Disease- and Glucocorticoid-Related Comorbidities in Classic Congenital Adrenal Hyperplasia: A Claims-Based Retrospective Cohort Analysis

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INTRODUCTION

- Classic congenital adrenal hyperplasia (CAH) is a condition most often caused by 21-hydroxylase deficiency (21-OHD), leading to impaired cortisol and aldosterone biosynthesis.[1]
- Glucocorticoids are currently used not only to replace the endogenous cortisol deficiency, but at supraphysiological doses (ie, higher than needed for cortisol replacement) to manage excess adrenal androgen production in these patients.[1-5]
- Long-term exposure to supraphysiologic doses of glucocorticoids leads to increased risk of cardiovascular, metabolic, and skeletal complications while excess androgen can lead to issues such as short stature and fertility problems.[2,4-10]

OBJECTIVE

- The objective of this research was to characterize the clinical burden related to disease treatment (supraphysiologic glucocorticoid dosing) and to the disease itself (excess androgen production).

METHODS

- A retrospective, cohort study was conducted analyzing insurance claims from 2020-2022 within the Merative MarketScan®Research Databases (commercial and multi-state Medicaid).
- The classic CAH cohort was defined using a proprietary algorithm, which includes patients with 2 or more instances of E25.0 diagnosis codes at least 30 days apart. The patient identification period was 2020-2022 and patients were required to have 12 months of continuous enrollment in 2022.
- Classic CAH patients were matched to a general population (GenPop) comparator cohort to quantify the net comorbidity burden faced by patients with classic CAH over 1 year (2022).
- The frequency of comorbidities related to androgens and/or supraphysiologic glucocorticoid dosing were captured using International Classification of Diseases, 10th Revision (ICD-10) codes.
- Matching between classic CAH and GenPop cohorts was based on age, sex, payer type, region, and enrollment duration, with a 1:5 ratio (ie, 5 GenPop patients for every classic CAH patient).

Outcomes

- Baseline and clinical characteristics included age, region, sex, Charlson Comorbidity Index (CCI), and health plan type.
- The frequency of comorbidities in classic CAH patients were compared to the GenPop, with a subgroup analysis of pediatric (age <18 years) and adult (age ≥18 years) classic CAH patients.

Statistical analysis

- Continuous variables were summarized with mean and standard deviation (SD) and categorical variables with count and percentage.
- Statistical significance (P<0.05) was tested between classic CAH and GenPop groups and between adult and pediatric groups using R4.2.2 (R Core Team, 2022).

RESULTS

- 687 classic CAH patients (total) were matched with 3,435 GenPop comparator patients with claims activity from 2020-2022. Over half (57%) of classic CAH patients were female and the mean age was 20 years (Table 1).

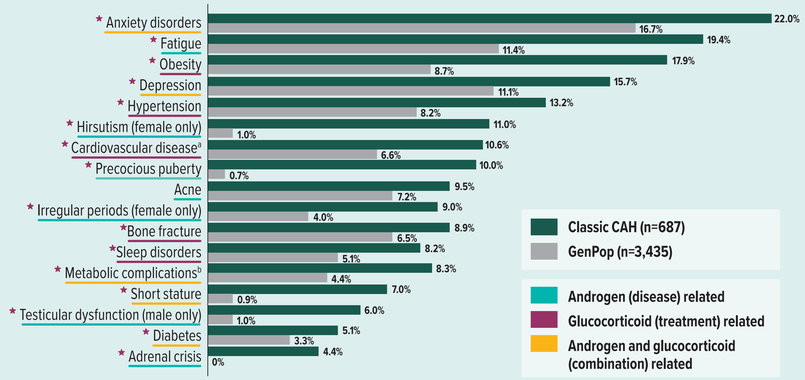
Table 1. Classic CAH and matched general population comparator cohort definitions

	Baseline characteristics	
	Classic CAH	GenPop
Overall sample size, n	687	3,435
Commercial health plan, n (%)	420 (61)	2,100 (61)
Age, years, mean (SD)	20 (15)	20 (15)
Adults (≥18 years), n (%)	324 (47)	1,620 (47)
Regional distribution, n (%)		
Midwest	70 (10)	350 (10)
Northeast	70 (10)	350 (10)
South	149 (22)	745 (22)
West	68 (10)	340 (10)
Unknown	330 (48)	1,650 (48)
Enrollment duration, months, mean (SD)	19 (9)	19 (9)
Charlson Comorbidity Index, mean (SD)	0.3 (0.8)	0.2 (0.7)

Overall comorbidity rates between classic CAH vs general population

- Compared to GenPop, classic CAH patients had significantly greater rates of multiple chronic conditions related to both excess androgens and supraphysiologic glucocorticoid doses, including short stature (7.0% vs 0.9%), anxiety disorders (22.0% vs 16.7%), and diabetes (5.1% vs 3.3%) (P<0.05) (**Figure 1**).
- Rates of conditions often related to excess androgens, such as hirsutism (11.0% vs 1.0%), irregular periods (9.0% vs 4.0%), testicular dysfunction (6.0% vs 1.0%), and precocious puberty (9.5% vs 0.7%), were significantly greater in classic CAH patients (P<0.05).

