Growth characteristics in children with congenital adrenal hyperplasia

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ABSTRACT

الأهداف : لتقييم نمو المصابين بتضخم الغدة الكظرية الخلقي في مدينة جدة ، المملكة العربية السعودية .

الطريقة : هذه دراسة وصفية على مدى 5 سنوات، شملت 90 مصابا، منهم 67.8% إناث و32.2% ذكور. تم تقييمهم في عيادة الغدد الصماء لطب الأطفال بمستشفى جامعة الملك عبدالعزيز، جدة، المملكة العربية السعودية خلال الفترة من يناير 2012م و يناير 2017م .

النتائج : كان 19.1% من الأطفال يعانون من نقص في الوزن، وفي حين كان 17.6% من الأطفال يعانون من السمنة المفرطة . ووجدت القامة القصيرة في 20 شخص أي ما يعادل (25.7%) من جميع الأطفال .

الخاتمة : أظهرت الدراسة تأثير تضخم الغدة الكظرية الخلقي على وزن وطول الأطفال ونموهم. ومن أهم العوامل المؤثرة هي المتابعة الدائمة، جرعة الدواء والانتظام بأخذ الادوية .

Objectives: To evaluate the growth parameters in congenital adrenal hyperplasia patients in Jeddah, Saudi Arabia.

Methods: This is a descriptive retrospective study over the period of 5 years. Data analysis was using Statistical Package for Social Science. The study included 90 participants in which 61 were girls and 29 were boys aged 0 to 18 years . They were evaluated in Pediatric Endocrinology Clinic at King Abdulaziz University Hospital in Jeddah, Saudi Arabia, between January 2012 and January 2017.

Results: A total of 90 subjects, of which 67.8% were females and 32.2% were males. Subjects who were underweight constituted 19.1% of the population, while those who were obese were estimated up to 17.6% of the population. Of the children, 25.7% were suffering from short stature and 74.3% had normal height. Approximately 11.8% of the children who suffered from short stature also suffered from hypothyroidism. Mid-parental height of those who suffered from short stature is 159.8 cm.

Conclusion: This study showed a significant effect of congenital adrenal hyperplasia on both height, weight, and body mass index. Risk factors includes glucocorticoids dosage, compliance to treatment, and regular follow up. Personalized treatment approach should be followed with all patients diagnosed with congenital adrenal hyperplasia as well as close monitoring and targeted therapy.

Congenital adrenal hyperplasia (CAH) is the most common inherited adrenal disorder in childhood.[1] It is a group of autosomal recessive disorders that occur as a result of a mutation in the genes.[2,3] This interferes with the cortisol synthesis pathway and leads to decreased cortisol synthesis with or without aldosterone deficiency and increased production of adrenocorticotropic hormone through negative feedback.[2,4] In consequence, a hyper androgenic state with accelerated growth results in early epiphyseal closure and compromised final adult height.[4] A German study has established that children and adolescents with CAH have a higher risk of obesity. Glucocorticoid dosage, chronological age, and parental obesity were all shown to be contributing factors to the elevated BMI.[2] Clinical observations highlight the

difficulty in maintaining the adequate adrenocortical suppression in spite of optimal substitution therapy which is necessary to achieve optimal growth.[4] This is a well-recognized challenge in the treatment of CAH: the fear of incurring the deleterious effects of glucocorticoid overtreatment, which in terms of growth is parallel to the same clinical picture of the hyperandrogenic state associated with uncontrolled CAH.[5] However, early diagnosis and good compliance appear to improve outcome. It is hard to maintain this suppression while at the same time performing the optimal substitution therapy. Therefore, efforts should be directed at early detection and improving compliance with traditional medical therapy.[6]

In this study, we aimed to evaluate the growth parameters in congenital adrenal hyperplasia patients in a single territory center in Jeddah, Saudi Arabia, over a period of 5 years. This study could help healthcare professionals in managing causes with this disease. The need to monitor the weight and height of these patients is also highlighted in the study, and this supports previous studies conducted in this context. This study may add to the body of research regarding the activity of this disease among children who live in Saudi Arabia.

