Thyroid Dysfunction is Prevalent in Autoimmune Hepatitis: A Case Control Study

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ABSTRACT: Background: Autoimmune hepatitis (AIH) may be associated with other autoimmune diseases. Autoantibodies are common in AIH suggesting their potential role in the pathogenesis of the disease. Among these autoantibodies, thyroid autoantibodies have been reported in patients with chronic hepatitis, with greater prevalence in patients with chronic hepatitis C infection. Objectives: To assess the prevalence of thyroid dysfunction among patients with AIH. Methods: In this case-control, retrospective study, we examined patients diagnosed with AIH according to both the original and revised international AIH group scoring systems. Patients with other hepatic pathologies were excluded AIH was evaluated as an independent risk factor for thyroid disease by a logistic regression model. Univariate and multivariate regression analyses were conducted using hypothyroidism and hyperthyroidism as the dependent variables. Results: Our cohort comprised 16 patients diagnosed with AIH and 1104 healthy age- and gender-matched controls. Hypothyroidism was more prevalent among those with AIH compared to controls (17.7% vs. 5%, respectively, 95% confidence interval [95%CI] 1.68–2.48, P < 0.001). Hyperthyroidism was more prevalent in AIH patients compared to controls (odds ratio 3.2% and 1.2%, respectively, 95%CI 1.68–2.47, P < 0.001). Using a multivariate logistic analysis, we found an independent association between AIH and hypothyroidism but not with hyperthyroidism. Conclusions: Thyroid dysfunction is more prevalent in patients with AIH. Whether thyroid dysfunction is the cause or a risk factor for AIH, or vice versa, is still unclear. Screening for thyroid dysfunction is warranted after AIH is diagnosed. IMAI 2020; 22: 100–103

KEY WORDS: autoantibodies, autoimmune hepatitis (AIH), thyroid dysfunction

Autoimmune hepatitis (AIH) is a chronic autoimmune disease of the liver characterized by an inflammatory process involving the liver and biliary ducts with several systemic manifestations. Circulating autoantibodies and elevated serum globulin levels are the main means of disease diagnosis. AIH may begin as acute or fulminant hepatitis and it may present as a chronic disease with a fluctuating pattern that can progress to chronic liver disease and cirrhosis. The cirrhosis can be compensated or decompensated with the specific manifestations and complications of end-stage liver diseases [1]. AIH can present at any age and in all ethnicities, but it is most common among women [2,3].

Previous studies have shown that both the incidence and prevalence of AIH are rising [4], although it is still considered a rare disease with a prevalence ranging from 16 to 18 cases per 100,000 people in Europe. In Europe and the United States, AIH accounts for 2–3% of pediatric and 4–6% of adult liver transplantations [5]. AIH can occur in association with other co-existing extraportalic conditions, which may also be autoimmune-mediated disorders. Associated autoimmune disorders among AIH patients are described in 20–50% of patients with AIH, both in adults and children. Common autoimmune diseases associated with AIH include autoimmune thyroiditis, rheumatoid arthritis, type 1 diabetes mellitus, ulcerative colitis, and celiac disease. The presence of these diseases has been assimilated into both the original and revised international AIH group scoring systems [6].

Autoantibodies are common in most types of AIH suggesting that they may be implicated in the pathophysiology of the disease. Thyroid autoantibodies occur frequently in patients with chronic hepatitis with greater prevalence in patients with chronic hepatitis C infection [7]. The prevalence and the possible link between autoimmune thyroid disorders and AIH are not well established. The aim of this study was to assess the prevalence of thyroid dysfunction among patients with AIH.

PATIENTS AND METHODS

We conducted a case control, retrospective study, using databases from the Nazareth Hospital, EMMS (Nazareth, Israel) and Shaare Zedek Medical Center (Jerusalem, Israel). The study comprised patients diagnosed with AIH based on the original and revised international AIH group scoring systems [8] who were admitted to either of the hospitals between 2010 and 2018. We included healthy asymptomatic age- and sex-
matched patients as the control group. Patients with other hepatic pathologies, including nonalcoholic fatty liver disease, alcoholic liver disease, drug-induced liver injury, viral hepatitis, cholestatic liver diseases, and metabolic/genetic liver disease, were excluded. The exclusion was based on specific clinical, laboratory, radiological, and/or histological criteria/tests. Patient data included demographic variables (age, gender, and smoking history), body mass index (BMI), and the following laboratory parameters: alanine transaminase, aspartate transaminase, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, hemoglobin A1c, anti-thyroid peroxidase antibodies (anti-TPO Ab), and C-reactive protein (CRP). Moreover, the rate of thyroid dysfunction among our cohort was determined from medical records as the diagnosis was mainly based on laboratory findings of thyroid stimulating hormone, Triiodothyronine (T3), and Thyroxine (T4). The diagnosis was determined by an endocrinologist.

