RESEARCH BRIEF

Bone Mineral Content and Density in Indian Children with Congenital Adrenal Hyperplasia

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ABSTRACT

Objective: To study the bone mineral content and density in children with congenital adrenal hyperplasia.

Methods: 35 children with congenital adrenal hyperplasia and 35 healthy controls were enrolled. Bone mineral content and density were studied by Dual Energy *X*-ray absorptiometry.

Results: The mean (SD) of lumbar spine bone mineral density (g/cm2) in children with congenital adrenal hyperplasia was 0.590 (0.100), and in controls it was 0.589 (0.088) *(P* = 0.97). The mean (SD) of Total Body less head bone mineral density (g/cm2) in children with congenital adrenal hyperplasia was 0.536 (0.090), and in controls it was 0.548 (0.111) *(P* = 0.64). The mean (SD) of lumbar spine bone mineral content (g) in children with congenital adrenal hyperplasia was 29.85 (27.63), and in controls it was 31.03 (29.19) *(P*=0.86). The mean (SD) of Total Body less head bone mineral content (g) in children with congenital adrenal hyperplasia was 254.27 (281.25), and in controls it was 273.07 (330.71) (*P*=0.79).

Conclusion: Bone mineral density and content in children with congenital adrenal hyperplasia are maintained in the normal range.

Keywords: *DXA scan, Lumbar spine, Osteoporosis*.

INTRODUCTION

Children with Congenital adrenal hyperplasia (CAH) require lifelong glucocorticoid treatment in order to replace the deficient cortisol, suppress the excess adrenal androgens, and thereby to promote normal growth and development. Glucocorticoid induced osteoporosis (GIO) is an important cause of secondary osteoporosis [1], and skeletal fractures can occur in 30-50% of patients receiving long-term glucocorticoid therapy, especially during the first few weeks of treatment [2]. Glucocorticoid administration even in supplemental doses might result in decreased Bone mineral density (BMD) [3]. Studies from the West have shown normal or decreased BMD in children with CAH receiving glucocorticoids but there are no studies on BMD in Indian children with CAH.We evaluated BMD and Bone mineral content (BMC) in children with CAH being followed-up from a tertiary care hospital in Chennai, India.

METHODS

This cross-sectional analytical study was conducted in the department of Pediatrics and Pediatric Endocrinology from June 2011 to May 2015 in Kanchi Kamakoti CHILDS Trust Hospital, Chennai. The study protocol was approved by the Institutional Ethics Committee. A convenience sample size of 35 children (age 14-18 yr) with CAH and 35 age- sex- and matched healthy controls were recruited for the study. Children with clinical features (vomiting, diarrhea, dehydration, shock, failure to thrive and ambiguous genitalia in females), biochemical parameters (hyponatremia (serum sodium <135 mmol/L) and hyperkalemia (serum potassium>5.5 mmol/L)) and hormonal levels (serum 17 hydroxy progesterone levels > 300nmol/L or >10,000 ng/dL) consistent with the diagnosis of classical salt wasting congenital adrenal hyperplasia due to 21-hydroxylase deficiency were included. Children with clinical, biochemical and hormonal diagnosis consistent with CAH due to classical simple virilising form and Non classical form of CAH due to 21-hydroxylase deficiency and other enzyme deficiencies were excluded. Healthy children attending the outpatient department for immunization and general health check-up and not having any chronic illness that affects bone mineral density were recruited as controls. Informed consent was obtained from parents of children with CAH and controls.

All children recruited with CAH (new and old cases) and controls underwent complete history and detailed clinical examination. They had their blood pressure, anthropometry and sexual maturity rating (SMR) recorded. Serum calcium, phosphorus and alkaline phosphatase were measured in both groups. Children with classical salt wasting CAH were treated withoral hydrocortisone at 10-15 mg/m^2/day. All cases and controls underwent Dual energy *X*-ray Absorptiometry (DXA) scan (Lunar DPX DXA system: GE health care analysis version 14.10) to study their lumbar spine and Total Body Less

Head (TBLH) BMD and BMC. This instrument was calibrated on a daily basis using the phantom provided by the manufacturer. All scans and their analysis were performed by the same operator. Infants and small children were sedated using Triclofos (50 mg/kg) during the scan whereas for older children, no sedation was used. During measurement of the lumbar spine, the child was made to lie supine and physiological lumbar lordosis was flattened by elevation of the knees. Areal BMC, BMD for the lumbar spine and TBLH were measured for all patients using DXA. As there is no normative data or *Z*-scores for BMC/BMD in Indian children, the measured BMC/BMD of children with CAH were compared with their age- and sex- matched healthy controls.

