Study of Physical Functioning in Children with Congenital Adrenal Hyperplasia

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Abstract

Background: Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder causing deficiency of enzymes involved in adrenal steroidogenesis. Steroid replacement therapy plays a vital role in the treatment. Hyperandrogenism due to the accumulation of intermediate metabolites is the important cause of symptoms. These hormonal imbalances would result in growth abnormalities and hence should be monitored stringently.

Aims and Objectives: The aim of this study is to study the physical functioning in children with CAH on treatment and to compare simple virilizers and salt wasters.

Materials and Methods: A total of 55 children between 2 and 12 years of age who met the inclusion and exclusion criteria were enrolled in the study. Detailed history, anthropometry, body mass index (BMI), blood pressure, X-ray for bone age, and 17-hydroxy progesterone levels were obtained.

Observation and Results: In our study, 82% (n = 45) were females and only 18% (n = 10) were males. CAH in males has been under diagnosed in our population. As expected salt-wasting type constituted the majority about 62% (n = 34). Simple virilizing type was only 38% (n = 21). Mean dose of steroid administered to our patients in this study is 16.3 ± 4.4 mg/m² body surface area. Mean height z-score in our study was −0.2 ± 2.1. About 67% (n = 37) of the total population had their height z-scores between −2 and +2. About 11% (n = 6) of them were >+3 z-score and 9% (n = 5) of them were <+3 z-score. Among the patients with height z-scores >+3 z-score, 5 patients were on recommended dose. 47% (n = 26) of our patients had normal BMI. 20% (n = 11) of them were obese while 18% (n = 10) of them were overweight.

Conclusion: 20% of the total study population had abnormal growth profile, and 53% of the kids had abnormal BMI due to infrequent monitoring. Hence, frequent monitoring of height, weight, and BMI is essential for all patients with CAH irrespective of the type of disease. Based on the clinical findings and hormonal assays, individualized dosage modification should be done regularly.

Key words: Congenital adrenal hyperplasia, Hydrocortisone, Hydroxyprogesterone, Hyperandrogenism, Virilization

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is defined as a genetic problem involving steroidogenesis in adrenal gland due to enzyme deficiencies, most common being 21 hydroxylase deficiency.¹ This would lead to by-product deficiency and accumulation of intermediate metabolites, thereby stimulating pituitary gland to produce more adrenocorticotropic hormone (ACTH). ACTH stimulates adrenal gland resulting in hyperplasia.² The accumulated metabolites are the cause for symptoms in CAH, in addition to steroid deficiency. Cortisol was used for its treatment first in the year 1950.³ Deficiency of specific enzymes involved in steroidogenesis in the adrenal would result in a lack of cortisol with or without aldosterone. This would also cause excessive production of precursors. These are then converted to androgens and hence hyperandrogenic features.

Most common enzyme deficiencies constituting CAH include 21-hydroxylase deficiency, 11-beta hydroxylase deficiency, and 11-beta hydroxylase deficiency.
deficiency, 3-beta hydroxysteroid dehydrogenase deficiency, 17-alpha hydroxylase deficiency, and 17, 20 lyase deficiency. Actions of glucocorticoids include increase in gluconeogenesis, increase in lipolysis, and redistribution of fat resulting in truncal obesity and moon facies when in excess. Skeletal maturation is inhibited by glucocorticoids. Decrease serum calcium levels by decreasing absorption from the intestine and increasing excretion in the kidneys and hence lead to osteoporosis. 21-hydroxylase deficiency may be of two types:
1. Classical

Classical type is again reclassified into:
1. Salt wasting
2. Simple virilizing.