The study was approved by the institutional review boards of the Nazareth Hospital EMMS and Shaare Zedek Medical Center, and was conducted according to the Helsinki Declaration and its subsequent amendments. Data were coded to preserve the anonymity of the patients. Informed consent was waived due to the non-interventional nature of the study.

STATISTICAL ANALYSIS
A logistic regression model was used to evaluate AIH as an independent risk factor for thyroid disorders. Means and standard deviations (SD) are presented for normally distributed continuous variables. Categorical variables were expressed as percentages. Univariate and multivariate regression analyses were conducted using hypothyroidism and hyperthyroidism as the dependent variables.

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 24 (SPSS, IBM Corp, Armonk, NY, USA). A P value < 0.05 was considered statistically significant.

RESULTS

DEMOGRAPHIC AND BASELINE CHARACTERISTICS
The study cohort comprised 163 patients with AIH (AIH group) and 1104 age- and sex-matched healthy patients (control group). Patients above 18 years of age were included in the study. The average age was 44.12 ± 10.5 years (range 18–74) among the AIH group vs. 45.2 ± 9.7 years (range 19–68) among the control group (P = NS). In the AIH group 57 patients (35%) and in the control group 724 patients (65.5%) were female. Other baseline characteristics of the study groups are shown in Table 1.

PREVALENCE OF THYROID DYSFUNCTION IN THE COHORT
The hypothyroidism rate among AIH patients was significantly higher compared to controls (17.7% vs. 5%, respectively, odds ratio [OR] 2.4, 95% confidence interval [95%CI] 1.68–2.48, P < 0.001). Similarly, hyperthyroidism was significantly correlated with AIH compared to controls (3.2% vs. 1.2% respectively, OR 2.2, 95%CI 1.68–2.47, P < 0.001) [Figure 1]. Using multivariate logistic regression analysis, AIH was independently associated with hypothyroidism (OR 1.324, 95%CI 1.21–1.38) but not with hyperthyroidism.

The prevalence of positive serum anti-TPO Ab was significantly higher in the AIH group compared to the controls (OR 1.32, 95%CI 0.87–1.98). The association was nearly unchanged after adjustment for bias such as smoking (OR 1.3 95%CI 0.92–1.93). Moreover, the age-adjusted prevalence of positive anti-TPO Ab among AIH was similar in women (OR 2.9, 95%CI 1.9–11.7) and men (OR 9.1, 95%CI 1.9–12.3).
PARAMETERS ASSOCIATED WITH HYPOTHYROIDISM DIAGNOSIS AMONG AHI PATIENTS

Several covariate parameters that were associated with hypothyroidism diagnosis among patients with AHI were identified by a multivariate logistic regression analysis [Table 2]. The pronounced association between AHI and hypothyroidism remained relatively consistent across all age groups. Notably, when the same model was performed to assess the association with hyperthyroidism, it was found to be non-significant. Regarding the diagnosis of AHI among thyroid dysfunction patients, approximately half of the patients previously diagnosed with thyroid dysfunction were later diagnosed with AHI.

DISCUSSION

In this retrospective study we investigated the prevalence and the possible relationship between thyroid dysfunction and AHI. We found that the prevalence of thyroid dysfunction, specifically hypothyroidism, was significantly higher among AHI patients compared to controls. In part, this association might be related to the presence of autoantibodies since we observed higher serum anti-TPO Ab (OR 1.32) levels among AHI patients.

Moreover, we found several risk factors predisposing for this association including age, female gender, smoking history, and BMI. However, whether there is a link between AHI and thyroid dysfunction, or both are within the autoimmune spectrum, is still unknown as is the role of autoantibodies in the pathogenesis of these two conditions.

