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Original Article

Paediatrics Section

Skeletal Maturation and Mineralisation of Children with Moderate to Severe Spastic Quadriplegia

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ABSTRACT

Introduction: Diminished bone mineral density and delayed skeletal maturation are common in children with spastic quadriplegia.

Aim: The purpose of our study was to evaluate the Bone Mineral Density (BMD) of children with moderate to severe spastic quadriplegia and its relationship with other variables like nutrition and growth.

Materials and Methods: This was a hospital based, cross-sectional, case-control study. Forty-two (28 males, 14 females) children with spastic quadriplegia and 42 (24 males, 18 females) healthy children were included in the study. BMD of cases and control were measured by Dual Energy X-ray Absorptiometry (DEXA). Radiographs of left hand and wrist of cases and controls were taken and bone age was determined.

Results: BMD values of upper extremity, lower extremity, thoraco-lumbar spine and pelvis in cases were lower than those of controls ($p < 0.0001$). In children with non severe malnutrition, 75% of the cases had lower bone age than chronological age, whereas all cases with severe malnutrition had lower bone age than chronological age. Step wise regression analysis showed that nutritional status independently contributed to lower BMD values but the BMD values did not correlate significantly with the use of anticonvulsant drugs and presence of physical therapy.

Conclusion: Decreased BMD and delayed bone age is prevalent in children with spastic quadriplegia and nutritional status is an important contributing factor.

Keywords: Anti-epileptic drugs, Bone mineral density, Cerebral palsy, Dual energy X-ray absorptiometry, Nutritional status, Physical activity

INTRODUCTION

Cerebral Palsy (CP) is a common physical disability of childhood [1]. Estimated prevalence of CP is 2.5 per 1000 population [2]. The motor disorders of CP are often accompanied by disturbances of sensation, cognition, communication and behaviour problems, epilepsy and secondary musculoskeletal problems [3].

Undernourishment is commonly seen in children with CP [4]. Co-morbidities like aspiration, gastro-oesophageal reflux, sleep disorders, osteoporosis, visual impairment, hearing loss and behaviour problems are associated [4]. Children with CP have a lower caloric intake as compared with normal children [5] due to the associated co-morbidities. A significant proportion of children with CP have gastro-oesophageal reflux [6]. Caloric loss may be related to frequent regurgitation and emesis. Up to 90% of the patients with CP have oromotor dysfunction which is a major contributor to malnutrition [7-9]. Problems with oral feeding due to dysfunctional sucking and swallowing, inadequate lip closure leading to drooling and inability to chew properly are commonly seen in children with CP [9].

Children with spastic quadriplegia may follow poor growth pattern [10] and they experience problems that have the potential to affect their skeletal development adversely. This problem might be grouped as nutritional inadequacy, ambulatory status, anti epileptic drug therapy, poor exposure to sunlight and the negative neuropathic effect on skeletal development [10].

In view of ambiguity of the factors influencing the skeletal maturation and mineralisation in children with CP and also due to the paucity of studies from India, we therefore decided to evaluate the baseline skeletal maturation and mineralisation and factors influencing them in both cases and controls.

MATERIALS AND METHODS

This was a hospital based, cross-sectional, case-control study, conducted at Department of Paediatric Medicine, Sir Padampat Mother and Child Health Institute (SPMCHI) attached to SMS Medical College, Jaipur, Rajasthan, India. Ethical clearance was taken from the Review and Research Board, SMS Medical College, Jaipur, Rajasthan, India.

The study group included 42 (28 males, 14 females) children of spastic quadriplegia (GMFC score 4 and 5) [11], and 42 (24 males, 18 females) age and sex matched healthy controls were taken. Both cases and controls were in the age group of 2 to 5 years and nutritional assessment was done using Indian Academy of Paediatrics (IAP) classification of malnutrition [12]. Children with metallic implants, family history of bone diseases or genetic disorders were excluded from the study.

The evaluation component included a detailed systemic and neurological examination, records of use of antiepileptic drugs, nutritional status was assessed by height, weight, weight/height and malnutrition grading according to IAP criteria [13]. IAP classification is based on weight for height values. The standard used in this classification for reference population was the 50th centile of Harvard standards. Each patient and control completed a questionnaire, asking about their physical therapy status, daily calories and calcium intake, exposure to sunlight, a radiograph of the left hand and wrist, and a measurement of bone mineralisation in subjects. A detailed systemic and neurologic examination and measurement of bone mineralisation of controls was done. Informed consent was obtained from parents. Serum phosphorus, alkaline phosphatase, calcium (by calorimetric method), parathyroid hormone and vitamin D were measured (by two site immunoradiometric assay).