Methods. This is a retrospective study carried out through reviewing electronic medical files using medical records system implemented at King Abdulaziz University Hospital (KAUH). Files of patients from January 2012 until January 2017 were included.

The inclusion criteria necessitated all patients have a documented history of classical CAH diagnosed during childhood and an age between 0 and 18 years. Exclusion criteria included all patients suffering from a significantly unstable medical condition, nonclassical CAH, other causes of adrenal insufficiency, and chronic use of medications unrelated to CAH. Growth parameters were interpreted in the context of the patients' age, gender, and pubertal stage.

The sample size constituted 90 subjects; gender distribution included 70.1% of the XX karyotype and 29.9% of the XY karyotype. The mean age of the patients was 6.7 months. All patients were of the classical CAH type. The salt losing (SW) variant was found in 47.8% while 50.7% were to be of the simple virilizing (SV) variant. Informed consent was obtained

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from the ethical committee at KAUH prior to accessing patient data.

The sample size was calculated according to the Epi-Tools Epidemiological calculator with a 0.95 confidence level. Each subject was evaluated for height, weight, BMI, mid-parental height, and predicted height.

Height was recorded in cm as the average of 3 measurements using a Harpenden stadiometer and results expressed in standard deviation (SD). Height was classified into 2 categories according to SD: short stature if it was 2 SD below the mean height for age and gender normal if within 2 SD above and below the mean height for age and gender. Weight was recorded in kg using an electronic scale and results were classified into 4 categories as follows according to BMI: underweight, normal, overweight, and obese. Body mass index was interpreted using the World Health Organization (WHO) BMI percentile chart for age and gender. Underweight was below the 5th percentile, normal weight ranged between the 5th and 85th, and overweight ranged between the 85th and the 95th, and above the 95th percentile was considered obese.[7]

Mid-parental target height was calculated according to the method of Tanner et al.[8] All height interpretation was determined according to the Boston Children's Hospital growth calculator, version 2.01.[8]

Statistical analysis. Data were interpreted using the 20th version of the Statistical Package for Social Sciences (SPSS). Simple descriptive statistics are reported as proportions for qualitative variables such as frequencies and percentages of initial gender types and initial presentation. The Spearman Correlation test was used to evaluate the significant relation between growth parameter (height, weight, and BMI) levels with the frequency of taking hydrocortisone. Chi-square was used to assess the relationship between compliance, weight, and height. The results were considered significant if the p-value was less than <0.05.

Results. The mean age among clinically controlled subjects was 17.7 ± 25.8 months. Of the 74 subjects, 25.7% were suffering from short stature and 74.3% had normal height. Approximately 11.8% of the children who suffered from short stature also suffered from hypothyroidism. No significant relationship between height in general and hydrocortisone dosage was found (p=0.659). Neither was a significant relationship determined between short stature specifically and the dose of hydrocortisone (p=0.942). On the other hand, a significant relationship existed between normal height and compliance with medication (p=0.013).

The mean of mid-parental height for children of normal height was 162.3 cm. The mean of mid-parental height for children of short stature was 159.8 cm. Subjects who were underweight constituted 19.1% of the population, while those who were obese were estimated up to 17.6% of the population.

A positive correlation between an increase in BMI levels and an increase in hydrocortisone dosage (**Table 1**) was estimated at a $p=0.010$ and $p=0.320$ respectively as obese children were found to be taking more than 15 mg/m²/day of hydrocortisone ($p=0.008$). Overweight children did not have a family history (FH) of obesity while 8.7% of obese children had a FH of obesity.

Clinical control was achieved in 80.3% of subjects, while 19.7% were not clinically controlled. Biochemical control was achieved in 73.8% subjects, while 26.2% subjects were not controlled (**Figure 1**). The mean age among clinically controlled subjects was 17.7 ± 25.8 months

Discussion. This study describes the growth parameters of patients with classic 21-hydroxylase-deficiency (210HD) at a single institution. Although CAH is an autosomal recessive disease and by this, it is presumed that both genders are at an equal risk for the disorder, 70.1% of the sample size was of the female gender. This discrepancy can be explained by the virilizing nature of the disease that is manifested by females through ambiguous genitalia and is therefore recognized earlier and eludes to the notion that male patients are more likely to go by unnoticed at birth only to present later with a salt-wasting crisis. Patients with the non-classical form suffer a milder form of the disease and are usually only identified around the age of puberty as a result of hormonal imbalance. Therefore, we stress on the importance of neonatal screening especially in the male newborns of consanguineous marriages to prevent the delayed presentation with a life threatening crises.

