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Prevalence of APECED-Like Clinical Disease in an Electronic Health Record Database, USA

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To the Editor:

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), also known as autoimmune polyglandular syndrome type-1 (APS-1), is a monogenic autoimmune disease most often caused by biallelic loss-of-function mutations in the autoimmune regulator (*AIRE*) gene, which impair central immune tolerance [1]. APECED clinically features a characteristic classic triad of chronic mucocutaneous candidiasis (CMC), primary adrenal insufficiency (AI), and primary hypoparathyroidism (HPT). Developing any diagnostic dyad among the classic triad manifestations is used to establish a clinical diagnosis [2, 3]. Beyond the classic triad manifestations, we have recently shown that APECED patients from the Americas can also develop >25 other endocrine and non-endocrine manifestations, many of which remain poorly recognized among clinicians, and some may occur before the development of a classic diagnostic dyad [4, 5]. The prevalence of APECED is higher in certain populations such as Persian Jews (1:9000), Sardinians (1:14,400), and Finns (1:25,000) [5]. However, the prevalence of APECED remains unknown in the USA.

To attempt to address this question, we obtained data from the Cerner *HealthFacts* dataset, an electronic health record database containing >400 million inpatient and outpatient medical encounters from across the USA (Supplementary Table 1). For our analysis, we extracted all patients from 2009 to 2017 who had at least one International Classification of Diseases (ICD) 9th and 10th revision diagnosis code for the APECED classic triad manifestations of CMC, AI, or HPT (Supplementary Table 2). Patients needed to have ICD codes for CMC at two or more separate encounters to exclude individuals who had a single occurrence of candidiasis due to other causes (e.g., antibiotic or corticosteroid use). We

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calculated the number of individuals who had the APECED classic triad, or any diagnostic dyad (i.e., CMC and AI, or CMC and HPT, or AI and HPT). To increase the specificity of our definition for a diagnostic dyad or triad, we excluded individuals who only had vulvovaginal candidiasis (VVC) or dermal candidiasis without evidence of oropharyngeal and/or esophageal candidiasis because (a) VVC is relatively common in the general population affecting ~75% of all women during their reproductive years, and (b) VVC and dermal candidiasis seldom develop in APECED patients without concurrent oropharyngeal and/or esophageal candidiasis [5]. Moreover, because the vast majority of APECED patients also develop non-triad clinical manifestations [5], we assessed the incidence of several autoimmune comorbidities observed in APECED patients and considered that their co-existence together with a classic diagnostic dyad or triad may further increase specificity in the estimation of the prevalence of APECED-like disease (Supplementary Table 2). We also assessed the number of individuals who had the ICD-10 code E31.0 “Autoimmune polyglandular failure.” No ICD-9 code exists for autoimmune polyglandular failure or alternative disease names. The rate of APECED-like illness per 100,000 patients and 95% confidence intervals (CIs) were calculated as the number of patients with APECED-like clinical disease over the total number of patients in the Cerner *HealthFacts* database from 2009 to 2017.

Among a total of 62,294,953 unique patients, we identified 505,080 patients who had at least one ICD code of interest. Of these, 1677 had a classic diagnostic dyad or triad. Specifically, 64 had ICD codes for all classic triad manifestations of CMC, AI, and HPT. Of the remaining 1613 patients, 1098 had ICD codes for AI and CMC, 380 had ICD codes for AI and HPT, and 135 had ICD codes for CMC and HPT (Table 1). When we applied the filter excluding individuals with only VVC or dermal candidiasis, the total number of patients dropped to 1436, resulting from a 15% loss of cases from the AI-CMC group, 33% from the AI-CMC-HPT group, and 40% from the CMC-HPT group. When we required the presence of at least one additional non-classic triad autoimmune comorbidity, the total number of patients with APECED-like clinical disease dropped to 662, with 70% of individuals filtered out from the AI-CMC group, 25% from the AI-CMC-HPT group, 39% from the AI-HPT group, and 62% from the CMC-HPT group. Finally, when we applied both exclusion criteria together, we found 565 individuals with APECED-like clinical illness, with most individuals filtered out from the AI-CMC and CMC-HPT groups (Table 1). Of note, when the dataset was queried for ICD-10 E31.0 “Autoimmune polyglandular failure,” we found 279 individuals. However, only 149 of these patients had one of the AI, CMC, or HPT diagnostic codes, and only 23 of them were in patients meeting the classic triad or any of the classic dyads. Specifically, 5 patients had the classic diagnostic triad, 14 patients had the diagnostic dyad of AI-HPT, and 4 patients had the diagnostic dyad of AI-CMC. No patients were identified within the CMC-HPT group. Thus, most patients coded as manifesting “Autoimmune polyglandular failure” in the Cerner *HealthFacts* database appear likely to suffer from the polygenic autoimmune syndromes APS type-2 and APS type-3.