For each patient, bone maturation as bone age from the left hand and wrist radiographs were taken and assessed for bone age by using the sex specific standards of Greulich and Pyle [14] and compared with the controls.

Bone mineralisation in both the patient and control group was measured (total body mineral content) [15] with a dual energy x-ray absorptiometry (Hologic DQR-1000/w scan). The BMD (bone mineral density) is the bone mineral content (in grams) per unit area (cm^2). Dual Energy X-ray Absorptiometry (DEXA) is the most widely used method for assessment of BMD and is considered the gold standard [15,16].

STATISTICAL ANALYSIS

Statistical analysis was performed using EPI INFO software. Results were analysed for statistical significance by using student t-test and ANOVA test for continuous variable and chi-square test for discrete variables. We studied BMD z-score with other parameters by using Pearson´s correlation coefficient method. Multivariate analysis was performed to evaluate factors predictive of low BMD z-score. Variable with significant correlation were entered into stepwise linear regression model and model with greatest r-value was finally considered.

Laboratory Parameters	Group	Mean	Std. Deviation	Std. Error	95% Confidence Interval For Mean		Minimum	Maximum	p-value
					Lower Bound	Upper Bound			
S.Calcium(mg/dl)	Case	8.6857	.88361	.13634	8.4104	8.9611	6.10	9.80	0.001
	Control	9.5048	1.29633	.20003	9.1008	9.9087	7.20	13.70	
S.Phosphorus(mg/dl)	Case	4.4214	.83565	.12894	4.1610	4.6818	2.00	5.50	0.173
	Control	4.6810	.89367	.13790	4.4025	4.9594	3.20	7.20	
S.ALP(iu/l)	Case	265.6190	131.18837	20.24280	224.7379	306.5002	22.00	760.00	<0.0001
	Control	164.9524	83.02217	12.81060	139.0809	190.8239	78.00	433.00	
S.PTH(pg/ml)	Case	84.6667	100.86713	15.56414	53.2343	116.0991	3.00	510.00	0.05
	Control	52.8952	22.48870	3.47008	45.8873	59.9032	23.00	105.00	
S.Vit.D(nmol/l)	Case	42.3538	30.94055	4.77423	32.7121	51.9956	11.80	138.00	0.962
	Control	42.0810	20.96384	3.23479	35.5482	48.6137	16.70	89.30	

[Table/Fig-1]: Laboratory parameters in cases and controls.

	Group	Sex	Mean	Std. Deviation	p-value*	Sex	Mean	Std. Deviation	p-value*
Left Arm	Case	Male(28)	.3199	.08481	<0.001	Female(14)	.3019	.09006	.001
	Control	Male(24)	.4128	.05808		Female(18)	.4132	.07604	
Right Arm	Case	Male(28)	.3324	.08995	<0.001	Female(14)	.3166	.08831	<0.001
	Control	Male(24)	.4487	.11019		Female(18)	.4669	.11279	
Lumber Spine	Case	Male(28)	.4456	.05544	<0.001	Female(14)	.4216	.09958	<0.001
	Control	Male(24)	.5775	.07023		Female(18)	.5823	.10132	
Pelvis	Case	Male(28)	.4023	.08601	<0.001	Female(14)	.3808	.09393	<0.001
	Control	Male(24)	.6304	.09913		Female(18)	.6510	.10685	
Left Leg	Case	Male(28)	.3583	.11475	<0.001	Female(14)	.3509	.12068	<0.001
	Control	Male(24)	.5749	.10304		Female(18)	.6307	.12755	
Right Leg	Case	Male(28)	.3706	.09057	<0.001	Female(14)	.3430	.12743	<0.001
	Control	Male(24)	.6140	.09519		Female(18)	.6352	.11754	
Total	Case	Male(28)	.5951	.10689	<0.001	Female(14)	.5719	.08714	<0.001
	Control	Male(24)	.7363	.08455		Female(18)	.7346	.09006	

[Table/Fig-2]: Bone mineral density (g/cm^2) values of subjects compared with sex-matched controls.* Highly significant

	Group	Sex	Mean	Std. Deviation	p-value*	Sex	Mean	Std. Deviation	p-value*
Z-Score	Case	Male(28)	-1.4857	1.20145	<0.001	Female(14)	-1.3286	1.65967	<0.001
	Control	Male(24)	1.2500	.79564		Female(18)	.6278	1.04814	