AHI is a progressive chronic parenchymal inflammatory liver disease that occurs in children and adults of all ages. It is characterized by the presence of autoantibodies specific for this condition [9-11]. AHI has been shown to be associated with several autoimmune diseases [12-18] as well autoimmune thyroid dysfunction. Muratori et al. [19] reported almost 30% prevalence of extrahepatic autoimmune diseases among AHI patients, with autoimmune thyroid disease (ATD) diagnosed in 51.4% of the patients. Similarly, ATD was reported to be the most common extrahepatic disease associated with AHI [20]. ATD was shown to be prevalent in 18.3% of patients with AHI and primary biliary cirrhosis (PBC) [21]. A large multicenter study, which included 562 patients with AHI, found an 18% prevalence of ATD, mostly in females [22]. Our findings showing an approximately 20% prevalence rate of thyroid dysfunction were comparable to those reported in the literature.

Notably, we found a higher prevalence of anti-TPO Ab among AHI patients. Nakamura and colleagues [23] reported a higher level of anti-thyroglobulin antibodies among AHI patients, while they observed a higher prevalence of anti-TPO Ab among patients with PBC. These results might explain in part the increased prevalence of autoimmune diseases among patients with AHI possibly mediated through various autoantibodies.

LIMITATIONS

The limitations of our study include the retrospective nature of data collection and the absence of other autoantibody levels.

CONCLUSIONS

We found a higher prevalence of thyroid dysfunction, specifically, hypothyroidism among patients with AHI. High clinical suspicion and routine screening laboratory tests should be performed, especially when the risk factors predisposing for this association are present (age, female gender, BMI, and smoking history) to enable timely co-diagnosis of the two conditions. Further studies, especially regarding the possible mutual pathogenesis and the role of autoantibodies, are necessary.

Acknowledgments

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Table 2. Multivariate logistic regression of covariates association with hypothyroidism

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>P value</th>
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<td>Age</td>
<td>1.01</td>
<td>1.01-1.04</td>
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<tr>
<td>Female gender</td>
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<td>2.85-3.58</td>
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<td>BMI</td>
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<td>Smoking</td>
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<tr>
<td>AHI</td>
<td>1.33</td>
<td>1.21-1.38</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

AHI = autoimmune hepatitis, BMI = body mass index

References


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**Capsule**

**Death suppression resolves inflammation**

Impaired signaling of tyrosine-protein phosphatase non-receptor type 6 (PTPN6) has been linked to skin disorders. In neutrophilic dermatoses, inflammatory immune cells called neutrophils accumulate in the skin. PTPN6 normally plays a role in limiting inflammatory responses that are mediated through the interleukin-1 (IL-1α/β) cytokine receptor. Using mice with mutations in the Ptpn6 gene, Speir and colleagues examined IL-1α/β released from neutrophils and asked how PTPN6 prevents inflammatory skin lesions. The researchers found that PTPN6 suppresses both apoptotic and necrotic cell death in neutrophils, which in turn dampens IL-1-dependent inflammation. Controlling the nature and timing of neutrophil cell death in these diseases may therefore promote resolution of skin inflammation.

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**Capsule**

**Aberrant B cell repertoire selection associated with HIV neutralizing antibody breadth**

A goal of human immunodeficiency virus (HIV) vaccine development is to elicit antibodies with neutralizing breadth. Broadly neutralizing antibodies (bNabs) to HIV often have unusual sequences with long heavy-chain complementarity-determining region loops, high somatic mutation rates, and polyreactivity. A subset of HIV-infected individuals develops such antibodies, but it is unclear whether this reflects systematic differences in their antibody repertoires or is a consequence of rare stochastic events involving individual clones. Roskin and colleagues sequenced antibody heavy-chain repertoires in a large cohort of HIV-infected individuals with bNAbs responses or no neutralization breadth and uninfected controls, identifying consistent features of bNAbs repertoires and encompassing thousands of B cell clones per individual with correlated T cell phenotypes. These repertoire features were not observed during chronic cytomegalovirus infection in an independent cohort. These data indicate that the development of numerous B cell lineages with antibody features associated with auto-reactivity may be a key aspect in the development of HIV neutralizing antibody breadth.

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"Out of the quarrel with others we make rhetoric; out of the quarrel with ourselves we make poetry"

William Butler Yeats (1865–1939), writer, Nobel laureate