CAH and Its Effect on Physical Growth
Children with CAH have alterations in their growth pattern. The cause may be either hyperandrogenism or hypercortisolism when treated with excess steroids. In some children, inspite of steroids used at physiological doses, there may be growth alteration. The reason quoted for the same is transient hypercortisolism immediately after the absorption of the drug which has been used for long term. Other reason may be increased serum cortisol level up to supraphysiological doses during initiation of treatment, in the first year of life. This is the main cause for the delayed bone maturation and short stature in the adult life. Other causes quoted were that the inadequate suppression of hyperandrogenic state which may advance the bone age in children but ultimately cause early epiphyseal fusion resulting in short stature among adults. Other reason for early epiphyseal fusion in some may be due to central precocious puberty. There had been a meta-analysis which showed mean final height in adults was −1.37 SD. Glucocorticoid replacement therapy would cause a reduction in height and osteoporosis in later life when used in higher doses than recommended.

There had been recommendations for normal pubertal development, and in a recent study, it has been quoted that the dose of hydrocortisone should not exceed 17 mg/m². At the same time, hyperandrogenism would also result in advancement of bone age and its consequences. There are also differences in the type of disease. This is because salt wasters are diagnosed early and started on treatment early and are said to have better outcomes as far as physical functioning is considered. However, 25% of classic CAH have salt-wasting crisis which may influence on the final height. Hence, it can be concluded that final height is influenced by age at diagnosis, dose of steroid, adequacy of treatment, and type of CAH.

Studies have stated that though clinical examination is the most efficient way of monitoring the adequacy of treatment, still day to day changes could not be reflected, and hence, it is recommended to use biomarkers such as androstenedione for perfect monitoring. For these patients, whom there had been a reduction in growth, treatment with short-term growth hormone replacement and GnRH analog would result in a growth of about 11 cm than expected. Selection of patients for such a treatment is based on presence of psychological stress and adjustment difficulties owing to their short stature.

In our study, we are going to observe the growth pattern of CAH children who are on treatment with standard treatment regimen. The treatment goal in CAH is to attain normal growth and development by judicious dosing of glucocorticoid and mineralocorticoid and close monitoring to avoid under- and over-treatment. To meet the balance between too little or too much steroids is the major challenge, especially in children with varied growth potential. There had been a very few studies on physical functioning in our CAH population. Hence, we are proceeding with this study.

Aims and Objectives
The aim of this study is to study the physical functioning in children with CAH on treatment and to compare simple virilizers and salt wasters in various aspects.

MATERIALS AND METHODS

Design of the Study
This was a descriptive study (cross-sectional).

Place
Pediatric Endocrinology Department, Institute of Child Health, Department of child guidance clinic, ICH.

Period of the Study
The period of duration was from February 2015 to August 2015.

Sample Specifications - Case Definition
All clinically and biochemically confirmed cases of CAH on treatment at endocrinology department.

Inclusion criteria
All children from 2 to 12 years who were diagnosed as CAH and on treatment were included in the study.

Exclusion criteria
Other causes of growth abnormalities: Familial short stature, growth hormone deficiency, nutritional causes, chronic systemic diseases, chronic medications unrelated
to CAH, and known psychiatric illness were excluded from the study.

Sample size - all children with above inclusion criteria who presented during the study period.

Ethical committee clearance was obtained from the institutional review board.

Children of age 2-12 years diagnosed to have CAH and satisfying the inclusion and exclusion criteria were recruited into the study, after obtaining informed parental consent.

Subjects with CAH those satisfying the inclusion and exclusion criterion were enrolled into the study.

Detailed history and old record analysis to look for the following:
• Type of the disease - salt wasting or simple virilizing,
• Age at diagnosis,
• Consanguinity,
• Siblings affected or not,
• Antenatal history,
• Social and demographic data,
• Period of drug intake,
• Compliance,
• Dose adjustments,
• Hospital admissions and school absentism.

Anthropometric measurements: Height, weight, and BMI calculation are plotted on standard charts and assigned proper z-scores.

Blood pressure measurement - both systolic and diastolic checked thrice (on three different occasions) and average of the three taken. Sexual maturity rating is done for all children as per Tanner’s staging. Features of steroid excess - cushingoid features, obesity, hypertension, striae, and hepatomegaly were noted. Systemic examination done to rule out all other causes. Investigations done include X-ray for bone age and biochemical - levels of 17-hydroxyprogesterone.

