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High prevalence of serum antibodies to hepatitis C virus in patients with Hashimoto's thyroiditis

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Given the reports of thyroid dysfunction and various autoimmune disorders such as Sjögren's syndrome in patients infected with hepatitis C virus,[1,2] we hypothesised a link between autoimmune thyroid disease, mainly Hashimoto's thyroiditis, and such infection. We looked for antibodies to hepatitis C virus in the serum of patients with thyroid disease.

Subjects, methods, and results

We studied stored serum samples from 200 patients (190 women) with thyroid disease (simple goitre (n=50), Graves' disease (n=50), and Hashimoto's thyroiditis (n=50)) randomly selected from all patients seen at five centres between 1987 and 1992.

Thyroid function was assessed by standard radioimmunoassays for serum thyroxine, triiodothyronine, and thyroid stimulating hormone. Receptor antibodies for thyroid stimulating hormone were detected with radioreceptor assay (Trak-asay, Henning Laboratories, Berlin). Serum antibodies to thyroid microsome and thyroperoxidase were used to diagnose Hashimoto's thyroiditis, depending on the centre. Serum antibodies to thyroid microsome were detected with indirect immunoinflorescence assay by using cryostat sections of human thyroid or by passive haemagglutination with a commercial kit (Thymune-M, Wellcome Laboratories, Beckenham). Serum antibodies to thyroperoxidase were assessed by radioimmunoassay (Dynotest anti-TPO, Henning Laboratories, Berlin) and antibodies to thyroglobulin by passive haemagglutination (Thymune-T, Wellcome Laboratories, Beckenham).

A second generation enzyme linked immunosorbent assay (ELISA) (Diagnostics Pasteur, Marnes la Coquette, France) was used to detect antibodies to hepatitis C virus. Samples yielding positive results were retested with a second generation recombinant immunoblot assay (RIBA, Ortho Diagnostic Systems, Raritan, New Jersey). Serum concentrations of immunoglobulin G were assayed by laser nephelometry in the serum of patients with Hashimoto's thyroiditis.

Fisher's exact test and the Mann-Whitney U test were used for statistical analysis. Results are expressed as means (SD).

The table summarises the results of the assays. No significant difference was noted for age or serum concentration of immunoglobulin G in patients with Hashimoto's thyroiditis with or without hepatitis C virus antibodies.

Comment

We found a higher prevalence of serum hepatitis C virus antibodies in patients with Hashimoto's thyroiditis than in those with any other thyroid disease. Among patients with Hashimoto's thyroiditis those with a positive result on ELISA and a negative result on immunoblot assay had lower serum concentrations of immunoglobulin G than those with positive results in both tests, though this result was not significant. This suggests that false positive reactions because of high serum concentrations of immunoglobulin G are unlikely.

The disappearance of hepatitis C virus is followed by decreasing titres of serum hepatitis C virus antibodies, which become undetectable after several months or years of follow up,[3] though those patients with negative results in both assays may have low titres of antibodies not recognised by the highly specific but less sensitive immunoblot assay. If the result of the immunoblot assay becomes negative before the ELISA result, a few of these patients may be in fact infected with hepatitis C virus. The high prevalence of such antibodies in patients with Hashimoto's thyroiditis compared with other groups of thyroid disease and with the normal population[4] suggests that hepatitis C virus may be responsible for triggering Hashimoto's thyroiditis.

Results of assays for serum antibodies to hepatitis C virus in four groups of patients with thyroid disease*

Type of thyroid disease	ELISA		RIBA	
	Negative result	Positive result	Indeterminate result	Positive result
Simple goitre	50	0	—	—
Graves' disease	49	1	1	—
Myxoedema	48	2	—	1
Hashimoto's thyroiditis	38	12†	—	5
Total		15‡	1	6

RIBA=recombinant immunoblot assay.
*Difference for detection of hepatitis C antibodies in patients with Hashimoto's thyroiditis *v* other thyroid diseases combined, $P<0.0001$ for ELISA and $P=0.01$ for recombinant immunoblot assay.
†24% (95% confidence interval 12% to 36%).
‡75% of all patients with thyroid disease.

