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

Raffi Tachdjian,[1] Sujana Borra,[2] Dylan Supina,[3] Ami S. Patel[3]

[1]David Geffen School of Medicine, University of California-Los Angeles, Los Angeles, California, USA; [2]STATinMED Research, Plano, Texas, USA; [3]CSL Behring, King of Prussia, Pennsylvania, USA

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 early 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.[4]
- 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.[5,8]
- With the objective of better understanding the association of comorbid autoimmune disorders in patients with HAE, the prevalence of certain 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 in 2016 from private US commercial insurance plans.

Study Population

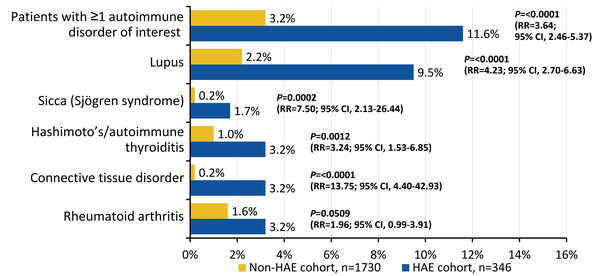
- Patients with HAE were included if they:
  - Had ≥1 prescription claim for HAE-specific medications (icatibant, ecallantide, or intravenous or subcutaneous C1-INH) at any time during the identification period (from April 1, 2013 to September 30, 2016).
  - Were ≥12 years of age on the index date (defined as the date of first HAE prescription claim).
  - Had continuous health plan enrollment for ≥6 months pre-index (baseline) 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/ICD-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: **lupus** (ICD-9, 710; ICD-10, M320), **Hashimoto's thyroiditis/autoimmune thyroiditis** (ICD-9, 245,2; ICD-10, E063), **connective tissue disorder** (ICD-9, 710.8 and 710.9; ICD-10, M351 and M359), **rheumatoid arthritis** (ICD-9, 714; ICD-10, M0549), and **sicca (Sjögren syndrome)** (ICD-9, 710.2; ICD-10, M3500).

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

Patient characteristics	HAE cohort (n=346)	%	Non-HAE cohort (n=1730)
Age, mean (SD)	40.0 (14.2) years		40.0 (14.2) years
12-19 years	40	11.6%	200
20-29 years	51	14.7%	255
30-39 years	69	19.9%	345
40-49 years	74	21.4%	370
50-59 years	89	25.7%	445
60 years	23	6.7%	115
Sex			
Female	102	29.5%	510
Male	244	70.5%	1220
US geographic region			
Northeast	78	22.5%	390
North central	51	14.7%	255
South	147	42.5%	735
West	63	18.2%	315
Unknown	7	2.0%	35
Health plan type			
HMO	44	12.7%	220
POS	37	10.7%	185
PPO	204	59.0%	1020
Consumer driven health plan	27	7.8%	135
Others	34	9.8%	170

HMO = health maintenance organization; POS = point of service; PPO = preferred provider organization.

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



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 ≥1 autoimmune disorder 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*=0.0012), connective tissue disorder (3.2% vs 0.2%, *P*<0.0001), and sicca (1.7% vs 0.2%, *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 8.8%; *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.

Presented at the AAAAI Annual Meeting, March 13-16, 2020, Philadelphia, Pennsylvania, USA.

Funding: CSL Behring

References: **1.** Zilberberg MD, Nathanson BH, Jacobsen T, Tillotson G. Descriptive epidemiology of hereditary angioedema hospitalizations in the United States, 2004-2007. *Allergy and Asthma Proceedings.* 2011;32(3):248-254. **2.** Brickman CM, Tsokos GC, Balow JE, et al. Immunoregulatory disorders associated with hereditary angioedema. I. Clinical manifestations of autoimmune disease. *J Allergy Clin Immunol.* 1986;77(5): 749-757. **3.** Farkas H, Csuka D, Gács J, et al. Lack of increased prevalence of immunoregulatory disorders in hereditary angioedema due to C1-inhibitor deficiency. *Clin Immunol.* 2011;141(1):58-66. **4.** Honda D, Ohsawa I, Sato N, et al. Diminished capacity of opsonization and immune complex solubilization, and detection of anti-C1q antibodies in sera from patients with hereditary angioedema. *Allergol Int.* 2017;66(4):603-609. **5.** Kessel A, Peri R, Perricone R, et al. The autoreactivity of B cells in hereditary angioedema due to C1 inhibitor deficiency. *Clin Exp Immunol.* 2012;167(3):422-428. **6.** Dortas Junior SD, Valle SO, Levy SA, et al. Prevalence of autoantibodies in a group of hereditary angioedema patients. *An Bras Dermatol.* 2012;87(2):332-334. **7.** Muhlemann MF, Macrae KD, Smith AM, et al. Hereditary angioedema and thyroid autoimmunity. *J Clin Pathol.* 1987;40(5):518-523. **8.** Triggianese P, Guarino MD, Ballanti E, Chimenti MS, Perricone R. Hereditary angioedema and autoimmunity. *Isr Med Assoc J.* 2014;16(10):622-624.

CSL Behring