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Prevalence of hepatitis C serum antibody in autoimmune diseases

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ABSTRACT

Objective: To evaluate the prevalence of serum antibodies against hepatitis C virus and other infectious agents in a large cohort of well-characterized patients with autoimmune diseases (AID).

Methods: We utilized 1322 sera from patients with 18 different AID and 236 sera from healthy controls from the same countries and with similar age and sex distribution. All sera were tested for the presence of serum anti-hepatitis C virus (HCV) antibodies as well as antibodies directed at other infectious agents and autoantibodies.

Results: Anti-HCV antibody was detected in 115/1322 (8.7%) of patients with AID and 0.4% of matched healthy controls ($P < 0.0001$). The prevalence of anti-HCV antibody was significantly higher in 7/18 different AID (i.e. cryoglobulinemia, mixed cryoglobulinemia pemphigus vulgaris, vasculitis, secondary anti-phospholipid syndrome, Hashimoto's thyroiditis, and inflammatory bowel disease) compared to controls. Patients with AID and serum anti-HCV positivity had an increased prevalence of antibodies against hepatitis B virus, *Toxoplasma gondii* and *Cytomegalovirus* as opposed to a lower frequency of serum autoantibodies.

Abbreviations: ANA, anti-nuclear antibody; RF, rheumatoid factor; anti-SMA, anti-smooth muscle antibodies; aCL, anti-cardiolipin antibodies; anti-LKM1, anti-liver kidney microsomal 1 antibodies; AID, autoimmune disease; PV, pemphigus vulgaris; MC, mixed cryoglobulinemia; CY, cryoglobulinemia; WG, Wegener's granulomatosis; MPA, microscopic polyangiitis; CS, Churg–Strauss vasculitis; GCA, giant cell arthritis; pAPS, primary anti-phospholipid syndrome; sAPS, anti-phospholipid syndrome associated to other diseases (secondary); HT, Hashimoto's thyroiditis; GR, Graves' disease; IBD, inflammatory bowel disease; PBC, primary biliary cirrhosis; PM, inflammatory myopathies; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; SS, Sjögren's syndrome; MS, multiple sclerosis; HCV, hepatitis C virus; CMV, *Cytomegalovirus*; EBV, Epstein–Barr virus; VCA, viral capsid antigen; NA, nuclear antigen; EA, early antigen.

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Conclusions: The enhanced prevalence of anti-HCV serum antibodies in AID may suggest a role for HCV in tolerance to breakdown, similarly to its established role in mixed cryoglobulinemia. This immune mediated effect does not rule out the role of other infectious agents.

1. Introduction

The link between infectious diseases and autoimmune diseases (AID) has been repeatedly suggested based mostly on epidemiological and experimental data [1–4]. Various infectious agents are known to trigger tolerance breakdown, as in the case of hepatitis C virus (HCV) in specific conditions [2,5]. Chronic liver disease associated with HCV affects 70–90% of infected subjects [6] and is frequently associated with extra hepatic manifestations [7]. The worldwide prevalence of HCV chronic infection is estimated to range between 2 and 3% of the general population [8,9]. Indeed, extra hepatic manifestations of chronic HCV-infection [10] include autoimmune phenomena [11] and hematopoietic malignancy [12]. Among the former, it is not uncommon to detect serum antinuclear antibodies (ANA), cryoglobulins, rheumatoid factor (RF), anti-smooth muscle antibodies (SMA), anti-cardiolipin (aCL), anti-liver kidney microsomal 1 (LKM1), and anti-thyroid antibodies [13–19], along with overt autoimmunity (as in the case of cryoglobulinemia) or variants of AID (i.e. Sjögren-like syndrome) [13,15,20,21].

The mechanisms linking HCV with autoimmunity are unclear. HCV targets hepatocytes but can also replicate in other cells, such as lymphocytes [14] particularly B-cells [7,8,22]. Studies from our group [19] and others [23–25] demonstrated an increased level of B-lymphocyte activating factor (BAFF), a B-cell's survival factor, in chronic HCV-infection and suggest that B-cells activation and increased survival might play a role in HCV-associated autoimmunity. Other proposed mechanisms include the potential of HCV to induce auto-reactive CD8+T cells by molecular mimicry [26], the induction of high levels of endogenous IFNα [27], direct viral invasion and bystander activation [14,28,29].

