n), patients with CHB	Design	Country
Dionigi ⁴¹	2016	>17	100	1 (1)	2 (2)	P	Brazil
Chuamanochan ²³	2016	>17	184	0 (0)	13.3 (8)	R	Thailand
İnci ¹⁴	2015	>17	56 ^a	0 (0)	3.5 (2)	R	Turkey
Colgecen ⁴²	2015	>4	369 ^a	1.6 (6)	3.8 (14)	R	Turkey
Dinu ⁶⁶	2014	-	168	2.4 (4)	5.3 (9)	P, CC	Romania
Zhong ³³	2014	>17	1845	-	2.7 (35)	P, CS	China
Kibsgaard ⁶⁷	2014	>5	15	-	0 (0)	CS	Denmark
Tak ³⁰	2013	>7	40 ^a	5 (2)	-	P, CC	Turkey
Rahman ⁶⁸	2012	>7	77 ^{a,b}	7.8 (6)	-	R	Pakistan
Al-Duliami ⁶⁹	2012	>4	36 ^a	0 (0)	-	R	Iraq
Halawani ⁷⁰	2012	>17	70 ^a	7.1 (5)	2.9 (2)	P, CC	Saudi Arabia
Bhatt ¹⁷	2011	>15	70 ^a	0 (0)	2.8 (2)	P, CC	India
Köse ⁷¹	2011	>20	140 ^a	1.4 (2)	4.3 (6)	R	Turkey
Chen ¹⁸	2009	>8	150	-	19.3 (29)	CC	China
Malik ³⁴	2008	>11	45	11.1 (5)	4.1 (2)	P, CC	Pakistan
Kulthanan ⁵	2007	>14	337	3.0 (10)	4.2 (14)	R	Thailand
Buss ²⁰	2006	>17	300 ^a	0 (0)	1.7 (5)	R	Germany
Pongpreuksa ²⁴	2004	>3	38	0 (0)	2.6 (1)	R	Thailand
Sackesen ¹⁹	2004	-	17	0 (0)	0 (0)	P	Turkey
Ahmed ⁷²	2003	>10	114	13.2 (15)	-	P	Pakistan
Tousi ²⁵	2002	>6	40 ^a	0 (0)	-	P, CC	UK
Zauli ²⁹	2001	-	115	0.8 (1)	-	CC	Italy
Arinkal ³¹	2001	>4	55	7.3 (4)	-	R	Turkey
Erel ¹⁵	2000	>17	50 ^a	0 (0)	30 (15)	-	Turkey
Bilen ²⁶	1999	>8	34	0 (0)	2.9 (1)	CC	Turkey
Cribier ²¹	1999	>18	110	0.9 (1)	-	CC	France
Llanos ²⁸	1998	>4	148 ^a	≤2 (≤3)	-	R	France
Doutre ⁷³	1988	-	50 ^a	2 (1)	-	-	France
Gül ¹⁶	1998	>19	50 ^a	0 (0)	6 (3)	CC	Turkey
Smith ²⁷	1997	-	50	0 (0)	-	R	UK
Kanazawa ⁷	1996	>17	58 ^a	25.8 (15)	0 (0)	P, CC	Japan
Vaida ⁶	1983	>18	83	-	2.4 (2)	P	USA

-, no data, not defined in the paper or in the abstract; CC, case-control study; CHB, chronic hepatitis B; CHC, chronic hepatitis C; CS, cross-sectional study; CSU, chronic spontaneous urticaria; P, prospective study; R, retrospective study.

^aIt is not clear from the paper whether patients with chronic urticarial vasculitis and/or chronic inducible urticaria were excluded.

^bIt was not defined in the paper whether patients with acute urticaria were excluded.

patients) or HCV (7 patients) infection was not effective in reducing CSU disease activity (Table 3).