***Statistical analysis*:** Data were entered in Microsoft Excel sheet and analyzed using SPSS version 17. Mann Whitney U test was used to calculate the statistical significance at $P<0.05$.

RESULTS

Thirty-five children with CAH and 35 controls were recruited for the study. Four cases, the mean (SD) age at the time of onset of symptoms was 26.1 (62.7) days, at diagnosis was 22.1 (62.8) days, and at recruitment was 32.7 (38.2) months. The mean (SD) age of controls was 32.7 (38.2) months. Three (16.6%) boys and twelve (70.5%) girls were diagnosed on day 1 of life and all were symptomatic. Of the 35 children, 20 (57%) were born to parents of consanguineous marriage. All girls with CAH had ambiguous genitalia. The common clinical features observed in both sexes were vomiting in 15 (42.8%), skin hyperpigmentation in 15 (42.8%), poor weight gain in 13 (37.1%), diarrhea in 7 (20%) and shock in 5 (14.3%). The comparison of anthropometry, BMD and BMC between cases and controls is presented in ***Table* I**. Linear regression analysis of anthropometric parameters with Lumbar spine and TBLH BMD and BMC in CAH children showed good correlation between TBLH BMD with weight (r=0.87) and height (r=0.83). There was good correlation between height with Lumbar spine and TBLH BMC (r=0.84, 0.93 respectively). There was no correlation between BMI with Lumbar spine/TBLH BMC and BMD.

DISCUSSION

In the present study, there was no difference in mean lumbar spine and TBLH BMD between children having CAH and controls. Lumbar spine and TBLH BMC in CAH children were lower than controls, although, this difference was not statistically significant.

The major limitations of this study were small sample size due to rarity of the disease condition, single center study, and young age at recruitment of the study population. Moreover, they had not

received glucocorticoid replacement therapy even for atleast 3 months. DXA was done only at recruitment, and we have not analyzed the impact of total cumulative glucocorticoid dose on BMD and BMC.

Glucocorticoids form the mainstay of treatment of children with CAH, and it is reported to be the most common cause of drug-induced osteoporosis. Regarding the effect of glucocorticoids on BMD in children with CAH, studies from various parts of the world [4-14] have shown conflicting results. Gussinye, *et al*. [8] reported that BMD values of adolescent and young adult CAH patients were lower than the controls, whereas in prepubertal patients, there was no difference in BMD when compared with age-sex matched controls. Chakhtoura, *et al*. [9] reported that BMD was mostly affected by glucocorticoid therapy during puberty [9]. In our series, all 35 children were in the prepubertal age group at recruitment, and hence the BMD of lumbar spine and TBLH were similar to healthy controls. A normal BMD in CAH patients could probably be explained by the androgen excess, leading to increased peripheral conversion to oestrogens, thus opposing the deleterious effect on bone architecture by increasing osteoblast activity, inhibiting the removal of calcium from the body to decrease the formation and activity of osteoclasts and stimulating the longitudinal growth of long bone [4].

The normal BMD/BMC observed in our patients does not rule out development of glucocorticoid-induced osteoporosis at an older age [12], and they should be followed-up for a longer period of time in order to observe the impact of duration of glucocorticoid therapy on BMD and BMC. Bone health is considered to be an important aspect in managing children with CAH who receive long term glucocorticoids to reduce the risk of fractures in later life.

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WHAT THIS STUDY ADDS?

- Bone mineral density and Bone mineral control in CAH children with congenital adrenal hyperplasia, who are treated with oral corticosteroids, are maintained in the normal range.

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TABLE I BASELINE CHARACTERISTICS OF CHILDREN WITH CAH AND HEALTHY CONTROLS *Values in mean (SD)*

Characteristics	*CAH (n=35)*	*Controls (n=35)*	*P value*
Weight (kg)	12.1 (9.9)	12.9 (9.4)	0.71
Height (cm)	83.4 (31.0)	84 (28.2)	0.93
BMI (kg/m^2)	14.6 (2.6)	16.1 (2.1)	0.01
Lumbar spine BMD (g/cm2)	0.590 (0.100)	0.589 (0.088)	0.97
TBLH BMD (g/cm^2)	0.536 (0.090)	0.548 (0.111)	0.64
Lumbar spine BMC (g)	29.85 (27.63)	31.03 (29.19)	0.86
TBLH BMC (g)	254.27 (281.25)	273.07 (330.71)	0.79

BMI: Body mass index: BMD: Bone mineral density; TBLH: Total body less head; BMC: Bone mineral content; CAH: Congenital adrenal hyperplasia.