Several authors have evaluated the prevalence of AID in HCV-infection using case-control studies, with conflicting results [11,21,27,28,30–33]. We herein report a complementary approach that investigated a large series of patients with defined AID for the prevalence of anti-HCV-antibodies as well as antibodies directed at other infectious agents and autoantigens. Our data support a significantly higher prevalence of serum anti-HCV antibody in patients with autoimmune diseases compared to healthy controls.

2. Subjects and methods

2.1. Subjects

Sera from 1322 patients with 18 different AID were collected from referral centers in Europe and Latin America and all patients fulfilled the international criteria for each specific disease while patients with more than one AID were excluded with the exception of sAPS. The European group of patients included patients with mixed cryoglobulinemia, cryoglobulinemia, pemphigus vulgaris (PV), vasculitis [including Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and Churg–Strauss vasculitis (CS)], giant cell arthritis (GCA), primary anti-phospholipid syndrome (pAPS) and APS secondary to other diseases (sAPS), Hashimoto's thyroiditis (HT), Graves' disease (GD), inflammatory bowel disease (IBD), primary biliary cirrhosis (PBC), inflammatory myopathies (PM), and systemic sclerosis (SSc). The Latin American group included patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome (SS), and multiple sclerosis (MS). Control sera were obtained from 236 healthy subjects (97 from Europe, 139 from Latin America) of similar age and sex distribution (37 ± 10 years of age, 82% females) compared to patients. The study received approval of the local ethics committees and fulfilled the ethical guidelines of the most recent declaration of Helsinki (Edinburgh, 2000).

2.2. Serum markers of infection and autoantibodies

Sera from patients and controls were tested for anti-HCV (recombinant hepatitis C virus antigen: c22-3, c200 and NS5) using the HCV encoded antigen ORTHO HCV Version 3.0 ELISA test system (Johnson & Johnson, Bio-Rad, Hercules, CA, USA) according to the manufacturer's protocol. Briefly, sera were added at dilution of 1:21 to hepatitis C recombinant c22-3, c200 and NS5 antigen-coated ELISA plates and the binding was detected by anti-human-IgG-peroxidase and appropriate substrate. Positive results were calculated according to the manufacturer's equations for cut-off value determination.

Antibodies to hepatitis B virus (HBV) and *Helicobacter pylori* were tested using MONOLISA anti-HBc plus commercial kit and MONOLISA pylori - IgG commercial kit (Bio-Rad, Hercules, CA), respectively, according to the manufacturer's instructions. Antibodies directed at rubella, toxoplasma, *Cytomegalovirus* (CMV), Epstein–Barr virus (EBV) and *Treponema pallidum* were tested alongside a panel of autoantibodies using the Bio-Rad BioPlex 2200 (Bio-Rad) as described elsewhere [1,34]. Briefly, the BioPlex 2200 is a fully automated random-access analyzer built on a synthesis of multiplex, magnetic beads and flow cytometry technologies. At the core of the technology there are 25 different populations of 8-μm magnetic beads, which are dyed with two fluorophores for classification purposes. The amount of antibody bound to the bead was determined by fluorescence analysis; raw data were subsequently converted to the fluorescence ratio using a pre-dyed internal normalizer the detector signal. Elevated titers were determined as above the cut-off of 2 standard deviations from the normal control group.

2.3. Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation. For purpose of comparisons, Fisher's exact test and the Chi-square test were used for categorical variable while the *t*-test and the ANOVA test were used for $N \geq 20$ in the presence of continuous variables. In the case of non-parametric variables the Kruskal–Wallis test was used. P values ≤ 0.003 were considered as statistically significant following Bonferroni correction for multiple testing.

3. Results

3.1. Serum HCV antibody prevalence

Anti-HCV antibodies were found in 115/1322 (8.7%) patients with AID while detected in 0/97 European and 1/139 Latin American

controls leading to a cumulative 0.4% prevalence in the whole control group. Of note, patients with autoimmunity and HCV-infection were more frequently men (32% *vs.* 18% compared with controls, $P = 0.04$) and older (62 ± 14 *vs.* 37 ± 10 years of age; $P < 0.0001$ compared with controls). When patients were arrayed according to their clinical subgroups, the prevalence of serum anti-HCV antibodies was significantly higher ($P \leq 0.003$) in 7/18 autoimmune diseases (i.e. cryoglobulinemia, mixed cryoglobulinemia, PV, vasculitis, sAPS, Hashimoto's thyroiditis, IBD) (Fig. 1 and Table 1). In particular, 37 patients with IBD from Italy manifested a 13.5% prevalence of serum anti-HCV ($P = 0.0002$ compared to controls).