RESULTS

A total of 55 children with CAH on treatment were studied in the age group between 2 and 12 years. As shown in Figure 1, 82% of our study population were females and only the remaining 18% were males. 42% of our total population were between 8 and 12 years. 29% of them were between 2 and 4 years, and 29% of them were between 5 and 7 years. Among girls, 38% were between 8 and 12 years, whereas among boys, 60% were between 8 and 12 years. Between 5 and 7 years, 20% of the total boys and 31% of the total girls were included in the study. The difference was not statistically significant. 84% of them were diagnosed in the neonatal period during salt-wasting crisis, and only 16% were diagnosed later. The difference is not statistically significant with a P value of 0.078, about 62% were salt wasters and 38% were simple virilisers. The difference is statistically significant as the p value is 0.03253. A total of 16% had their siblings affected, and it was significantly associated with simple virilizing type of disease at P = 0.0196 in our study.

In this study, 67% of the total population had normal height z-scores as in Table 1. 20% of them had either short stature (9%) or tall for their age (11%). Height (score) was not associated with types of disease at P = 0.2658. 72% of the kids had their weight z-score normal. 7% of them had fallen under >+3 z-score. Weight (score) was not associated with types of disease at P = 0.1076. Only 47% of them had normal BMI as in Table 2.

In our study, about 27% of the total kids are found to have features of steroid excess as in Figure 2. Cushingoid features are more with salt wasters though the difference is not statistically significant. 78% of them had normal blood pressure. 22% of them had their BP in the pre-
hypertensive stage. Systolic BP percentiles were not associated with types of disease at \( P = 0.7505 \). The difference was due to chance. In this study, only 24% of them had the expected fair control levels of 17OHP. 44% of them were under tight control. 33% of them had higher levels of the hormone. 17OHP was not associated with types of disease at \( P = 0.729 \). The difference was due to chance.

In this study, about 4% of them had advanced bone age by 3 years and 4% of them had delayed bone age by 2 years as shown in Table 3. Bone age was not associated with types of disease at \( P = 0.5053 \). The difference was due to chance. (−2 imply that the bone age is delayed by 2 years and 3 indicate that bone age is advanced by 3 years).

**DISCUSSION**

This study was conducted at the Endocrinology Department of Institute of Child Health and Hospital for children at Chennai between the period of February 2015 and August 2015. We studied the demographic characteristics and physical functioning in CAH children. CAH is the most common cause of hyperandrogenism in children. Incidence of the disease is as high as 1 in 15,000.

Totally 55 children between 2 and 12 years of age who met the inclusion and exclusion criteria were enrolled in the study. Although the incidence of the disease does not have any significant sex difference, it has been shown that CAH in males has been underdiagnosed in our population. There had been studies stating that incidence of the disease is more in boys than girls between 0 and 12 years. The reason for discrepancy in our study may be due to:

1. Male children may go undiagnosed in simple virilizing type.
2. Males with salt-wasting type may die undiagnosed.

The main cause for this is the absence of newborn screening programs for CAH in India.

Median age of diagnosis in our study is <1 month, though the range may be from 1 to 72 months. Similarly in a study done by Silva et al., the range of age at diagnosis was between 0 and 79 months with a median age of 2.9 months. The reason for this wide range in age at diagnosis is mainly the difference in cultural practices leading on to ignorance among parents. Interview with these parents has shown us the hesitancy in bringing their kids to the notice of physician. In our study, the proportion of girls being diagnosed in the neonatal period is more up to 89% (\( n = 40 \)) than boys (60%). On the whole, about 84% of the kids were diagnosed at the neonatal period in our study. Most of them were diagnosed with salt-wasting crisis. This is again due to the absence of newborn screening programs. However, still, range of age at initial diagnosis is wide in our population compared to many other studies. Male children may have advanced bone age as the only sign, and hence, it is diagnosed very late or else left undiagnosed.
In our study, as expected salt-wasting type constituted the majority about 62% \((n = 34)\). Simple virilizing type was only 38% \((n = 21)\). In the study done by Mueller et al.,\(^1\) it has been shown that even among the male population, prevalence of salt-wasting type is about 70%. Sanches et al., in their study, clearly stated that boys were more diagnosed\(^2\) as salt wasters compared to girls (boys - 80% were salt wasters and only 50% girls were salt wasters). The cause for this discrepancy in our study may be due to the early death of salt waster males before being diagnosed to have the disease. Hence, it is very clear that early diagnosis and treatment are essential for the prevention of mortality in our patients. This again explains the role of newborn screening programs.

