Is There an Association Between Heparin-Induced Thrombocytopenia (HIT) and Autoimmune Disease?

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Abstract

Background: Heparin-induced thrombocytopenia (HIT) is a drug-induced, IgG medicated autoimmune disorder. HIT that occurs in hospitalized patients is associated with several negative clinical outcomes including increased morbidity, mortality, and increased medical costs. Previous studies have shown associations between comorbid autoimmune diseases, but there is little known about associations between HIT and autoimmunity.

Purpose: To provide clinical data to suggest an association between HIT and autoimmunity

Setting: A single, large Upper Midwest health care system

Design: Retrospective case control study

Methods: Retrospective chart review of 59 cases with a diagnosis of HIT and 251 matched controls without a HIT diagnosis comparing the prevalence of autoimmunity in each group.

Results: Patients with a diagnosis of HIT were significantly more likely to have a comorbid autoimmune disease than those without a HIT diagnosis (55.9% vs. 10.8%, p=0.000). In disease specific analyses, patients with a diagnosis of HIT were significantly more likely to have a diagnosis of antiphospholipid syndrome (15.3% vs. 0.0%, p=0.000), systemic lupus erythematosus (8.5% vs. 0.4%, p=0.001), rheumatoid arthritis (5.1% vs. 0.0%, p=0.007), Hashimoto’s thyroiditis (13.6% vs. 3.6%, p=0.006), or nonischemic cardiomyopathy (5.1% vs. 0.0%, p=0.007). HIT cases were significantly older than controls in this study (p=0.000).

Conclusion: This novel study gives evidence to suggest an association between heparin-induced thrombocytopenia and autoimmune disease. This study suggests a need for more research into the relationship between HIT and autoimmunity. These results could alter the anticoagulation management of venous thromboembolism (VTE) and acute coronary syndrome (ACS) in patients with a previously identified autoimmune disease.

Introduction

Associations between specific autoimmune diseases have been widely documented and often complicated the management of these disease entities.1–4 It is also widely believed that autoimmune diseases are grossly underdiagnosed or unrecognized, which further conceals important associations and shared risk factors between these clinical syndromes. Given the current lack of understanding of autoimmunity, the likely shared
commonalities in pathogenesis and etiology, and clinical ramifications of autoimmunity on patient outcomes, it is important to elucidate the relationships between autoimmune conditions to improve patient care.\textsuperscript{5}

Heparin-induced thrombocytopenia (HIT) is a believed to be a drug-induced, IgG mediated autoimmune disorder, in which autoantibodies are formed against and bind to conformationally altered epitopes on platelet factor 4 (PF4) when complexed with heparin-based therapeutic agents. This clinical syndrome has the potential to lead to several serious complications, most commonly thromboembolic events including deep-vein thrombosis, pulmonary embolism, myocardial infarction, stroke, peripheral arterial thrombosis, and critical limb ischemia.\textsuperscript{6} Less commonly, HIT has been associated with bleeding complications, including adrenal hemorrhage and gastrointestinal bleeding.\textsuperscript{7,8} HIT can also manifests in acute systemic (anaphylaxis and anaphylactoid) reactions, which have the potential to be fatal, and local skin necrosis.\textsuperscript{9,10} The mortality associated with heparin-induced thrombocytopenia is approximately 5 to 10%, usually secondary to thrombotic complications.\textsuperscript{6}

The commonly held belief that HIT is an idiosyncratic drug reaction is inadequate. It has been well-documented in the past that anti-PF4 autoantibodies can exist in patients who have never been exposed to a heparin-based therapeutic agent.\textsuperscript{11,12} Even more enlightening is the fact that a HIT-like syndrome, meeting both the clinical and serologic features of the disease, has been described in heparin-naïve patients as well.\textsuperscript{13,14} This seemingly suggests that a complex autoimmune pathogenesis may indeed underlie the etiology of this disease entity.