3.2. Serum antibodies to other infectious agents and anti-HCV in patients with AID

The prevalence of antibodies to seven other infectious agents was compared between patients with AID ($N = 115$) and without ($N = 1207$) anti-HCV antibodies (Table 2). Among patients with autoimmune diseases and anti-HCV antibodies 31% had anti-HBV core antibodies compared to 10% of patients without anti-HCV positivity ($P < 0.0001$). Similarly, significantly higher rates of anti-toxoplasma and anti-CMV antibodies were observed in patients with antibodies to HCV while no differences were observed between the two groups for other antibodies against infectious agents.

3.3. Serum autoantibodies and anti-HCV in patients with AID

The prevalence of serum autoantibodies in patients with AID arrayed according to their anti-HCV antibody status is illustrated in Table 3. Autoantibodies associated with vasculitis (i.e. anti-GBM, anti-MPO and anti-PR-3) and gastrointestinal diseases [i.e. anti-gliadin antibodies, anti-*Saccharomyces cerevisiae* (ASCA) and anti-tissue transglutaminase (TTG)] were detected in equal percentages among patients with or without serum anti-HCV antibodies. Similarly, autoantibodies associated with thrombophilia (i.e. anti-cardiolipin (CL), anti-β2GPI and anti-CL-β2GPI) did not differ between groups, yet we note a higher prevalence of anti-CL in patients with anti-HCV antibodies (6% *vs.* 1.5%; $P = 0.007$). Patients with autoimmune diseases and anti-HCV reactivity manifested a lower frequency of serum anti-nuclear autoantibodies (ANA) compared with anti-HCV negative patients (29% *vs.* 47% $P = 0.0002$). In particular, anti-SmRNP antibodies were significantly lower in patients with anti-HCV antibodies and a similar trend was observed for anti-dsDNA, anti-chromatin, anti-Smith, and anti-SSA antibodies.

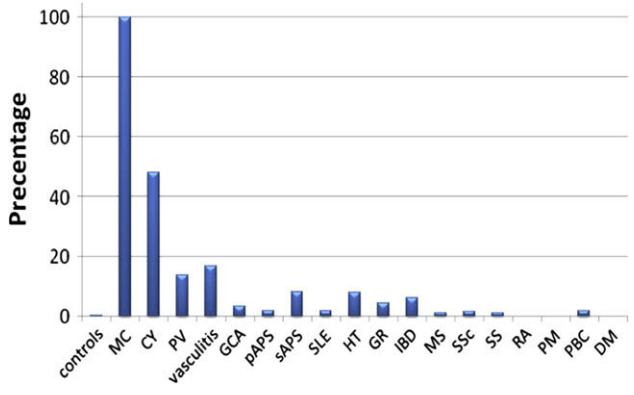

Fig. 1. Prevalence of anti-HCV antibodies in sera from patients with autoimmune diseases and healthy controls. *Abbreviations*: CY - cryoglobulinemia; MC - mixed cryoglobulinemia; PV - pemphigus vulgaris; sAPS - secondary APS; HT - Hashimoto's thyroiditis; IBD - inflammatory bowel disease; GR - Graves' disease; pAPS - anti-phospholipid syndrome; PBC - primary biliary cirrhosis; SLE - systemic lupus erythematosus; MS - multiple sclerosis; SSc - systemic sclerosis; SS - Sjögren's syndrome; RA - rheumatoid arthritis; PM - inflammatory myopathies; vasculitis [i.e. Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and Churg–Strauss vasculitis (CS)]; GCA - giant cell arthritis; DM - diabetes mellitus.

Table 1
Prevalence of anti-HCV antibodies in 1322 serum samples of patients with different autoimmune diseases and healthy controls. *P* values in the comparison with healthy controls are illustrated.

	N	Anti-HCV positive	*P* value
All patients with autoimmunity	**1322**	**115 (8.7%)**	**<0.0001**
Mixed cryoglobulinemia	39	39 (100%)	**<0.0001**
Cryoglobulinemia	77	36 (47%)	**<0.0001**
Pemphigus vulgaris	29	4 (14%)	**0.002**
Vasculitis (WG, MPA, CS)	24	4 (17%)	**0.0002**
Giant cell arthritis	29	1 (3%)	NS
Primary APS	97	2 (2%)	NS
Secondary APS	61	5 (8%)	**<0.002**
Systemic lupus erythematosus	108	2 (2%)	NS
Hashimoto's thyroiditis	100	8 (8%)	**0.0003**
Graves' disease	87	4 (5%)	0.02
Inflammatory bowel disease	98	6 (6%)	**0.003**
Multiple sclerosis	98	1 (1%)	NS
Systemic sclerosis	77	0	NS
Sjögren's syndrome	78	1 (1%)	NS
Rheumatoid arthritis	95	0	NS
Inflammatory myopathies	76	0	NS
Primary biliary cirrhosis	60	1 (2%)	NS
Diabetes mellitus	88	0	NS

$P \leq 0.003$ was considered statistically significant; NS = not significant.

