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Original Research Article

To Study the Clinical Features and Laboratory Profile of Children with Congenital Adrenal Hyperplasia

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Abstract

Background: Congenital adrenal hyperplasia (CAH) includes a group of disorders that result from reduced activity of several enzymes which are required for the synthesis of cortisol in the adrenal cortex. The prevalence of CAH varies according to the ethnicity and geographic area. Deficiency of 21- hydroxylase enzyme accounts for more than 90% of the cases of congenital adrenal hyperplasia with an incidence of 1 in every 15,000 to 20,000 births.23 Nearly 70% of the affected children due to21 hydroxylase deficiency present with salt wasting form and 30% present with simple virilising form. Prenatal diagnosis and treatment is offered to families who have an affected child with CAH and it has the advantage to prevent ambiguous genitalia in female fetus due to virilization.

Aim: To examine the clinical characteristics and test results of children with congenital adrenal hyperplasia.

Material and Method: Every child with CAH got a thorough clinical examination and full history. They had their anthropometry, sexual maturity rating (SMR), and blood pressure measured. For the purpose of comparing bone mineral values, 20 kids with congenital adrenal hyperplasia and 20 healthy age- and sex-matched controls were used as the sample size. Children with CAH had their serum levels of sodium, potassium, ionized calcium, and alkaline phosphatase measured using a Roche automated electrolyte analyzer. Hyponatremia was defined as serum sodium less than 135 mmol/L and hyperkalemia was defined as serum potassium more than 5.5 mmol/L. The normal serum ionized calcium level is 1.1-1.3 mmol/L and the alkaline phosphatase level is 72-307 IU/L. 17 hydroxy progesterone was measured by solid phase enzyme linked immunosorbent assay (ELISA)-DRG.

Results: There were a total of 20 children with congenital adrenal hyperplasia during the recruitment period (CAH). Five of the 20 children had the typical salt-wasting CAH, two had the straightforward virilizing CAH, and three had the non-classical CAH. Only 10 children with classical salt wasting CAH were enlisted for the study's purposes as the study group. Ten healthy youngsters who were age- and sex-matched were recruited as the controls.

Conclusion: The potential for prenatal and even preconception CAH diagnosis is provided by developing technologies. With growing knowledge of the potential effects of prenatal androgen exposure, ongoing conversations regarding the gender of raising for very virilized females are necessary, even though early diagnosis may be useful for counseling parents. Additionally, more research on this population's sexuality and quality of life indicators is necessary. Most importantly, cutting-edge therapy approaches like modified release hydrocortisone preparation may improve patients with CAH's quality of life.

Keywords: 17OHP, 21OHD, ACTH, BMC, BMD, CAH DXA.

Introduction

Congenital Adrenal Hyperplasia (CAH), an autosomal recessive condition of cortisol biosynthesis, is brought on by a flaw in one of the five enzymatic processes necessary for the production of cortisol from cholesterol. The name CAH is utilized because unregulated adreno corticotrophic hormone [ACTH] stimulation during fetal life caused the adrenal glands to be hyperplastic at birth. Over 90% of instances of the most prevalent type of CAH, 21 hydroxylase enzyme deficiency (21OHD), are caused by this condition. [1] Over 90% of instances of the most prevalent type of CAH, 21 hydroxylase enzyme deficiency (21OHD), are caused by this condition. [2] The additional enzymatic causes are deficiencies in the enzymes 11β hydroxylase, 3 β hydroxysteroid, 17α hydroxylase, Steroidogenic acute regulatory protein (StAR), congenital lipoid adrenal hyperplasia, and P 450 oxidoreductase.

Both classical and non-classical CAH are conditions where there is an inability to produce the enzyme 21 hydroxylase. Based on a person's capacity to generate the hormone aldosterone, which regulates salt retention, the classical form is further classified into salt wasting form (SW) and simple virilizing form (SV). [3] Children with classical salt wasting present usually in the newborn period or in early infancy. The clinical features of classic salt wasting CAH include ambiguous external genitalia in females and normal external genitalia in males. The other characteristic features are vomiting, diarrhea, dehydration, hypotension, shock and even death (due to combined deficiency of aldosterone and cortisol). A very high concentration of 17 hydroxy progesterone in seen in patients with 21 hydroxylase deficiency. [4] When basal 17OHP levels are insufficient to make a diagnosis, an ACTH stimulation test is carried out. Typically, stimulated 17 OHP levels in patients with classical CAH are greater than 1,00,000 ng/dl.