4 | DISCUSSION

The results of our systematic review indicate that patients with CSU do not show increased rates of CHC and/or CHB. In most studies analysed, the prevalence of CHC and CHB was ≤2% and ≤5% as compared to 0.5%-2.3% and 0.7%-6.2% worldwide, respectively.⁸ In almost half of the studies, none of any of the patients with CSU

investigated had CHC.^{14-16,19,20,23-27} Rates of HCV positivity in patients with chronic urticaria were similar to those in the general population of France,^{21,28} Turkey¹³⁻¹⁵ and Italy.²⁹ In six studies that also investigated control subjects, their prevalence of CHC was found to be comparable to that of patients with CSU.^{17,21,25,30-32} In one study from China, CHB was even found to be less prevalent in patients with CSU as compared to the general population.³³

The levels of viral hepatitis vary widely across regions. This could explain the discrepancy in the prevalence of CHC/CHB reported by the studies we analysed. For example, the highest number of HBV and/or HCV infections was seen in patients with CSU from Turkey,

TABLE 2 Prevalence of urticarial rash including CSU in patients with chronic hepatitis C

First author	Year	Age of patients, years	n, patients with hepatitis C	% (n), patients with urticarial rash	Type of urticaria	Design	Country
Satta ⁷⁴	2018	>17	293	0.3 (1)	U	R	Italy
Godara ⁷⁵	2017	>1	14	0 (0)	U	-	India
Hegab ⁷⁶	2015	>17	118	3.4 (4)	CU	P	Egypt
Ali ⁷⁷	2014	>15	205	6.8 (14)	U	P	Pakistan
Amin ⁹	2013	>15	325	5.2 (17)	U	R	Pakistan
Rauf ⁷⁸	2012	>17	180	7.8 (14)	U	P	Pakistan
Asim ⁷⁹	2012	>11	100	6 (6)	U	-	Pakistan
Ejaz ⁸⁰	2010	>19	100	9 (9)	CU	CS	Pakistan
Raslan ⁸¹	2009	>26	155	0.6 (1)	U	-	Egypt
Azfar ⁸²	2008	>17	371	2.4 (9)	U	-	Pakistan
Maticic ³²	2008	>18	171	1.2 (2)	U	P, CC	Slovenia
Soylu ⁸³	2007	>22	50	2 (1)	U	CC	Turkey
Crowson ¹⁰	2003	>33	35	2.9 (1)	NU	P	USA
Paoletti ⁸⁴	2002	>34	96	1 (1)	U	P	Italy
Zauli ²⁹	2001	-	105	0.9 (1)	U	CC	Italy
Origgi ⁸⁵	1998	-	33	3 (1)	U	-	Italy
Dega ⁸⁶	1998	>17	27	14.8 (4)	U	R	France
Cribier ⁴³	1998	>17	100	0 (0)	U	P, CC	France
Daoud ⁸⁷	1996	>33	611	0.3 (2)	U	R	USA, Syria
Dupin ⁸⁸	1995	>54	35	5.7 (2)	U	R	France

-, no data, not defined in the paper or in the abstract; CC, case-control study; CS, cross-sectional study; CU, chronic urticarial rash; NU, neutrophilic urticaria; P, prospective study; R, retrospective study; U, undifferentiated urticarial rash.

TABLE 3 Does the treatment of viral hepatitis lead to CSU remission?

First author	Year	Type of hepatitis	n, CSU patients	Treatment of VH	Efficacy of antiviral treatment		Country
					Viral hepatitis	CSU	
Dionigi ⁴¹	2016	CHC	1	Ribavirin, interferon	A negative viral load	Remission ^a	Brazil
		CHB	2	Specific treatment	-	Not effective	
Colgecen ⁴²	2015	CHC	6	Specific treatment	-	Not effective	Turkey
		CHB	14	Specific treatment	-	Not effective	
Foschi ⁸⁹	2010	CHC	1 ^b	Ribavirin, PEG, HLI	A negative viral load ^d	Remission in 10 d ^c	Italy
Raychaudhuri ⁹⁰	1995	CHC	1	Interferon- α	Improved	Not effective	USA

-, no data; CHC, chronic hepatitis C; CHB, chronic hepatitis B; HLI, human leucocyte interferon- α ; PEG, peginterferon-2 α .

^aAfter 6 mo of a negative viral load.

^bSkin biopsy was not carried out.