In this case-control study, we attempted to describe an association between HIT and autoimmunity, including specific disease-disease interactions between HIT and particular autoimmune diseases. To our knowledge, no associations have been made between HIT and autoimmunity in general before and previous published literature into this topic matter has been tenuous.\textsuperscript{15}

**Methods**

A hospital-based, case-control study was conducted using data from one large upper Midwestern integrated health system. We performed a retrospective chart review of adults (n=59), 18 years of age and older, diagnosed with heparin-induced thrombocytopenia (HIT), between May 1\textsuperscript{st}, 2009 and December 31\textsuperscript{st}, 2015 at Sanford Health System. The ICD-9 code used to identify HIT cases in our study was 289.84. The primary analysis was a comparison of the prevalence of any autoimmune disease in the group of patients with HIT to the prevalence of any autoimmune disease in a matched control group without HIT (n=251). Control patients were identified using the ICD-9 code V70.0. Secondary analyses were made to examine the association between the prevalence of any one specific autoimmune disease and HIT. For the purposes of this study “autoimmune disease” was defined as any disease that appears on the American Autoimmune Related Disease Association’s “List of Diseases: Autoimmune and Autoimmune-Related Diseases.”\textsuperscript{5,16} Excluded were patients < 18 years of age. Recorded data included the following: age, gender, race, and diagnoses.

SPSS 23.0 for Windows was used to analyze demographic and clinical characteristics of patients. Frequencies and relative percentages were computed for each categorical variable. Fisher’s exact test was performed to determine statistical significance of categorical data and t-test/ANOVA was used to determine the statistical significance continuous variables. All p-values were two-sided, and p-values < 0.05 were considered significant.

**Results**

A total of 60 HIT cases at the Sanford Health were matched with 251 controls without a HIT diagnosis. One case patient was excluded due to being less than 18 years of age at time of data acquisition. Baseline characteristics patients in both groups are reported in Table 1. The only statistical significant difference between the two groups
was age, in that the HIT patient group were significantly older than those in the control (mean age 57.47 vs. 31.75 p= 0.000).

The results of this study are reported in Table 2. Patients with a diagnosis of HIT were significantly more likely to have a comorbid autoimmune disease than those without a HIT diagnosis (55.9% vs. 10.8%, p=0.000). Subgroup analyses were conducted on the most frequently occurring autoimmune diseases. Patients with a diagnosis of HIT were significantly more likely to have a diagnosis of antiphospholipid syndrome (15.3% vs. 0.0%, p=0.000), systemic lupus erythematosus (8.5% vs. 0.4%, p=0.001), rheumatoid arthritis (5.1% vs. 0.0%, p=0.007), Hashimoto’s thyroiditis (13.6% vs. 3.6%, p=0.006), or nonischemic cardiomyopathy (5.1% vs. 0.0%, p=0.007). There was no statistical significance between the case and control groups in terms of a diagnosis of endometriosis (p=0.738). A second set of analyses was done to correct for difference in age between HIT case and control groups by eliminating extremes of age in both groups. This second adjusted analysis yielded similar results to the primary analysis reported here (see supplementary material).

**Table 1. Baseline Characteristics of the Study Patients**

<table>
<thead>
<tr>
<th>Explanatory Variable</th>
<th>Patients with HIT (N=59)</th>
<th>Control Patients (N=251)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>32.2% (N=19)</td>
<td>24.7% (N=62)</td>
<td>0.251</td>
</tr>
<tr>
<td>Female</td>
<td>67.8% (N=40)</td>
<td>75.3% (N=189)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>57.47 (95% CI: 52.1 to 62.84)</td>
<td>31.75 (95% CI: 31.02 to 32.48)</td>
<td>0.000</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>98.3% (N=58)</td>
<td>94.4% (N=237)</td>
<td>.319</td>
</tr>
<tr>
<td>Minority</td>
<td>1.7% (N=1)</td>
<td>5.6% (N=14)</td>
<td></td>
</tr>
<tr>
<td>American Indian</td>
<td>1.7% (N=1)</td>
<td>0.8% (N=2)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.0% (N=0)</td>
<td>1.6% (N=4)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0.0% (N=0)</td>
<td>2.0% (N=5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.0% (N=0)</td>
<td>1.2% (N=3)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Prevalence of Autoimmunity in HIT Cases and Controls**