Figure 1. Top comorbidities, classic CAH vs GenPop

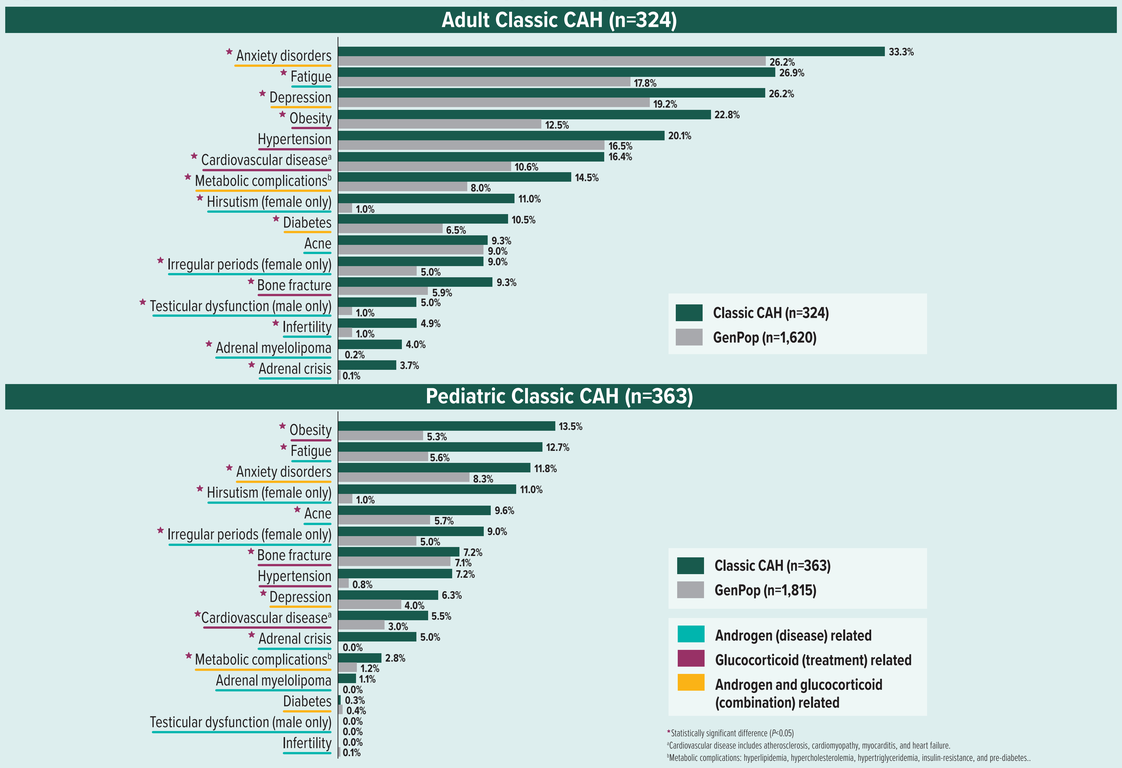


*Statistically significant difference (P<0.05).
[a]Cardiovascular disease includes atherosclerosis, cardiomyopathy, myocarditis, and heart failure.
[b]Metabolic complications: hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, insulin-resistance, and pre-diabetes.

Comparison of comorbidities across adult and pediatric classic CAH patients vs GenPop

- A similar trend of higher comorbidity rates in classic CAH was observed in the subgroup analysis of adult and pediatric patients with classic CAH (**Figure 2**).
- Adults patients with classic CAH had higher rates of comorbidities compared with pediatric patients with classic CAH.
- Cardiovascular disease and associated risk factors such as obesity (pediatric: 13.5% vs 5.3%; adult: 22.8% vs 12.5%) and hypertension (pediatric: 7.2% vs 0.8%; adult: 20.1% vs 16.5%) were more prevalent among adult vs pediatric patients with classic CAH.

Figure 2. Top comorbidities in classic CAH vs GenPop by patient age (2020-2022)



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[a]Cardiovascular disease includes atherosclerosis, cardiomyopathy, myocarditis, and heart failure.
[b]Metabolic complications: hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, insulin-resistance, and pre-diabetes..

LIMITATIONS

- Patient identification was reliant on ICD-10 coding, and some of the diagnosis data that captured medical conditions may be subject to miscoding and do not include qualitative inputs (eg, weight, blood pressure from medical notes), leading to underestimation of the most common comorbidities.
- Results from this study cannot be generalized to all patients with classic CAH, as patients who have less access to the healthcare system or who are uninsured are less likely to be captured in these data.

CONCLUSIONS

- Despite the use of supraphysiologic glucocorticoid dosing meant to control excess androgens, patients with classic CAH still presented with disease-related clinical complications. These complications demonstrate the challenge in balancing the negative effects of supraphysiologic glucocorticoid therapy with reducing excess androgens. Our results highlight the difficulty confronted by patients and healthcare providers to make an appropriate treatment decision and illustrate an unmet need in patients with classic CAH.
- A greater prevalence of many comorbidities was observed in adults compared to pediatric patients, reflecting that these conditions develop over longer periods of time with chronic exposure to supraphysiologic glucocorticoids.
  - The need for early treatment optimization is of great importance in pediatric patients to help prevent or delay these conditions.
- The overall burden of classic CAH as demonstrated by the presence of comorbidities in the cohort is most likely underestimated due to reliance of ICD-10 coding through administrative insurance claims.

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PRESENTED AT ISPOR ANNUAL 2024
MAY 5-8, 2024; ATLANTA, GA.