Linear Growth of Children with Congenital Adrenal Hyperplasia
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ABSTRACT

Background: Helping children with congenital adrenal hyperplasia (CAH) to reach a normal adult final height is the main goal of treatment. Objective: The aim of the current study is to evaluate the linear growth in kids and teens with congenital adrenal hyperplasia.

Patients and methods: A cross sectional study was conducted on 71 Egyptian children with CAH who attended the Diabetes and Endocrine Pediatric Unit at Assiut University Children Hospital, Assiut, Egypt in the period from the start of January 2020 to the end of December 2020. A control group included 71 healthy children matched for age and sex.

Results: A total 71 Egyptian children with CAH were recruited; 28 females and 43 males. Of the recruited children, 60 of them were salt loosing type and 11 of them were simple virilizing. The median age at presentation was 5 years and ranged from 1 up to 13 years old. Positive family history was documented in 13 (18.3%) patients. CAH cases were significantly stunted compared to controls (P<0.001). Those presented with salt loosing CAH have significantly lower height and significantly higher BMI as compared to their controls.

Conclusions: The multifaceted issue of linear growth in children with CAH is significant. In order to restore normal adult final height in these patients, it is crucial that the condition is appropriately controlled clinically and biochemically through stringent adherence to medicinal therapy as well as continued clinical and laboratory surveillance.

Keywords: Linear growth, Congenital adrenal hyperplasia, Final adult height, Case control study, Assiut University.

BACKGROUND

Congenital adrenal hyperplasias (CAHs) are a group of autosomal recessive diseases that impair the steroidogenesis of the adrenal glands.

Mutations in the 21-hydroxylase (CYP21A2) gene cause the most prevalent type, 21-hydroxylase deficiency (21-OHD). Other types include 11b-hydroxylase deficits linked to mutations in the HSD3B2 and 3b-hydroxysteroid dehydrogenase type 2 (HSD3B2), respectively, genes (1).

According to reports, about one in every 1800 British babies is born with CAH. The incidence ranges from 1:15000 to 1:16000 in North America.

The Yupik people of Alaska have recorded CAH rates as high as 1:280, while the French island of Réunion in the Indian Ocean has reported rates of 1:100; both of these communities are geographically isolated. The documented prevalence of CAH is 1:11655 in the southern state of Santa Catarina and 1:10325 in the middle state of Goiás, both of which routinely include CAH in their public new-born screening programmes (2,3).

About three-quarters of recorded cases of CAH are salt-losing, while just one-fourth are not. In white populations, non-classical is more prevalent, with an estimated 1 in 1000–2000 cases. Particular ethnic groups, like Ashkenazi Jews, are more likely to experience it. Hyperandrogenism is frequently brought on by the moderate non-classic variety (4).

Replacement doses of glucocorticoids (GC) and mineralocorticoids are used to treat typical 21-OHD in order to minimise excess androgen and promote appropriate linear growth. However, according to numerous series, these kids’ growth is below average when compared to both the reference population and the goal height (TH) (5).

Uncertainty surrounds the causes of insufficient growth and final height (FH) impairment. One of the main factors is the challenge of striking a delicate balance between the suppression of excessive androgen production, which stimulates bone maturation, and appropriate GC replacement, which can be harmful to growth even at slightly supraphysiologic dosages.

The aim of the current study is to evaluate the linear growth in kids and teens with congenital adrenal hyperplasia.

PATIENTS AND METHODS

A cross sectional study was conducted at one of major tertiary health care hospitals Assiut University Children Hospital (AUCH), Assiut, Egypt in the period from the start of January 2020 to the end of December 2020.

Participants in the current study were all children diagnosed with CAH receiving glucocorticoid and/or mineralocorticoid replacement treatment and receiving routine follow-up at the Diabetes and Endocrine Pediatric Unit, AUCH, during the study period. As a control group, an equal number of youngsters of both sexes who appeared to be normal were included.