To address suboptimal growth in those patients, replacement therapy offers the only means to optimize their growth and maintain their quality of life. Glucocorticoid therapy remains the standard treatment for patients with CAH, with a goal to reach the optimal level of adrenal steroid suppression. The optimal therapeutic range is difficult to attain, and often short and long-term complications arise, consequences of over- or under treatment.[9,10]

Growth suppression in CAH children is multifactorial, and it is still not clear which factor contributes the most to the complications associated with the disorder. Many researchers have extensively

Table 1 Dosage of hydrocortisone.

Hydrocortisone dosage m² frequency	n	(%)	Valid (%)	Cumulative (%)
Valid				
<12 mg/m²/day	32	(35.6)	36.8	36.8
12-15 mg/m²/day (optimal)	22	(24.4)	25.3	62.1
>15 mg/m²/day	25	(27.8)	28.7	90.8
No follow up	8	(8.9)	9.2	100.0
Total	87	(96.7)	100.0	
Missing	3	(3.3)		
Total	90	(100.0)		
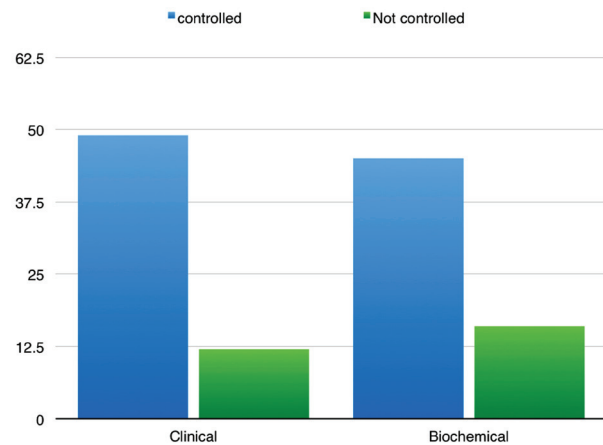
Figure 1 - Clinical and biochemical control in patients affected with congenital adrenal hyperplasia.

studied the possible causes, starting from the clinical presentation, age at start of therapy, dosage of glucocorticoids, and control of glucocorticoids alone are widely known to suppress linear growth.[11,12] Moreover, chronic treatments with glucocorticoids, even at therapeutic doses, have been associated with poor growth.[12] A study published in biomedical journal (BMJ) suggests that high hydrocortisone dosages during early childhood, especially during infancy, lead to growth impairment and might be linked to a permanent loss of final length.[13,14] Moreover, if CAH is not treated, the disease itself will accelerate the velocity of epiphyseal fusion, resulting in a limitation in the height potential.[9,15]

In this study, most of the patients were of normal height, while about a fourth (25.6%) suffered from short stature. Familial short stature could have been a factor in these patients because their target height falls below the 3rd percentile, and the mean of mid-parental height among the children of short stature was 159.8 cm. Data concluded from recent literature implies that classical

CAH patients often reach a suboptimal final height as opposed to their final target height. It is widely believed that a reduced final height in those patients is multifactorial, However, there are still uncertainties pertaining to certain factors affecting normal growth and optimal strategies to improve final height in this group. It must be noted that retrospective studies have demonstrated that the final height of well-controlled patients is independent of the degree of the hormonal control which implies that hypercortisolism might aggravate the previously noted short stature. Moreover, final height SDS and height SDS were not significantly associated with age at diagnosis, gender, mid-parental height (p=0.415), the dose of hydrocortisone, or disease control. Most children who were compliant with medication had a normal height (p=0.013). Furthermore, in our institute, the 5-year follow-up rate was approximately 71.9% in CAH patients, with 65.5% follow-up rate. The mean of mid-parental height among parents whose children did not suffer from short stature was 162.3 cm, which may suggest that patients with CAH who are diagnosed early, make regular follow-up visits, and are treated exclusively with hydrocortisone can have a satisfactory final height prognosis and limit short stature to some extent.