Congenital adrenal hyperplasia in children necessitates lifelong glucocorticoid therapy to restore the missing cortisol, control the overactive adrenal androgens, and support healthy growth and development. A significant contributor to secondary osteoporosis is glucocorticoid-induced osteoporosis (GIO). [5] Following the first six months of glucocorticoid therapy, bone loss increases by 5%, then by one to two percent every year after that. [6] It has been suggested that using glucocorticoids, even at supplementary dosages, may cause a decline in bone mineral density. Dual energy X ray absorptiometry [DXA] is the method of choice for determining the density and mineral content of bones in youngsters, and is regarded as the gold standard among methods for measuring these parameters. To discriminate between tissues with varying radiographic densities, the DXA technique uses differential X-ray absorption at two different energy levels. DXA measures bone mineral content (BMC) in grams and bone mineral density (BMD) in g/cm2. [7] According to the International Society for Clinical Densitometry's (ISCD's) official policy statement on pediatric DXA, children should only have their total body less head [TBLH] BMD and BMC measurements taken. [8]

The present study was necessary because there is a lack of information on the impact of glucocorticoid therapy on bone mineral parameters in Indian children with CAH.

Several studies have reported that BMD is normal or decreased in children with congenital adrenal hyperplasia.

Material and Methods

Both the parents of the controls and the parents of the children with CAH gave their informed consent. Every child with CAH got a thorough clinical examination and full history. They had their anthropometry, sexual maturity rating (SMR), and blood pressure measured. Children were weighed at body 50 using an electronic scale, and their weight was recorded to the nearest 0.1 kg. Children under the age of 2 years had their length measured using an infantometer, while children over 2 years had their height measured to the nearest 0.1 cm. Weight in kg/Height in m2 was the formula used to calculate BMI. The WHO Growth Charts were used to plot these anthropometric parameters according to age and sex.

Study type: Observational cross-sectional study

Sample size: For the purpose of comparing bone mineral values, 20 kids with congenital adrenal hyperplasia and 20 healthy age- and sex-matched controls were used as the sample size. The setting for this investigation is a hospital. 4 new cases of CAH are typically reported to this hospital each year (based on hospital inpatient and outpatient records)

Exclusion criteria: Children with congenital adrenal hyperplasia due to other enzyme deficits were excluded if their clinical, biochemical, and hormonal diagnoses were in agreement. Children with the non-classical type of CAH caused by a 21 hydroxylase deficit as well as those with the conventional simple virilizing variant were also eliminated.

Measurement of serum electrolytes: Children with CAH had their serum levels of sodium, potassium, ionized calcium, and alkaline phosphatase measured using a Roche automated electrolyte analyzer. Serum sodium levels below 135 mmol/L were considered hyponatremia, whereas serum potassium levels above 5.5 mmol/L were considered hyperkalemia. Alkaline phosphatase levels of 72–307 IU/L and 1.1–1.3 mmol/L for serum ionized calcium are considered normal.

Measurement of serum 17 hydroxy progesterone: The solid phase enzyme linked immunosorbent assay (ELISA)-DRG ELISA (Germany) was used to measure 17-hydroxy progesterone. This method relies on the concept of competitive binding, and the microtiter wells were coated with a polygonal antibody that is directed against an antigenic site of the 17-hydroxy progesterone molecules.

Bone mineral parameters: Dual energy X ray absorptiometry (DXA) -Lunar DPX DXA system- produced by GE health care analysis version 14.10 was used to quantify the bone mineral content (BMC) in g and bone mineral density (BMD) in (g/cm2) of the Total Body Less Head (TBLH) and Lumbar spine (LS) -region of interest.

Statistical analysis: Data were entered in Microsoft Excel sheet and analyzed using SPSS version17. Data are expressed as Mean ± Standard Deviation or median wherever indicated. Independent t test was used to calculate significance if mean < 2 SD and Mann Whitney test was used to calculate significance if mean > 2 SD.

Result

There were a total of 20 children with congenital adrenal hyperplasia during the recruitment period (CAH). Five of the 20 children had the typical salt-wasting CAH, two had the straightforward virilizing CAH, and three had the non-classical CAH. Only 10 children with classical salt wasting CAH were enlisted for the study's purposes as the study group. Ten healthy youngsters who were age- and sex-matched were recruited as the controls.

Clinical features: The genitalia of all the girls with CAH were unclear. Vomiting was seen in three cases, skin hyperpigmentation was seen in two, poor weight growth was seen in three cases, diarrhea was seen in one case, and shock was seen in one case.

Table 1: Anthropometry of Children with CAH and healthy controls

Anthropometry	CAH	Control
Weight (Kg)	8.11±4.22	7.44±6.27
Length/Height (cm)	63.20±21.02	60.02±18.15
BMI (kg/m^2)	10.16±3.22	5.12±1.03

Children with CAH had a mean weight (kg) of 8.11 ±4.22, whereas controls had a mean weight of 7.44 ±6.27. Children with CAH had a mean height/length of 63.20 ±21.02 cm, compared to 60.02 ±18.15 cm for healthy controls. Children with CAH had a mean BMI of 10.16 3.22 kg/m2, whereas healthy control children had a BMI of 5.12 ±1.03. Children with congenital adrenal hyperplasia were similar to controls in terms of weight, length, and height.