4. Discussion

We report that serum anti-HCV antibodies are found in 8.7% of patients with AID, being associated with male gender and older age in agreement with former studies [35,36]. The prevalence of anti-HCV antibodies in the general European and Latin American population ranges between 0.5 and 2.5% [8,9,37,38] compared to 0.4% in our healthy control group. This discrepancy may be secondary to the younger age of our control group which does not account for the higher prevalence at older ages (i.e. the cohort effect of HCV epidemiology) and is thus not representative of the general population.

We observed several associations between HCV reactivity and specific AID. First, our data confirm the association between HCV and cryoglobulinemia or mixed cryoglobulinemia [25,31,39,40]. In fact, cryoglobulins are detected in 40–60% of patients with chronic HCV-infection [41] and overt cryoglobulinemia has been reported in up to 56% of them according to their genetic variability

Table 2
Prevalence of serum antibodies against different infectious agents in 1322 patients with autoimmune diseases arrayed according to their anti-HCV status.

Anti-infectious agents antibodies	Anti-HCV positive ($N = 115$)	Anti-HCV negative ($N = 1207$)	*P* value
HBV core antigen	31%	10.3%	**<0.0001**
Helicobacter pylori	45%	56%	NS
Toxoplasma gondii	64%	48%	**0.002**
Rubella	90%	91%	NS
Cytomegalovirus	94%	83%	**0.002**
Treponema pallidum	3%	1.7%	NS
Epstein–Barr - Viral capsid antigen	93%	94%	NS
Epstein–Barr -Nuclear antigen	94%	93%	NS
Epstein–Barr -Early antigen	24%	28.5%	NS

$P \leq 0.003$ was considered statistically significant; NS = not significant.

Table 3
Prevalence of autoantibodies in 1322 patients with autoimmune diseases in regard to the presence (no. 115) or absence (no. 1207) of anti-HCV-reactivity.

Autoantibodies	Anti-HCV positive ($N = 115$)	Anti-HCV negative ($N = 1207$)	*P* value
Vasculitis associated:			
Glomerular basement membrane	0	0	NS
Myeloperoxidase (MPO)	1%	2%	NS
Proteinase-3 (PR-3)	3%	1.5%	NS
Gastrointestinal associated IgG			
Gliadin	6%	10.5%	NS
Tissue transglutaminase	3%	3.6%	NS
Saccharomyces cerevisiae	6%	6%	NS
Thrombophilia associated IgG			
Cardiolipin	6%	1.5%	0.007
B2GPI	11%	15%	NS
CL-B2	8%	5%	NS
Anti-nuclear antibodies	29%	47%	**0.0002**
dsDNA	16%	25%	0.05
Chromatin	12%	25%	0.02
RNP	4%	8%	NS
Smith	1%	6%	0.06
SmRNP	0	8%	**0.0001**
SS-A	8%	17%	0.02
SS-B	3%	7%	NS
Scl70	1%	4%	NS
Jo-1	0	1%	NS
Centromere	3%	6.6%	NS
Ribosomal-P	0	2.4%	NS

$P \leq 0.003$ was considered statistically significant; NS = not significant.

[21,42,43]. An association of HLA–DR11 phenotype with type II MC in patients with chronic HCV was reported, whereas HLA–DR7 appeared to protect HCV-infected patients from the development of MC [44]. Moreover, current treatments for HCV ameliorate and may cure mixed cryoglobulinemia [43]. A suggested mechanism for this association is that HCV chronically stimulates B-cell polyclonal proliferation from which a monoclonal population may emerge [45] and mixed cryoglobulinemia ultimately reflects the polyclonal and monoclonal expansion of B-cells producing IgM with rheumatoid factor activity [41]. The association between other vasculitides and HCV has been reported by Lidar et al. [46] following the current study, showing a higher prevalence of anti-HCV positivity in patients with Wegener's granulomatosis.