<table>
<thead>
<tr>
<th>Explanatory Variable</th>
<th>Patients with HIT (N=59)</th>
<th>Control Patients (N=251)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune Disease</td>
<td>55.9% (N=33)</td>
<td>10.8%(N=27)</td>
<td>0.000</td>
</tr>
<tr>
<td>Antiphospholipid Syndrome</td>
<td>15.3% (N=9)</td>
<td>0.0% (N=0)</td>
<td>0.000</td>
</tr>
<tr>
<td>Systemic Lupus Erythematous</td>
<td>8.5% (N=5)</td>
<td>0.4% (N=1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>5.1% (N=3)</td>
<td>0.0% (N=0)</td>
<td>0.007</td>
</tr>
<tr>
<td>Hashimoto’s Thyroiditis</td>
<td>13.6% (N=8)</td>
<td>3.6% (N=9)</td>
<td>0.006</td>
</tr>
<tr>
<td>Nonischemic Cardiomyopathy</td>
<td>5.1% (N=3)</td>
<td>0.0% (N=0)</td>
<td>0.007</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>0.0% (N=0)</td>
<td>1.6% (N=0)</td>
<td>0.738</td>
</tr>
</tbody>
</table>

**Discussion**

Our first of its kind study gives evidence to suggest an association between heparin-induced thrombocytopenia and autoimmune disease. Our study is also the first to establish a relationship between 2 of the “organ-specific” autoimmune diseases, Hashimoto’s thyroiditis and nonischemic cardiomyopathy, and HIT. These findings imply that the underlying disease mechanisms that allows for the development of HIT has some commonality with other
autoimmune diseases. Although a cause-and-effect relationship cannot be inferred from a single study our data provides evidence that comorbid autoimmune disease may indeed be a risk factor for the development of HIT. Additionally, our findings confirm and extend those of other studies which suggested a relationship between HIT and antiphospholipid syndrome (APS). Our results are also apparently consistent with a previous report of an increase incidence of HIT in female patients, although there was no statistically significant difference in gender between the HIT and control groups in our study.

The strength of our evidence is supported by the fact that prevalence of autoimmunity the HIT group in our study was more than five times the rate in the control group. This association is further supported by the fact that the 10.8% prevalence rate of autoimmunity in the control group in our study is consistent with the estimated nationwide prevalence of autoimmunity suggested by the National Institutes of Health (~7%) and the American Autoimmune Related Diseases Association (~15%). A similar finding was also observed in our study in the Hashimoto’s thyroiditis subgroup.

Our case-control study does have some limitations. In using the V70.0 ICD-9 code in an attempt to select appropriately matched controls without other disease or procedure confounders for our study, we developed a statistically significant difference in age between HIT cases and controls. There is a limited amount of data provided by one study to suggest that age is a risk factor for HIT, although little collaborating evidence exists. In an attempt to rectify this unintended difference between cases and control in this study, we performed a secondary analysis of the data to control for age, which indicated no major changes in our reported findings (see supplementary material). Nevertheless, age may be an important confounding factor in our study. No other statistically significant difference between cases and control were found in term of gender or race.

Another limitation of our study is that it does not establish a timeline between the diagnosis of an autoimmune disease and the diagnosis of HIT in any particular patient. However the validity of designing a study that would accomplish this feat would be in question, given that autoimmune disease are often underdiagnosed and unreported, likely due the lack of provider knowledge of autoimmune disease and the episodic and unspecific presentation of many autoimmune diseases. It also would be difficult to determine at which point an autoimmune disease might confer a risk of HIT given that autoimmune diseases are mainly diagnosed based on both subjective and objective clinical criteria, and that the immunological evidence of an underlying autoimmune disease often predates a diagnosis by a considerable amount of time. For example, it has also been reported that up to 88% patients with diagnosed systemic lupus erythematosus (SLE) have a SLE autoantibody present before the diagnosis, sometimes up to over 9 years before their eventual diagnosis.

Finally, our study is limited in that only 59 HIT cases were indentified using the ICD-9 diagnosis code of 289.84. We would have liked to have an equal amount of cases and control in our study, however HIT is an uncommonly diagnosed clinical entity. Previous studies have determined the incidence of HIT in trauma patients who receive low-molecular-weight heparin (LMWH) as thromboprophylaxis to be 0.36%, and 0.51% in admitted adult medical patients receiving unfractionated heparin (UFH) to prevent venous thromboembolism (VTE).