Eligible children were subjected to complete history taking using structured questionnaire through interview of the patient’s parents. The data included age, sex, consanguinity and positive family history, age at onset, and age at diagnosis. Clinical data included the state of virilization in females and salt-losing manifestations, and laboratory data including cortisol level, ACTH level at 8 AM and 8 PM, 17-hydroxy progesterone (17-OHP), electrolytes (Na+, K+), blood glucose level, wrist x-ray for bone age and greulich and pyle atlas was used as a reference. Androstenedione and
testosterone were not done as they were not available in our hospital.

Therapeutic history included type of steroid (Hydrocortisone, prednisone, dexamethasone), dose (mg/kg/day) for those receiving hydrocortisone and for those receiving prednisone dose was multiplied by 4 and for those receiving dexamethazone dose was multiplied by 25, and treatment compliance.

Complete physical examination of patients and controls included weight measurement using the same electronic digital weighing scale, height measurement using stadiometer while the patient in Frankfurt position, and BMI were calculated by dividing the weight in kilograms by the height square in meters. All measures were plotted on the proper z-score growth Chart. Finally, blood pressure was measured using suitable sphygmomanometer and suitable cuff size. At least 2 measurements of height were obtained 6 months apart to assess the rate of growth.

Follow up investigations every 6 months included blood sugar by using glucometer and patient finger prick, electrolytes (Na+, K+), cortisol, ACTH, and 17-OHP levels, and wrist x-ray for bone age using the method of Greulich and Pyle (6).

Ethical Approval:
The study adhered to the guidelines set forth by Assiut University's Ethical Committee. Assiut University Ethics Board approved the study, and the guardians of the patients received all the information they require regarding the study. All adults who provided care for the children who were a part of the study provided written informed consent. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis
The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 20 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test.

Qualitative data were represented as frequencies and relative percentages. Chi-square test ($\chi^2$) was done to calculate difference between two or more groups of qualitative variables. When the anticipated frequency is less than 5, Fisher’s exact test was utilized in its place. Quantitative data were expressed as mean and standard deviation (SD). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data) or Mann-Whitney U test (non-parametric data). P value ≤0.05 was considered significant.

RESULTS
Our case control study included 71 Egyptian children with CAH (case group) who attended the Diabetes and Endocrine Pediatric Unit at Assiut University Children Hospital, Assiut. A control group included 71 healthy children matched for age and sex. Table 1 provides a summary of the clinic-demographic information for the participants in the study.

Table 1 Clinico-demographic data of studied cases of CAH (N= 142).

<table>
<thead>
<tr>
<th>Variable name</th>
<th>CAH cases (n=71)</th>
<th>Controls (n=71)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td>0.806</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>5.85 ± 3.38</td>
<td>5.96 ± 3.37</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>5 (1.3 – 13.2)</td>
<td>5 (1.3 – 13.2)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>43 (60.6)</td>
<td>39 (54.9)</td>
<td>0.497</td>
</tr>
<tr>
<td>Female</td>
<td>28 (39.4)</td>
<td>32 (45.1)</td>
<td></td>
</tr>
<tr>
<td>Consanguinity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>16 (22.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>55 (77.5)</td>
<td></td>
<td></td>
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<tr>
<td>Family history of CAH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>58 (81.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>13 (18.3)</td>
<td></td>
<td></td>
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<tr>
<td>Type of CAH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salt loosing</td>
<td>60 (84.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple virilizing</td>
<td>11 (15.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>40 (56.3)</td>
<td></td>
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<tr>
<td>Hydrocortisone</td>
<td>29 (40.8)</td>
<td></td>
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<tr>
<td>Dexamethasone</td>
<td>2 (2.8)</td>
<td></td>
<td></td>
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<tr>
<td>Dose (mg/m²/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>13.6 (8.9 – 25.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic</td>
<td>64 (90.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>3 (4.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>4 (5.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fludrocortisone dose (mg/kg/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.1 (0.025 – 0.20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic</td>
<td>61 (85.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>8 (11.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>2 (2.8)</td>
<td></td>
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</tbody>
</table>

CAH: congenital adrenal hyperplasia. Quantitative data are presented in the form of mean ± SD and median (range). Qualitative data are presented in the form of number (percentage). *Significance defined by p ≤0.05.
Table 2. Comparison of anthropometric measurement of the studied CAH cases and matched controls (N= 142).