Mean dose of steroid administered to our patients in our study is 16.3 ± 4.4 mg/m\(^2\) body surface area. Among females, it is 16.3 ± 4.56 mg/m\(^2\), and among males, it is 15.5 ± 3.8 mg/m\(^2\). Hence, dose requirement among females may be higher and this may be because of the reason that more salt wasters in our study are females. The recommended dose is 15-20 mg/m\(^2\). Few articles have quoted that the dose required should be maintained at a very low levels ranging from 10 to 15 mg/m\(^2\). The physiological production of steroids in our body is only in the rate of 4-8.7 mg/m\(^2\). Hence, in our study, about 75% of the total kids receive within or less than this recommended range, whereas the remaining 25% of the kids receive slightly higher dose than recommended. The reason is due to the poor compliance, hyperandrogenic state may not be controlled with the so-called physiological dose, and hence, the requirement may go high in some. Other cause is the failure to decrease the dose after stepping up during stress period. Poor follow-up by some of these patients is yet another cause.

Among the 75% of these patients, few of them (7%) take only 5-10 mg/m\(^2\). This group of children either may have good control with this small amount of drug or may not be under strict follow-up (in our study, two kids who were reported to take this amount of drug were found to have a very high 17OHP levels and not under good control). Hence, we can conclude that 50% of these kids who were with low dose than recommended can still have normal control when they were followed up stringently with both clinical assessment and laboratory analysis.

CAH has an autosomal recessive inheritance pattern. Hence, history regarding consanguinity was taken into account. In our study, it has been shown that 85% \((n = 47)\) of kids were born of consanguineous marriage and remaining 15% \((n = 8)\) alone were born of non-consanguinity. About 88% \((n = 30)\) of the salt wasters and 81% \((n = 17)\) of simple virilisers were born of consanguineous marriage. Although the difference is not statistically significant, from our study, it appears that majority of salt wasters were born of consanguineous marriage.

Considering sibling history, we had 4 pairs of siblings being affected and all the 8 were enrolled in the study. One kid has lost her sister due to salt-wasting crisis. Hence, totally 16% \((n = 9)\) of these kids had a positive sibling history. The difference according to the two types of disease was statistically significant \((P < 0.05)\). This had clearly shown the lack of knowledge about the prenatal diagnosis and treatment for CAH in some areas. Dexamethasone treatment should have been given to the mothers immediately after confirming pregnancy. If these kids were diagnosed early and started on treatment early, even from the antenatal period, outcome would have been better.

Anthropometric measurements which are included in our study are height, weight, and body mass index. These measurements are plotted on standard charts. CAH is a disease which is well known to cause alteration in growth patterns, which may be due to both disease process and treatment of the same. Hence, it is vital to measure height at regular intervals. In our study, influence of type of disease, dose of steroid, and various other factors on height were studied. Mean height z-score in our study was \(-0.2±2.1\) among the patients with height z-scores >+3 z-score, 5 patients were on recommended dose, and only one of them was on low dose. However, all 6 of them had 17OHP values above normal range. Hence, this suggests that the requirement of steroids in these patients for control of hyperandrogenic state is higher. Out of the five patients with height z-scores <−3, only two of them were taking more than recommended dose of steroids. Three of them had their 17OHP values less than the normal range. Hence, in these patients, the steroid dose should be slowly decreased.