The role of another agent or epidemiological factor related to hepatitis C virus, however, cannot be excluded.

Hepatitis C virus is not the first viral agent suspected of initiating an autoimmune thyroid process. Some viruses may be implicated in animals, and the role of retroviruses has been suggested in humans.[5] The possible role of infection with hepatitis C virus in triggering Hashimoto's thyroiditis does not rule out other agents such as exoviruses or endoviruses,[5] and other detailed studies of such associations are needed.

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Hepatitis C in asymptomatic British blood donors with indeterminate seropositivity

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False positive results are common when low risk populations, such as volunteer British blood donors, are screened for antibodies to hepatitis C virus. In this setting a confirmatory assay is required, but an indeterminate result may still be obtained. This regional blood transfusion service uses a second generation recombinant immunoblot assay (RIBA HCV, Ortho diagnostics) to confirm positive results on enzyme linked immunosorbent assay (ELISA). Donors with indeterminate results in the confirmatory assay are excluded from the donor pool and advised that the use of their blood may not be safe.

We examined 61 such donors for evidence of hepatitis C and liver disease.

Patients, methods, and results

Consecutive patients referred to this liver unit were interviewed and examined. Liver function was checked, and serum was stored at −70° C. Liver biopsy was performed, and histology was scored according to a modified Knodell activity index (maximum possible score 13). Part of the biopsy specimen was snap frozen and stored at −70° C. Stored serum samples and biopsy specimens were examined for hepatitis C virus RNA (assay detection sensitivity 0·4-4 copies of target complementary DNA).

Six donors had had blood transfusions, and 55 had no overt risk factor for hepatitis C. All were asymptomatic, with no physical signs of liver disease. One obese donor had raised serum alanine transaminase activity (45 U/l, normal <41), and the remainder (including the six donors who had had transfusions) had normal results. All serum samples were negative for hepatitis C virus RNA.

Fifty nine liver biopsies were performed. Histological abnormalities were mild, and most specimens (49/59) had an activity index of 0 (table). The most commonly observed abnormality was steatosis, sometimes accompanied by an inflammatory infiltrate. Of six patients with a history of transfusion, four had an index of 0 and the two others scored 1. Significant abnormality was observed in a single biopsy specimen (mild chronic active hepatitis, activity index 5). This donor had persistently normal serum transaminase activity during two years' follow up. Twenty biopsy specimens, selected to represent a range of histological changes (table), were negative for hepatitis C virus RNA.

Results for 59 liver biopsy specimens from asymptomatic blood donors with indeterminate seropositivity for hepatitis C virus

Histological activity index	Histological feature	No of specimens	No of specimens examined for HCV RNA
0	Normal	35	14
	Non-specific inflammation	3	
	Steatosis	11	2
1	Portal inflammatory infiltrate	3	1
	Lobular inflammatory infiltrate	4	1
	Fibrosis	1	
2	Portal and periportal inflammation	1	1
5	Mild chronic active hepatitis	1	1

HCV=hepatitis C virus.

Comment

When the confirmatory assay for antibodies to hepatitis C virus is positive, British blood donors are nearly always viraemic with histological evidence of liver disease.[1] They should be excluded from blood donation and referred for investigation and management of chronic hepatitis.

Interpretation of indeterminate results on recombinant immunoblot assay is more difficult and is principally dependent on the clinical context. Patients with such indeterminate results with known or suspected liver disease probably have hepatitis C, and viral RNA will usually be detected in their serum.[2] Blood donors with such indeterminate results, however, usually have no known risk factor for hepatitis C.[3] In other studies a minority of such donors in Britain (about 5%) were serum positive for hepatitis C virus RNA.[4]

In our cohort risk factors for parenteral exposure were uncommon and liver function was normal (except for an obese man with slightly increased serum alanine transaminase activity). All 61 serum samples and a representative selection of liver biopsy specimens, were negative for hepatitis C virus RNA.