^cUrticaria did not reappear for 2 y despite the relapse of viral replication.

^dHCV-RNA was negative 1 mo from the beginning of treatment.

China, Saudi Arabia and Pakistan. This is consistent with the data that Western Pacific Region, European Region and Eastern Mediterranean Region have the greatest burden for HBV and/or HCV infection.⁸

In the few studies that reported significantly higher rates of anti-HCV positivity in patients with urticaria including CSU as compared to controls, the samples included were small, risk factors of urticaria patients were not matched with those of the control group, and/or some of the patients may have had urticarial vasculitis.^{7,34} For example, in half of all HCV+ patients described by Kanazawa and

coworkers, wheals lasted >24 hours and left pigmentation suggesting urticarial vasculitis rather than chronic urticaria.⁷ It is well known that CHC can cause urticarial vasculitis and that the treatment of hepatitis with interferon alfa can clear urticarial vasculitis.³⁵ Therapy of viral hepatitis has also been shown to improve cold urticaria.³⁶ As for CSU, the results of studies are inconsistent, and it remains unclear if hepatitis can cause CSU.³⁷ In some patients, chronic urticaria reportedly developed in the prodromal phase of acute hepatitis B or following acute hepatitis A and resolved after hepatitis

improvement.^{38,39} In one patient, CSU reportedly appeared upon HCV reactivation.⁴⁰

In two of nine patients reported, remission of CSU was seen after HCV-specific treatment and improvement (Table 3). In 16 patients with CHB, specific antiviral therapy did not reduce CSU disease activity.^{41,42} This is in line with the assessment by Kulthanan et al⁵ that the treatment of chronic viral diseases including hepatitis usually does not result in the remission of CSU or the improvement of its symptoms.

Little is known about the prevalence of CSU in patients with viral hepatitis. The point prevalence of CSU in the general population is around 1%,³ and $\leq 3\%$ of patients with CHC have urticarial rash as reported by most studies. Some of these patients may have had acute urticaria, urticarial vasculitis or chronic inducible urticaria. In a study from France, none of 100 HCV-infected patients had urticaria at the time of the study and/or in their past medical history.⁴³ The data available, therefore, do not support the notion that patients with hepatitis show higher rates of CSU.

Whether or not there are pathogenic links between CSU and viral hepatitis remains unclear. Several hypotheses exist that could explain how hepatitis leads to CSU. HBV and/or HCV infection may enhance IgE-induced mediator release from mast cells and basophils.^{6,44} Patella and coworkers showed that protein Fv produced during viral hepatitis can activate human basophils and skin mast cells to release histamine and other mediators.⁴⁵ Later, the same authors confirmed that protein Fv acts as an endogenous superantigen by interacting with the VH3 domain of IgE to induce the activation of mast cells.⁴⁴ Although this reaction was similar to that of IgG anti-IgE, protein Fv was approximately 100 times more potent.⁴⁶ Moreover, protein Fv contributes to the release of IL-4 from basophils. IL-4 promotes the synthesis of IgE by B lymphocytes and may explain the high serum levels of IgE reportedly found in patients with active viral hepatitis.^{47,48} Interestingly, Chicharro et al⁴⁹ noted a reduction in viral load in CSU patient with CHB after 6-month treatment with omalizumab, monoclonal anti-IgE.

There is clinical and experimental evidence for circulating immune complexes (CICs) in viral hepatitis.^{11,50,51} Urticarial vasculitis in viral hepatitis can be explained by the presence of mixed cryoglobulinemia, the deposition of CICs containing viral antigens, HBsAg or HCV, in the vessel wall of urticarial lesions, and consequent activation of the complement pathway.^{52,53} Mixed cryoglobulinemia as well as lichen planus and porphyria cutanea tarda are the most common dermatologic manifestations of HCV infection (Table 4). Cryoglobulins are cold-insoluble antibodies which form CICs containing rheumatoid factor, polyclonal IgG and HCV RNA and cause end-organ damage and vasculitis by precipitating in small- to medium-sized blood vessels.⁵⁴ Whether CICs are also important in the development of CSU due to CHB/CHC is still unclear. Lockshin and Hurler suggested that the urticarial lesions are induced by antigens from the inflamed liver.⁵⁵ These antigens would form CICs^{7,50} and cause degranulation of mast cells via activation of complement and the production of anaphylatoxins. IgG- and C5a-dependent histamine release from mast cells and basophils is relevant in CSU.^{56,57} On the other side, C5a levels were significantly increased in patients with CHB.⁵⁸ Neumann and coworkers found HBsAg, C1q and C3 deposits in the small blood vessels in lesional but not normal skin of patients with acute hepatitis B and acute urticaria (urticarial vasculitis was excluded).¹¹ Although the presence of C1q was suggestive of the classical complement activation and the presence of immune complexes, the authors hypothesized that virus particles play a major role.