We next calculated the prevalence rate for each of the definitions we used. Including all individuals with any classic diagnostic dyad or the classic triad, the prevalence of APECED-like clinical disease was 2.7 (95% CI, 2.6–2.8) per 100,000 patients. Excluding VVC/dermal candidiasis-only designations of CMC resulted in a prevalence of 2.3 (95% CI, 2.2–2.4) per

100,000 patients. Requiring the co-existence of a classic diagnostic dyad or triad together with at least one additional non-triad autoimmune comorbidity resulted in a prevalence of 1.1 (95% CI, 1.0–1.1) per 100,000. Finally, when applying the most stringent definition of carrying a classic diagnostic dyad or triad together with at least one additional non-triad autoimmune manifestation while also excluding VVC/dermal candidiasis-only CMC, we found a prevalence of APECED-like clinical disease of 0.9 (95% CI, 0.8–1.0) per 100,000 patients (Table 1).

Herein, we exploited an electronic health record database containing >400 million medical encounters from 2009 to 2017 to estimate the prevalence of APECED-like clinical disease in the USA. We applied a series of stringent criteria to increase the specificity of our analyses and found that the prevalence of APECED-like clinical disease appears to be at least 0.9 per 100,000 patients. Our study has limitations. As with any study evaluating ICD codes, there could be misclassification if codes are missing or used incorrectly, resulting in either overestimation or underestimation of disease prevalence. Indeed, the sensitivity of ICD codes varies widely by disease and code. Additionally, the *HealthFacts* dataset does not capture all medical encounters across the USA and therefore might not be representative of APECED prevalence in the entire country. Moreover, because many US healthcare recipients do not always stay within network, it is possible that medical encounters using relevant ICD codes have been missed if that facility did not participate in the Cerner electronic health record, resulting in an underestimation of the true prevalence of disease. Underestimation could also result from patients in this dataset who have not yet developed a diagnostic dyad, as these manifestations may develop years apart [4, 5]. Furthermore, prevalence overestimation in this analysis could result from miscoding or alternative etiologies of candidiasis or iatrogenic adrenal insufficiency not captured in ICD codes, although by creating increasingly stringent filters, we attempted to show the lower and upper limits of our estimates. Nonetheless, our study provides a first analysis of the prevalence of APECED clinical disease in the USA and indicates that several hundred-to-thousand patients with this autoimmune syndrome likely exist in the USA. Increased awareness by clinicians from multiple specialties should enhance recognition and diagnosis, which should improve the prognosis of affected patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Estimates of prevalence of APECED-like clinical disease in the US derived from analysis of the *Cerner HealthFacts* dataset

Grouping	Number of distinct patients in APECED group				Prevalence per 100,000 patients (95% CI)			
	Any dyad (2+ distinct episodes of candidiasis for CMC)	Any dyad (2+ distinct episodes of candidiasis excluding VVC- or skin-only CMC)	Any dyad (2+ distinct episodes of candidiasis for CMC) + ≥1 additional autoimmune comorbidity	Any dyad (2+ distinct episodes of candidiasis excluding VVC- or skin-only CMC) + ≥1 additional autoimmune comorbidity	Any dyad (2+ distinct episodes of candidiasis for CMC)	Any dyad (2+ distinct episodes of candidiasis excluding VVC- or skin-only CMC)	Any dyad (2+ distinct episodes of candidiasis for CMC) + ≥1 additional autoimmune comorbidity	Any dyad (2+ distinct episodes of candidiasis excluding VVC- or skin-only CMC) + ≥1 additional autoimmune comorbidity
AI-CMC	1098	932	330	280	1.763 (1.66, 1.868)	1.496 (1.402, 1.594)	0.53 (0.474, 0.588)	0.449 (0.398, 0.504)
AI-CMC-HPT	64	43	48	29	0.103 (0.079, 0.129)	0.069 (0.05, 0.091)	0.077 (0.057, 0.1)	0.047 (0.031, 0.065)
AI-HPT	380	380	233	233	0.61 (0.55, 0.673)	0.61 (0.55, 0.673)	0.374 (0.328, 0.424)	0.374 (0.328, 0.424)
CMC-HPT	135	81	51	23	0.217 (0.182, 0.255)	0.13 (0.103, 0.16)	0.082 (0.061, 0.106)	0.037 (0.023, 0.054)
Total	1677	1436	662	565	2.692 (2.565, 2.822)	2.305 (2.188, 2.426)	1.063 (0.983, 1.145)	0.907 (0.834, 0.983)

APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; *CMC*, chronic mucocutaneous candidiasis; *AI*, adrenal insufficiency; *HPT*, hypoparathyroidism; *VVC*, vulvovaginal candidiasis