Table 2: Laboratory parameters of children with CAH

Sr.No	Lab parameters at diagnosis	Mean ±Std. Deviation
1	Serum Sodium mmol/L	110.21± 6.43
2	Serum potassium mmol/L	9.67±60.56
3	Serum bicarbonate	17.44±3.62
4	Serum alkaline phosphatase	186.33±55.34
5	Serum ionized calcium mmol/L	1.17±0.13
6	Serum 17 OHP ng/dl	14221.33±11064.121

At the time of diagnosis, children with CAH had an average 17 hydroxy progesterone level of 14221.33±11064.121 ng/dl. At the time of diagnosis, the average blood sodium level was 110.21± 6.43 mmol/L, the average serum potassium level was 9.67± 60.56 mmol/L, the average serum ionized calcium level was 1.17 ±0.13 mmol/L, and the average serum alkaline phosphatase level was 186.33 ±55.34.

Table 3: Lumbar Spine & TBLH BMD of Children with CAH and healthy controls

BMD (g/cm^2)	CAH (n=20)	Control (n=20)
Lumbar Spine	0.342±0.95	0.389±0.078
TBLH	0.438±0.085	0.348±0.108

The mean ± SD of lumbar spine BMD in children with CAH is 0.342±0.95 (g/cm^2) and in controls is 0.389±0.078 (g/cm^2). The mean ± SD of TBLH BMD in children with CAH is 0.438±0.085 (g/cm^2) and in controls is 0.348±0.108. In this series lumbar spine and total body less head BMD of children with CAH were comparable with that of healthy controls.

Discussion

Congenital adrenal hyperplasia (CAH) includes a group of disorders that result from reduced activity of several enzymes which are required for the synthesis of cortisol in the adrenal cortex.

Bajpai et al [9] had reported that the mean age at diagnosis of children with salt wasting CAH was 1.8 months in their series. Begum et al [10] had reported that 68.75% of children with CAH had their onset of symptoms below 3 months of age

in their series. The present study shows equal distribution of males and females with CAH similar to the study by Perry et al [11] from Canada. In this series, the diagnosis of CAH was established in newborn period in 10 males and in 15 females.

Begum et al [10] & Bhanji et al [12] had reported female predominance in children with CAH in their series. The reason postulated for female preponderance in studies reported by Begum et al [10] & Bhanji et al [12] is that girls have ambiguous genitalia at birth and hence diagnosis is established earlier than boys who do not have any external abnormality. Normal growth of bone mass occurs throughout childhood, peaking by late adolescence or early adulthood. An essential factor in determining the risk of osteoporosis and the subsequent fractures in later life is reaching maximal bone mass during the time of growth.

Elnecave et al from Brazil has studied bone mineral density in 16 girls with congenital adrenal hyperplasia due to 21 hydroxylase deficiency and observed that there was no significant difference in BMD between CAH patients versus their age matched healthy controls. [13]

Fleischman et al from Boston, USA has analyzed bone mineral density in 17 children aged 8-20 years with congenital adrenal hyperplasia due to 21 hydroxylase deficiency and have reported normal bone mineral density in children with CAH. [14]

Girjis et al from Canada has reported bone mineral parameters in 28 children with congenital adrenal hyperplasia and observed that there was no significant difference in the BMD in CAH children. [15]

Stikkelbroeck et al from Netherlands has analyzed bone mineral density in 30 patients with congenital adrenal hyperplasia due to 21 hydroxylase deficiency and observed that there was significant difference in total body BMC in CAH males when compared with the controls. [16]

According to Chakhtoura Z et al, glucocorticoid medication during puberty mostly influenced BMD. [17] According to Gussinye et al., there was no difference in BMD between prepubertal patients and age- and sex-matched controls, although BMD values were lower in young adult and adolescent CAH patients than in controls. [18]

To the best of our knowledge, this is the first study to describe the clinical spectrum in children from India with CAH caused by a 21-hydroxylase deficit, including genetic characterisation and bone mineral indicators. [19] In order to lower the risk of fractures in later life, managing children with congenital adrenal hyperplasia who receive long-term glucocorticoids should take bone health into consideration. Small sample size due to the rarity of the disease condition, recruitment of children from only one institution, the young age of the participants at recruitment, the option for participants to refuse certain aspects of the study protocol, measurements taken only at one-time point (DXA at recruitment), the impact of total cumulative glucocorticoid dosage on bone parameters not analyzed, and other markers of bone turnover like serum RANKL are some of the limitations of the current study. [20-21]

Conclusion

The potential for prenatal and even preconception CAH diagnosis is provided by developing technologies. With growing knowledge of the potential effects of prenatal androgen exposure, ongoing conversations regarding the gender of raising for very virilized females are necessary, even though early diagnosis may be useful for counselling parents. Additionally, more research on this population's sexuality and quality of life indicators is necessary. Most importantly, cutting-edge therapy approaches like modified-release hydrocortisone

preparation may improve patients with CAH's quality of life.

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