Interestingly, atypical yellow-colour urticaria has been described in patients with hepatitis C and/or liver cirrhosis.^{59,60} The cause is thought to be hyperbilirubinemia and accumulation of the excess bilirubin in the dermis due to increased vascular permeability.^{55,59-62} This was confirmed by skin biopsy studies with Hall's staining for bilirubin, which revealed focal deposits of olive-green crystals.⁶² Finally, bile acids can be elevated in serum of patients with viral hepatitis⁶³ and were shown to activate cutaneous mast cells.⁶⁴ Taken together, there are several possible mechanisms that could explain

TABLE 4 Skin diseases associated with hepatitis B and C

Hepatitis-associated skin diseases ^b	Prevalence, %			
	Hepatitis B in skin diseases	Skin diseases in hepatitis B	Hepatitis C in skin diseases	Skin diseases in hepatitis C
Mixed cryoglobulinemia	36.7 ^{c,91}	4.6-12.0 ^{c,92,93}	80.0-90.0 ^{c,94}	30.0-40.0 ^{c,94}
Lichen planus	0.9-4.0 ^{95,96}	29.5 ^{d,97}	22.3 ^{c,d,e,98}	0.1-4.9 ^{d,e,94,98}
Polyarteritis nodosa ^a	22.0-33.7 ^{c,99,100}	1.1 ¹⁰¹	5.0-20.0 ¹⁰²	2.8 ¹⁰
Porphyria cutanea tarda	17.0 ¹⁰³	-	47.0-94.0 ^{c,d,e,104,105}	<1.0-5.0 ⁹⁴
Urticarial vasculitis ^a	0.0-1.3 ¹⁰⁶⁻¹⁰⁸	Case reports ⁵²	1.3-4.3 ^{c,107,108}	$\leq 3.0^e$ (this review)
Necrolytic acral erythema	-	-	$\approx 100^{c,94}$	0.2-1.7 ^{c,94}

^aCryoglobulinemia can be present.

^bOther common cutaneous manifestations of hepatitis B are serum sickness-like prodrome, papular acrodermatitis of childhood (Gianotti-Crosti syndrome) and pitted keratolysis.

^cAuthors of one or several studies suggested that this skin disease was due to hepatitis.

^dStatistically significant association and/or increased risk.

^eA systematic review and/or a meta-analysis.

how viral hepatitis could lead to urticaria. At present, the available data on the rates of CSU in patients with viral hepatitis and the rates of CSU in hepatitis do not support this.

Larger systematic and prospective studies, preferably multicentric ones, are needed to clarify whether viral hepatitis is causally linked to CSU and whether hepatitis treatment affects the course or disease activity of CSU. The global GA²LEN network of urticarial centres of reference and excellence (UCAREs) appears to be suitable to perform such studies.⁶⁵

5 | CONCLUSION

The rates of HBV/HCV infection do not appear to be increased in patients with CSU suggesting that viral hepatitis and CSU are not usually linked. Whether viral hepatitis can cause CSU in some patients and whether the course and disease activity of CSU are affected by antiviral treatment should be investigated in further studies. For now, routine investigations of HCV/HBV infection in patients with CSU do not appear relevant or cost-effective and should only be considered if risk factors of hepatitis are present, liver function tests are abnormal, or urticarial vasculitis is suspected.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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