Growth-Related Characteristics of Patients <18 Years of Age with Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency (21OHD): Real World Evidence from the I-CAH Registry

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INTRODUCTION

- Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD) is a rare, autosomal recessive condition of the adrenal cortex leading to a lack of cortisol production and compensatory elevated ACTH secretion, which drives excess androgen production[1]
- Chronic exposure to excess androgens, coupled with treatment involving supraphysiologic glucocorticoid doses, can lead to premature epiphyseal closure and shorter final adult height[2]
- Data from the International CAH (I-CAH) Registry were analyzed to identify growth-related characteristics of children and adolescents with 21OHD CAH

METHODS

PATIENT POPULATION

- Analyses were based on data from the I-CAH Registry, an international database of pseudonymised patient information as approved by the National Research Ethics Service in the United Kingdom[3]
  - Clinicians depost data into the registry with informed consent from patients or guardians
  - The database currently has >1500 cases of CAH from 65 sites in 29 countries, with longitudinal data from patient visits dating back to 1989
- The I-CAH Registry was queried on April 2, 2021 for patients who met the following criteria:
  - Clinical diagnosis of CYP21A enzyme deficiency
  - Age <18 years at visit
  - ≥1 available growth-related assessment (height, weight, or bone age [BA])
  - Available date of birth (day/month/year or month/year)
- Patient data were categorized based on sex and age at time of visit
  - Due to the longitudinal nature of the database, patients may be included in >1 age subgroup

ANALYSES

- Cross-sectional assessments included patient characteristics (sex, country, number of visits) and growth-related assessments (chronological age [CA], height, weight, and BA)
- Median standard deviation scores (Z scores) were calculated for height for CA (height-CA Z) and height for BA (height-BA Z) using LMS parameters as follows:
  - Z = [((value / M)^L) – 1] / (S * L)
  - L (skew), M (median), and S (generalized coefficient of variation) values were from CDC growth chart reference data[4]
  - Z scores for patients 0 to <2 years are not presented since only two choices were available for BA ("0" or "1") due to limitations of the measurement technology; this may limit interpretability in this subgroup, but their data are included in the overall analyses for completeness
  - Visits with extreme height/weight outliers were excluded (see figure footnotes)
- CA and BA from matched patient visits were compared using analysis of covariance (ANCOVA)

RESULTS

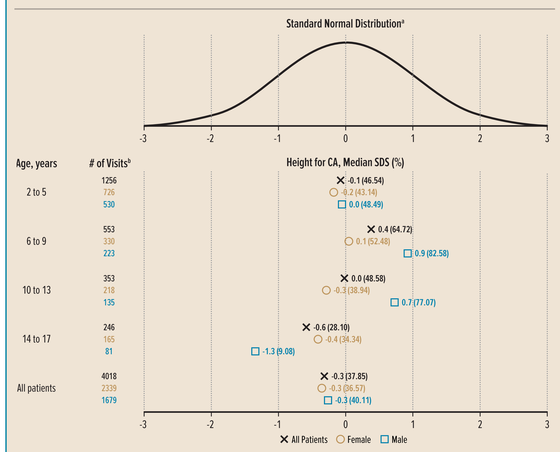
- Of 429 patients who met the inclusion criteria, 247 (57.6%) were female; most (58.7%) were from Europe (**Table 1**)

Table 1. Patient Characteristics

	0 to <2 Years (n=333)	2 to 5 Years (n=302)	6 to 9 Years (n=132)	10 to 13 Years (n=90)	14 to 17 Years (n=73)	All Patients (n=429)
Number of visits, n	1610	1256	553	353	246	4018
Sex, n (%)						
Female	191 (57.4)	167 (55.3)	76 (57.6)	54 (60.0)	49 (67.1)	247 (57.6)
Male	142 (42.6)	135 (44.7)	56 (42.4)	36 (40.0)	24 (32.9)	182 (42.4)
Country, n (%)						
Turkey	53 (15.9)	50 (16.6)	24 (18.2)	11 (12.2)	3 (4.1)	65 (15.2)
Brazil	45 (13.5)	40 (13.2)	24 (18.2)	21 (23.3)	20 (27.4)	61 (14.2)
Germany	53 (15.9)	49 (16.2)	11 (8.3)	3 (3.3)	5 (6.8)	58 (13.5)
United Kingdom	23 (6.9)	25 (8.3)	17 (12.9)	24 (26.7)	25 (34.2)	54 (12.6)
Netherlands	36 (10.8)	31 (10.3)	0 (0)	0 (0)	0 (0)	36 (8.4)
Belgium	17 (5.1)	13 (4.3)	11 (8.3)	2 (2.2)	4 (5.5)	27 (6.3)
Italy	24 (7.2)	25 (8.3)	0 (0)	0 (0)	0 (0)	26 (6.1)
Egypt	20 (6.0)	18 (6.0)	4 (3.0)	2 (2.2)	0 (0)	23 (5.4)
Switzerland	17 (5.1)	16 (5.3)	13 (9.8)	11 (12.2)	6 (8.2)	19 (4.4)
Sweden	14 (4.2)	16 (5.3)	14 (10.6)	6 (6.7)	4 (5.5)	16 (3.7)
Argentina	14 (4.2)	8 (2.6)	3 (2.3)	2 (2.2)	0 (0)	14 (3.3)
Serbia	8 (2.4)	8 (2.6)	6 (4.5)	8 (8.9)	4 (5.5)	14 (3.3)
Sri Lanka	5 (1.5)	0 (0)	3 (2.3)	0 (0)	2 (2.7)	10 (2.3)
Israel	4 (1.2)	2 (0.7)	0 (0)	0 (0)	0 (0)	4 (0.9)
Romania	0 (0)	1 (0.3)	1 (0.8)	0 (0)	0 (0)	1 (0.2)
Bulgaria	0 (0)	0 (0)	1 (0.8)	0 (0)	0 (0)	1 (0.2)