Second, we observed a statistically significant association between anti-HCV antibodies and HT and to a minor degree with GD. Anti-thyroid antibodies are reported in 6–48% of patients with chronic HCV-infection [27,47] while increased prevalence of overt thyroid disorder (mainly hypothyroidism caused by autoimmune thyroiditis) was reported [11,48,49] despite conflicting evidence [27,50]. Of note, HCV was documented in the thyroid gland [43] and it was also demonstrated that HCV envelope glycoprotein E2 can bind directly to thyroid cells and activate a cascade of signaling leading to cytokine [29] and chemokines [40] production. Furthermore, high levels of endogenous IFNα are induced by the virus and may also be involved in the appearance of thyroid autoimmunity in genetically predisposed subjects [27,51,52] while exogenous IFNα (i.e. anti-HCV therapy) may also induce the development of HT or GD in 5–12% [11,53]. Third, we found a significantly higher prevalence (14%) of anti-HCV antibodies in sera from patients with pemphigus vulgaris, in contrast with previous reports [54,55]. To evaluate whether this observation is merely stochastic or possibly associated with anti-HCV treatment, a prospective study of a larger number of patients is warranted. Fourth, although many infectious agents were found to be associated with APS [56–58], we failed to observe an association between the presence of anti-HCV antibodies and pAPS, in agreement with previous studies [16,59]. However, 8% of patients with sAPS had detectable anti-HCV, similar to reported associations between HCV and atypical APS or catastrophic APS [60,61]. Thus, an association of HCV with certain features of APS might be suggested. Fifth, an association between IBD and HCV-infection has been reported in patients of Italian origin with Crohn's disease [62] while we have reported a prevalence of 6% following this study [63]. Of note, Italian patients with Crohn's disease included in our study manifested a striking prevalence of anti-HCV antibodies (13.5%). Whether invasive procedures (i.e. endoscopy and surgery) [62] or HCV-infection and treatment play a role in this association remain to be determined [63,64]. Lastly, the absence of associations between HCV and Sjögren's syndrome, SLE, and systemic sclerosis is somewhat surprising [42,47]. In the case of Sjögren's syndrome, we should note that the current diagnostic criteria include the lack of HCV-infection [65].

In our series, patients with anti-HCV antibodies and autoimmune diseases also had a higher frequency of serum antibodies against other infectious agents. In particular, 30% of AID and anti-HCV also manifest anti-HBV core antibodies compared with 10% of those without HCV reactivity. The co-existence of HBcAb and anti-HCV antibodies is not uncommon [9,66,67] as both viruses share major risk factors [68]. Co-infection with both viruses increases the progression of liver disease and complicates its treatment [68–71]. The role of toxoplasmosis in the pathogenesis of AID is unclear. In a previous study we reported an association between toxoplasmosis and several autoimmune diseases as thyroid diseases, vasculitides and PBC [63,64,72] but not with SLE, rheumatoid arthritis and multiple sclerosis (unpublished data). On the contrary, the role of *Cytomegalovirus* had been extensively studied, and this virus was found to be associated with several autoimmune diseases [1].

The occurrence of serum autoantibodies in HCV-infected patients has been extensively studied, and an increased prevalence of anti-nuclear, anti-cardiolipin, anti-smooth muscle and anti-thyroglobulin antibodies was reported as compared with uninfected controls, alongside high levels of cryoglobulins and rheumatoid factor [28,33,73,74]. Anti-nuclear antibodies have been detected in 10–30% of HCV-infected patients and their presence correlates with older age [75,76]. Our observation shows that lower prevalences of specific autoantibodies are associated with anti-HCV reactivity in patients with autoimmune diseases are not unexpected. As an example, a lower prevalence of anti-SSA and anti-SSB is characteristic of HCV-associated Sjögren's syndrome, and the absence of anti-CCP is typical of HCV-associated arthritis.

In conclusion, in line with the many interactions between infectious agents and autoimmunity [77] we have found anti-HCV antibodies to be significantly associated with cryoglobulinemia and thyroid autoimmune disease, in both of which HCV may play a pathogenic role. We have also found an association between HCV sero-reactivity and APS associated to other diseases, IBD, Wegener's granulomatosis and a possible novel association with pemphigus vulgaris. These associations might support a role of HCV in the pathogenesis of these AID or an increased susceptibility to HCV-infection in certain patients with AID. Large prospective studies are awaited to confirm the proposed associations.

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