Considering the type of disease, among the salt wasters, 62% \((n = 21)\) were between −2 and +2 z-score. Among the simple virilisers, 76% \((n = 16)\) were between −2 and +2 z-score. The difference is not statistically significant. About 7% of our patients were on inadequate steroid dose. Inadequate steroid dose would result in hyperandrogenism and hence would increase the height percentiles. In our study, out of the four kids who were on inadequate dose, two of them had their height z-score more than +3. It has also been proved in one study\(^3\) that children treated with 15 mg/m\(^2\) had better growth velocity than children treated with a dose of 25 mg/m\(^2\). Hence, proper growth monitoring and change in steroid dose accordingly is essential. If not monitored, they may land up as dwarf adults. The reason for loss of final height in most of them is quoted as the initial loss of linear growth.
during the first 2 years of life due to the hypercortisolism in this period.

BMI status of these patients was thus studied which showed that about 20% \((n = 11)\) of them were obese while 18% \((n = 10)\) of them were overweight. Among the 11 obese patients, eight of them were on an excess dose of steroids. Hence, regular monitoring of BMI is essential for all CAH patients. Among the types, 52% \((n = 12)\) of simple virilisers had normal BMI, whereas only 41% \((n = 14)\) of the salt wasters only had normal BMI. The difference is not statistically significant. However, in some studies,\(^{10}\) it has been clearly shown that simple virilisers have significantly increased BMI than reference values.

We have also studied for the features of steroid excess in our population. In our study, about 27% \((n = 15)\) of the total population had cushingoid features. Among salt wasters about 29% \((n = 10)\) and among simple virilisers, about 24% \((n = 5)\) had features of steroid excess. This difference was not statistically significant.

17OHP levels were compared between the two groups. Levels between 0.59 and 3.44 ng/ml were taken as normal from the laboratory reference values. From the results obtained, only about 24% \((n = 13)\) of the total study population had their 17OHP levels within their normal limits. 44% \((n = 24)\) of the patients had their levels below 0.59 ng/ml and hence could considered to have very tight control with steroids. The disadvantage is that they may land up finally with features of steroid excess, though some patients may need such high levels for adequate control of hyperandrogenic state. 33% \((n = 18)\) had their 17OHP levels more than 3.44 ng/ml showing their hyperandrogenic state.

Bone age measurements were done using X-rays in our study. It is compared with the chronological age and found that 51% \((n = 28)\) of the total population had bone age corresponding their chronological age. 4% \((n = 2)\) of them had their bone age advanced by 3 years, and 4% \((n = 2)\) had delayed bone age. Comparing between the two types of disease, 67% \((n = 14)\) of the simple virilisers and 41% \((n = 14)\) of the salt wasters had normal bone age. None of the simple virilisers had their bone age advanced by 3 years, but 6% \((n = 2)\) of salt wasters had the same. Although not statistically significant, it could be considered from our study that salt wasters may have poor control over their bone age than simple virilisers.

Limitations of the study are (1) growth velocity should be ideally measured rather than height, (2) other hormonal assays such as androstenedione should have been additionally measured for appropriate determination of hyperandrogenic state, and (3) small sample size.

**CONCLUSION**

Hence, from our study in our population, we found that inspire of being on standard treatment regimen, due to the absence of frequent monitoring both clinically and biochemically, about 20% of these kids had abnormal growth, 53% had abnormal BMI, 27% had features of steroid excess, 22% in the prehypertensive stage, 33% with poorly controlled biochemical marker, and 14% with abnormal bone age though not statistically significant. Comparing both salt wasters and simple virilisers, simple virilisers had more abnormal growth profiles than salt wasters. Features of steroid excess and abnormal BMI were more among salt wasters though not statistically significant.

Hence, we could conclude that modification of the treatment dosage should be individualized based on the clinical features and biochemical parameters of that particular kid. It is very essential to strictly monitor height,\(^{11}\) weight, and BMI for all patients with CAH irrespective of the type of disease, for better outcomes. Based on the clinical findings and hormonal assays, hydrocortisone\(^{12}\) and fludrocortisone levels should be modified at regular intervals. About 16% of them had positive cortisone history, hence, the need for prenatal diagnosis and treatment should be emphasized.

**REFERENCES**

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Source of Support: Nil, Conflict of Interest: None declared.