- No discernible pattern by age group was found for median height-CA Z scores, but males aged 14-17 years had height deficits relative to chronological age (**Figure 1**)

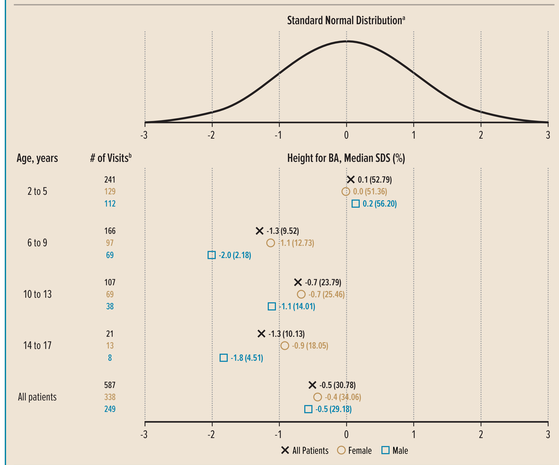
Figure 1. Median Height-CA Z Scores Indicate Height Deficits in Males Aged 14-17 Years



[a]CDC growth chart data were transformed to standard normal distribution to derive Z scores.
[b]Visits with extreme height or weight outliers (male 2-5 years, n=2; female 6-9 years, n=1; female 10-13 years, n=1) were excluded from analysis.
CA, chronological age; CDC, Center for Disease Control; SDS, standard deviation score.

- Height-BA Z scores indicated a trend for shorter height relative to bone age in patients older than 6 years of age (**Figure 2**)

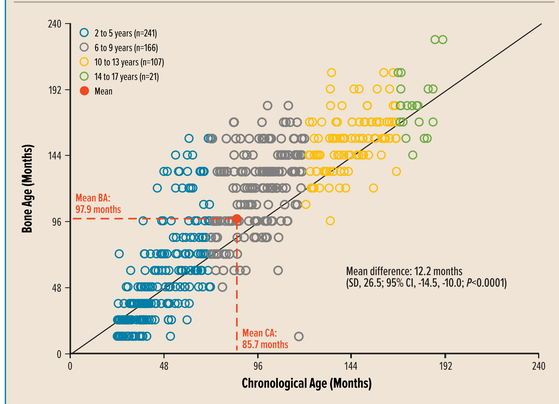
Figure 2. Median Height-BA Z Scores Indicate Shorter Height Relative to Advancing Bone Age



[a]CDC growth chart data were transformed to standard normal distribution to derive Z scores.
[b]Visits with extreme height or weight outliers (female 10-13 years, n=1) were excluded from analysis.
BA, bone age; CDC, Center for Disease Control; SDS, standard deviation score.

- Mean BA for 535 matched patient visits was advanced by 12.2 months compared to mean CA (p<0.0001) (**Figure 3, Table 2**)

Figure 3. Paired BA/CA Values[a] Indicate that Bone Age Advanced by 12 Months Relative to Chronological Age



[a]Based on matched BA and CA data from 535 patient visits (2 to 5 years, n=241; 6 to 9 years, n=166; 10 to 13 years, n=107; 14 to 17 years, n=21). Visits with extreme bone age outliers (2 to 5 years, n=3) were excluded from analysis.
BA, bone age; CA, chronological age; CI, confidence interval; SD, standard deviation.

CONCLUSIONS

- The I-CAH Registry offers the opportunity to study a variety of growth determinants and measurements in children and adolescents with classic CAH
- This is the first study to examine growth-related characteristics using global data from the I-CAH Registry (in contrast to previous analyses based on EU-only data)
- The current analyses suggest that children with classic CAH trend shorter than their peers (despite more advanced BA), which reduces their height potential and highlights the importance of proper disease management throughout childhood development, including puberty
- Analyses may have been limited by the usual constraints of real-world studies (e.g., erroneous data entries), but the number of patients in the dataset support the overall quality of these results

Table 2. Advanced BA Most Pronounced in Males Aged 6 to 9 Years

Mean difference (SD), months	2 to 5 Years	6 to 9 Years	10 to 13 Years	14 to 17 Years	All Patients
All patients	6.5 (26.6)	22.8 (28.1)	10.2 (18.9)	4.3 (21.4)	12.2 (26.5)
Male	11.2 (32.8)	36.2 (32.0)	16.7 (20.4)	1.2 (21.1)	19.4 (32.4)
Female	2.5 (19.1)	13.3 (20.3)	6.6 (17.1)	6.2 (22.2)	7.0 (19.6)

BA, bone age; CA, chronological age; SD, standard deviation.

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