<table>
<thead>
<tr>
<th>Anthropometric measurement</th>
<th>CAH cases (N= 71)</th>
<th>Controls (N= 71)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight measurement (z-score) Mean ± SD</td>
<td>-0.34 ± 1.59</td>
<td>-0.24 ± 1.19</td>
<td>0.520</td>
</tr>
<tr>
<td>Height measurement (z-score) Mean ± SD</td>
<td>-1.19 ± 1.76</td>
<td>-0.29 ± 1.29</td>
<td>0.000*</td>
</tr>
<tr>
<td>BMI measurement (z-score) Mean ± SD</td>
<td>0.75 ± 1.12</td>
<td>-0.18 ± 1.79</td>
<td>0.004*</td>
</tr>
</tbody>
</table>

CAH: congenital adrenal hyperplasia; BMI: body mass index. Quantitative data are presented in the form of mean ± SD and median (range). *Significance defined by P ≤0.05.

DISCUSSION

In Egypt, the reported prevalence of CAH is about ten times more than that of the worldwide prevalence (7). Additionally, recently implemented universal CAH screening revealed a prevalence of 1 in 6,400 live births.

The current study's objective was to evaluate the linear growth of Egyptian kids and teens who had CAH. The mean age of the studied CAH cases was 5.85 (SD 3.38) years and ranged from 1 year-3 months to 13 years-3 months. Out of 71 children, 43 (60.6%) were males and 28 (39.4%) were females with Male:Female ratio of 1.5:1. This disagree with Alzanbagi et al. (9) who reported that out of 90 studied CAH cases 67.8% were females and 32.2% were males. Al Shaikh et al. (8) reported that out of fifty-six children (31 were females). Also our finding was in contrast to what was documented by the recent Egyptian study of Elmougy et al. (7) who reported that among the studied CAH cohort 118 were genetic female subjects and 56 were genetic male subjects (2:1:1).

The fact that the sex assignment in infancy for patients with disorder of sex development (DSD) presents a difficult difficulty may be the cause of this discrepancy in sex. Some CAH patients have DSD, which may have an impact on their gender identity (10).

The majority of the cases (84.5%) in the current study had salt-losing signs, while just 15.5% had symptoms that were clearly virilizing. This emphasised the need of physicians' awareness as well as the requirement of a neonatal screening programme for early discovery and appropriate therapy. It also highlighted the need for early diagnosis of these individuals. This demonstrated that signs of salt loss were more prevalent in our research group.

In contrast to our study, Al Shaikh et al. (8) observed a reduction in the salt-losing manifestations which documented in (57.6%) when comparing his result with the previous national studies in Saudi Arabia population (9,11). The author explains this reduction in salt-losing manifestations mainly due to the national ongoing implanted screening programs that lead to early diagnosis of these patients.

Positive connection was archived in 77.5% of the concentrated-on cases. These outcomes were tantamount with different outcomes acquired at various past examinations, in Saudi Arabia. Al-Jurayyan et al. (11) and Al-Meshari et al. (12) announced high association rate in Saudi Arabia populace.

Likewise, our finding was tantamount to Elmougy et al. (7) who expressed that the cases brought into the world to consanguineous relationships involved 65.5% of the CAH concentrated on associate.

Our announced pace of relationship was higher than whatever was expressed by Bhanji et al. (13) and Al-Maghribi (14) as they announced relationship in 52.3% and 32.9% separately. The high pace of relationship (25-39%) that reported in Egyptian populace which might be thusly expands the pace of autosomal latent issues, (15) and could be a significant contributing variable for the high occurrence of CAH and requires hereditary guiding for impacted families.