If the results of our study could be replicated and confirmed, it could have paradigm-shifting effect on the treatment of VTE, VTE prevention strategies, and the management of acute coronary syndrome (ACS) in patients with a previously identified autoimmune disease, particularly those that we found to be the most commonly associated with HIT in our study. The associated mortality, morbidity, and increased medical costs of HIT could be potentially avoided through the use of agents which have not been associated with HIT. Additionally, many of these agents have already been shown to be a reasonable alternative or even superior to heparin-based therapeutic agents. Thus far, provider unfamiliarity and increased drug costs have prevented some of the
non-HIT associated agents from widespread use, however given that previously published studies have found that a HIT diagnosed increases the cost of a medical admission by more than $30,000, it could make sense to employ these agents more widespread when indicated.  

Fondaparinux is a synthetic, parenterally available, factor Xa inhibitor with favorable pharmacokinetic behavior versus LMWH or UFH. Previous studies have shown fondaparinux to be superior to enoxaparin for the treatment of acute coronary syndromes in term of reducing major bleeding and 30 day mortality.26 Fondaparinux (2.5 mg once daily) has also been shown to be more effective than standard 40-mg once-daily enoxaparin for the preventing venous thromboembolism and proximal deep-vein thrombosis following total hip replacement/hip fracture surgery.27 Caveats to using fondaparinux in HIT patients are that fondaparinux is contraindicated in patients with a creatinine clearance of less than 30 mL/min or a body weight less than 50kg.28 Fondaparinux also currently lacks the FDA approval for heparin-induced thrombocytopenia, however previous studies have shown it to be viable option for HIT.29,30

Currently, the only FDA-approved treatments for HIT are the direct thrombin inhibitors argatroban and bivalirudin (in patients undergoing percutaneous coronary intervention). Lepirudin, another direct thrombin inhibitor, did have an indication for HIT, however it has been discontinued by its manufacturer for nonclinical reasons.25 Of the FDA-approved options, argatroban has proven to be the therapy of choice, however it is a difficult agent to use clinically.31 Argatroban is given has a continuous IV infusion and has the potential to elevated INR making a therapeutic transition to warfarin or other vitamin K antagonists challenging.25 Additionally, argatroban is considerably cost prohibitive in that a 10-day infusion of argatroban costs approximately $7,440 more than fondaparinux.32

More recently, the FDA has approved several novel anticoagulants that could also be used instead of heparin-based therapeutics for common indications. The orally available factor Xa inhibitors rivaroxaban and apixaban are both FDA-approval for the prophylaxis and treatment of VTE and for the stroke prevention in patient with nonvalvular atrial fibrillation.25 Large randomized trials have shown these agents to be non-inferior to treatment with enoxaparin and warfarin for VTE with reduced rates of major bleeding.33,34 The most recent CHEST guidelines have adopted the Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) and the oral direct thrombin inhibitor (dabigatran) as their preferred treatment of acute venous thromboembolism.35

Given the results our study, clinical impact of HIT, and the availability and effectiveness of other non-heparin-based therapeutics, we believe that the association between HIT and autoimmune and specific autoimmune disease such as SLE, APS, and Hashimoto’s thyroiditis is nontrivial and deserves more study. A longitudinal study to look at long term outcomes of avoiding the use of heparin-based therapeutics in patients with a history of autoimmune disease and/or other documented risk factors for HIT could shed more light on the management of anticoagulation in this patient population. Furthermore, we believe our study should encourage more research into drug-disease interactions between autoimmune disease and other drugs with what is currently believed to be idiosyncratic adverse events. Further research may help to elucidate the underlying mechanisms that predispose certain patients to drug adverse events given the patient’s comorbidities.

Conclusion

In this novel case-control study, a statistically significant association between the prevalence of heparin-induced thrombocytopenia (HIT) and the prevalence of autoimmune and autoimmune-related disease was found. A statistically significant association was also found between the prevalence of HIT and several specific autoimmune disease including antiphospholipid syndrome, systemic lupus erythematosus, rheumatoid arthritis, Hashimoto’s thyroiditis, and nonischemic cardiomyopathy, but not endometriosis. To our knowledge, our study is also the first
to imply a relationship between HIT and two “organ-specific” autoimmune diseases: Hashimoto’s thyroiditis and nonischemic cardiomyopathy. Age was an important confounding variable in our study. This study emphasizes the need for further research into this relationship and for more study into other drug-disease interactions. The results of this study could suggest a need for change in the management of anticoagulation in patients with a history of autoimmune disease and improve patient outcomes by means of potentially reducing the incidence of HIT in this patient population.

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References