Congenital adrenal hyperplasia children can also suffer from obesity. While the cause of obesity among those patients remains uncertain, many factors play a role. It is widely speculated that obesity is linked to glucocorticoid dosage.[16] Moreover, an interesting hypothesis states that chronic adrenal hypofunction with decreased adrenaline synthesis may also have a role in the development of obesity.[17] Compared to healthy subjects, patients with classic 210HD deficiency display significantly lower plasma concentrations of epinephrine and meta-nephrine, as well as lower urinary epinephrine excretion.[17]

The number of patients who were underweight, of normal weight, overweight and obese is respectively 13 (19.1%), 39 (57.4%), 4 (5.9%), and 12 (17.6%). The condition of under-weight children may be attributed to poor nutrition and low socioeconomic status. Obese children had at least one BMI measurement ≥95th percentile and had at least one reading ≥85th percentile. Our data showed a significant association between hydrocortisone dose, BMI, and BMI SDS. We can note that most obese children were taking more than 15 mg/m^2/day of hydrocortisone (p=0.008, and p=0.027). Another study that was conducted in the United States had a similar result; about 50% of their sample size had a BMI reading above >95th percentile.[17]

It is essential to carefully adjust HC dosing in CAH children, especially during early childhood, to prevent increased weight gain and an early adiposity rebound.[18] The adiposity rebound is defined as the second increase in BMI that happens in preschoolers until the age of 7. An early age at adiposity rebound is a risk factor for adult obesity.[19] Compliance and regular follow-up and monitoring are factors that can affect the final height dramatically. Properly treated children with excellent compliance show better results than non-compliant patients.[9,15] The dose of steroid was quite variable, namely <12 mg/m^2/day, and more than >15 mg/m^2/day of hydrocortisone, averaging between 12 to 15 mg/m^2/day; on that dose, 38% were clinically controlled. On the minimal dose of <12 mg/m^2/day of hydrocortisone, 35.7% were found to be clinically controlled, while only 26.2% achieved clinical control in the patient group receiving a higher dosage of >15 mg/m^2/day. The mean age of those who were clinically controlled was 17.7 ± 25.8 months. The mean age among those who were not clinically controlled was 5.5 ± 5.9 months. Different clinical presentations in young CAH patients may contribute to control. The earlier the presentation, the earlier to initiate the treatment.

Family history is also an important factor to consider in these patients. A family history of obesity was found in 8.7% of obese children. Other endocrine diseases also play a major role in gaining weight. Hypothyroidism was a common finding, occurring in 13.6% of obese children. Other factors, such as lifestyle, can also affect the weight drastically. Saudi Arabia suffers from a high obesity rate, and recently obesity has been a major concern in the country. The latest studies have revealed that obesity in both genders is 28.7% of the total population (with a prevalence of 33.5% among women and 24.1% among men).[20] Saudi Arabia's rate of obesity is among the highest in the world. This could be attributed to the westernization of the society, high caloric consumption, and decreased physical activity.[10] A family history of consanguinity was a common finding in CAH patients; about 31.1% of all patients had a positive consanguinity. However, a family history of consanguinity was not associated with a stronger variant of CAH. There is no association between consanguinity and control, initial presentation, severe presentations (shock or salt-losing crises), response to medication, or frequent hospital admissions.

Study limitations. This study is subjected to the inherent limitations of a retrospective study design. Included subjects live in Saudi Arabia and therefore cannot be generalized to populations of children

throughout the world. Multiple factors, such as environmental and genetic factors, can affect the severity of the disease, and these vary regionally.

We conclude that a personalized treatment approach can prevent growth failure. Close monitoring of the patient's condition and the provision of treatments and compliance are essential factors. Also important are essential factors in promoting optimal growth which can affect the height, weight, health status, nutritional status and quality of life for the patient. The majority of our patients had normal growth parameters as a result of good follow-up and compliance with treatment, while a quarter had an abnormalities in weight and height. We highly recommend educating parents, caregivers, and children about the potential outcomes of the disease and side effects of medications. Global neonatal screening should be available throughout all hospitals for early detection and intervention.

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