Positive family ancestry archived in 18.3% of concentrated on cases that is lower than what was recorded by Elmougy et al. (7) in 35.1% of the concentrated-on CAH accomplice.

Bhanji et al. (13) reported that no case had a history of similar features in either parent but in 19 (30.6%) cases similar features were present in siblings. Sixteen cases (25.4%) had a history of sibling death in the neonatal period and 7 had a history of sibling death in infancy. Also Al Shaikh et al. (8) documented higher positive family history (53.6%) than that observed in our study.

Fludrocortisone is frequently used to treat CAH when salt wasting is present in addition to hydrocortisone (with or without salt supplementation) (16). In our study 85.9% and 90.1% of the studied cases were received normal dose of Fludrocortisone and Glucocorticoid respectively.

Most people believed that kids with CAH would grow up to be short adults who constantly performed below their genetic potential (17).

The median (range) of the Height measurement (z-score) for our entire cohort was -1.5 (-3.89 to 1.76) as opposed to -0.5 (-3.5 to 4.2) [P <0.001] when compared.
to their matched healthy controls. Patients with CAH are still typically treated with glucocorticoid medication. However, the early epiphysial fusion caused by the elevated androgens in CAH and the growth-suppressing effects of glucocorticoids limit the height potential of CAH patients. This small height may be caused by a variety of other circumstances. These factors include the degree to which hyperandrogenemia is controlled, the dosage of corticosteroids and mineralocorticoids used, and the patient's compliance with the medicine (8,17).

In our cohort, the median (range) of the BMI (z-score) was greater than the control group [0.9 (-2.4 to 2.86) versus -0.2 (-4.5 to 3.2), respectively (P= 0.004)]. Children with CAH are at an increased risk of developing obesity (8), as it is commonly accepted that children with CAH who get excessive glucocorticoid treatment gain weight. In other research, 50% of the kids had at least one BMI measurement that was in the 95th percentile, and roughly 70% had at least one that was in the 85th percentile (5). Cetinkaya and Kara’s (18) report that children with CAH have greater BMIs than a healthy control is consistent with our investigation. In the same year, Mendes-dos-Santos et al. (19) found that CAH patients had recuperated from their development capture and had mean levels equivalent to everyone. In any case, they likewise found that they had higher muscle versus fat, which seemed, by all accounts, to be instinctive since there was no distinction in skinfolds between the two gatherings. Albeit the exact etiology is yet obscure, numerous factors add to the advancement of corpulence in CAH patients. Many individuals imagine that how much glucocorticoids and weight are associated (20).

Another fascinating idea suggests that corpulence might be created because of persistent adrenal hypofunction and diminished adrenaline creation. When contrasted with sound people, patients with exemplary 210HD deficiency have fundamentally lower plasma centralizations of adrenaline and metanephrine as well as diminished urinary epinephrine excretion (9,20).

It is as yet muddled which component in CAH kids' development concealment is primarily answerable for the challenges connected to the condition. Various examinations have completely explored the expected causes, beginning with the clinical indication, age at treatment commencement, glucocorticoid dose, and the executives of glucocorticoids alone, which have been displayed to restrict direct development (22,23).

Besides, drawn out glucocorticoid treatment has been related with unfortunate development, even at helpful portions (24). As per a review distributed in the biomedical diary (BMJ), high hydrocortisone measurements all through early life, particularly during outset, may obstruct development and be connected to a drawn out loss of extreme length (25). Moreover, in the event that CAH is left untreated, the ailment will accelerate the course of epiphyseal combination, diminishing the potential for level (26).

CONCLUSIONS
This study demonstrated a significant impact of CAH on BMI, height, and weight. Children with CAH have a significant multifactorial problem with linear growth that requires thoughtful care. We urge future prospective, carefully monitored research on CAH kids to identify any potential risk factors affecting their linear growth.

DECLARATIONS
- Consent for publication: I attest that all authors have agreed to submit the work.
- Availability of data and material: Available
- Competing interests: None
- Funding: No fund
- Conflicts of interest: No conflicts of interest.

REFERENCES


