Burden of Autoimmune Disorders in Patients with Hereditary Angioedema in the United States

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INTRODUCTION
• Patients with HAE due to C1-INH deficiency have a high prevalence of medical comorbidities including hypertension, depression, hypothyroidism, diabetes, chronic pulmonary disease, fluid and electrolyte disorders, obesity, anemia, other neurological disorders, as well as autoimmune disorders.1
• Hereditary angioedema (HAE) due to C1-Inhibitor (C1-INH) deficiency has been associated with certain autoimmune diseases, including lupus, Sjögren syndrome, and thyroiditis.1, 2
• C1-inhibitor (C1-INH) has a regulatory role in the complement cascade and deficiency results in excessive complement activation as well as increased production of bradykinin which is responsible for the clinical manifestations of HAE.3
• In patients with HAE due to C1-INH deficiency, the unregulated activation of the early steps of the classic complement pathway results in low levels of complement components.4
• Low levels of complement components may decrease the elimination of apoptotic cells and immune complexes, which may potentially become sources of autoantigens that could lead to autoimmunity and other immunological abnormalities.5
• The prevalence of autoantibodies, including anticardiolipin, antinuclear antibody (ANA), and thyroid antibodies, is significantly higher in patients with HAE than in the general population.2, 5 Enhanced production of autoantibodies is thought to be related to increased activation of B cells in patients with HAE.1, 6
• With the objective of better understanding the association of comorbid autoimmune disorders in patients with HAE, the prevalence of certain comorbid disorders was characterized in a cohort of HAE patients and compared to a demographically matched non-HAE cohort.

METHODS

Study Design
• Cross-sectional study

Study Period
• The study period was from October 1, 2012 to September 30, 2017.

Data Source
• This real-world cross-sectional study used the Truven Health MarketScan® Commercial Claims Database which includes data on 43.6 million person years from 2016 to present of US private commercial insurance plans.

Study Population
• Patients with HAE were included if they:
  - Had ≥1 prescription claim for HAE-specific medications (icatibant, ecallantide, or intravenous or subcutaneous C1-INH) at any time from October 1, 2012 to September 30, 2016.
  - Had continuous health plan enrollment for ≥6 months pre-index and ≥12 months post-index date (follow-up period).

- Non-HAE patients were included if they had no evidence of a HAE diagnosis or HAE medication prescription. For HAE, the index date was assigned randomly. Each HAE patient was matched with 5 non-HAE patients who were identical in terms of age, region, sex, and health plan.

Patients with ICD-9-CM 10 (9th and 10th revisions of the International Statistical Classification of Diseases and Related Health Problems) diagnosis codes for the following autoimmune disorders were identified throughout the study period: ICD-9, 710; ICD-10, M320.

- Hashimoto’s thyroiditis/autoimmune thyroiditis (ICD-9, 245.2; ICD-10, E083), connective tissue disorder identified with ICD-9, 710.9 and ICD-10, M330.
- Rheumatoid arthritis (ICD-9, 710.1; ICD-10, M350).

• The prevalence of autoantibodies, including anticardiolipin, antinuclear antibody (ANA), and thyroid antibodies, is significantly higher in patients with HAE than in the general population.3, 5-7 Enhanced production of autoantibodies is thought to be related to increased activation of B cells in patients with HAE.1, 6
• With the objective of better understanding the association of comorbid autoimmune disorders in patients with HAE, the prevalence of certain comorbid disorders was characterized in a cohort of HAE patients and compared to a demographically matched non-HAE cohort.

RESULTS
• A total of 2076 patients (346 with HAE, 1730 without HAE) were included in the analysis (Table 1). The mean (SD) age was 40.0 (14.2) years. The female/male ratio was 70.5:29.5.
• Compared with the non-HAE cohort, the HAE cohort had a significantly higher proportion of patients with 2 autoimmune disorders of interest (11.6% vs 3.2%; P<0.0001; Figure 1).
• The HAE cohort had a significantly higher proportion of patients with lupus (9.5% vs 2.3%, P<0.0001), Hashimoto’s/autoimmune thyroiditis (3.2% vs 1.0%, P=0.051), connective tissue disorder (3.2% vs 0.2%, P<0.0001), and sicca (1.7% vs 2.0%, P=0.0002).
• There was no significant difference between the HAE and non-HAE cohorts in the proportion of patients with rheumatoid arthritis (3.2% vs 1.6%, P=0.051).
• Compared with demographically matched patients without HAE, the HAE cohort also had a significantly higher proportion of patients with allergic rhinitis (46.0% vs 18.4%; P<0.0001) and allergic asthma (22.3% vs 8.9%, P<0.0001).

LIMITATIONS
• A potential limitation of this study is misclassification bias (e.g. the presence of a code does not confirm that patient has the condition).

CONCLUSIONS
• Patients with HAE have a higher prevalence of lupus, sicca (Sjögren syndrome), Hashimoto’s thyroiditis/autoimmune thyroiditis, and connective tissue disorder compared with demographically matched non-HAE patients.
• HAE patients also have a higher prevalence of allergic rhinitis and asthma.
• Further research is needed to validate these results and assess the impact of HAE management on autoimmune disease.

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References:

Table 1. Demographic and clinical characteristics of patients with HAE and without HAE

![Table 1](https://example.com/table1.png)

Figure 1. Prevalence of autoimmune disorders in patients with and without HAE

![Figure 1](https://example.com/figure1.png)