[Table/Fig-3]: Bone mineral density (z score) values of subjects compared with sex-matched controls. * Highly significant

	Medication	Male					Female			
		N	Mean	Std. Deviation	Anova	Lsd	N	Mean	Std. Deviation	Anova
BMD	No	14	.6241	.12231	0.35	3	9	.5944	.09944	0.455
	1 Drug	9	.6103	.05769		3	4	.5358	.04635	
	>1 Drug	5	.4866	.06059		1,2	1	.5140	.	
	Total	28	.5951	.10689			14	.5719	.08714	
Z Score	No	14	-1.5286	.79462	0.12	3	9	-.7222	1.10542	0.171
	1 Drug	9	-.7667	.75333		3	4	-2.2500	2.32307	
	>1 Drug	5	-2.6600	1.91390		1,2	1	-3.1000	.	
	Total	28	-1.4857	1.20145			14	-1.3286	1.65967	

[Table/Fig-4]: Bone mineral density values of subjects taking more than one anticonvulsants compared with other subjects, those are taking one anti convulsant or who were not on medication.

RESULTS

Most of the cases as well as controls were in the age group of 4-5 years followed by 2-3 years age group (mean age for cases was 4.2 and for controls was 4.1 years). [Table/Fig-1] summarized the laboratory parameters. Among the subjects, most of the males (10/28) were in Protein Energy Malnutrition (PEM) grade 2, and females (6/14) were in PEM Grade 3. Eight subjects were not malnourished, whereas 20 subjects were in PEM grade 1&2 and 14 in PEM grade 3&4.

BMD in study population (in both males and females) was lower than the controls ($p<0.001$). Our results showed that the mean BMD in male and female subjects was lowest in upper extremities. Higher values were found in lumbar spine, followed by pelvis and lower extremities. The total mean BMD was higher in male compared to female subjects, but this difference was statistically insignificant ($p>0.05$). BMD values of upper extremities were compared with lumbar spine, pelvis and lower extremities, and we found significant difference in values of upper limb and other region ($p<0.05$) [Table/Fig-2]. p-value was <0.001 and was very highly significant when the BMD values of male and female subjects was compared with sex matched controls using Z scores [Table/Fig-3].

[Table/Fig-4] showed BMD values of subjects taking more than one anticonvulsants compared with other subjects who were taking one anti convulsant or who were not on medication.

No statistically significant difference was found in total BMD values of male and female subjects taking anticonvulsants compared with subjects not on anticonvulsant (p-values for males 0.854 and for females 0.063) [Table/Fig-4].

BMD values of male subjects with regular physiotherapy compared with other subjects was not significant (p-0.448) while in females, it was statistically significant (p 0.002).

Bone age of male and female subjects with non severe malnutrition was delayed in 21 subjects out of 28 children (in 75 % cases) and with severe malnutrition, it was delayed in 14 subjects out of 14 children (in 100% cases).

For identification of predictors of BMD z score among spastic quadriplegic patients, step wise multivariate regression analysis [Table/Fig-5] was done considering BMD z score as dependent variable.

Age, sex, diet (k.cal/day), calcium intake, history of medication use, regular physiotherapy, S.calcium, S.phosphorus, S.alkaline phosphatase, S.parathyroid hormone, S. Vit.D, and PEM grade were entered as independent variables as predictors of low BMD in spastic quadriplegic [Table/Fig-5].

PEM grade showed significant criteria of inclusion as predictor, while rest of the other independent variables were excluded from the model.

Variables Entered/Removed[a]

Model	Variables Entered	Variables Removed	Method
1	PEM GRADE	.	Stepwise (Criteria: Probability-of-F-to-enter <= .050, Probability-of-F-to-remove >= .100).

a. Dependent Variable: Z-SCORE

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.365[a]	.133	.111	1.27506

a. Predictors: (Constant), PEM GRADE

ANOVA[b]

Model	Sum of Squares	df	Mean Square	F	Sig.
Regression	9.982	1	9.982	6.140	.018[a]
Residual	65.031	40	1.626		
Total	75.013	41			

a. Predictors: (Constant), PEM GRADE

b. Dependent Variable: Z-SCORE

Coefficients[a]

Model	Unstandardized Coefficients		Standardized Coefficients	T	Sig.
	B	Std. Error	Beta		
(Constant)	-.706	.353		-2.000	.052
Pem Grade	-.391	.158	-.365	-2.478	.018

a. Dependent Variable: Z-SCORE

Excluded Variables[b]

Model	Beta In	T	Sig.	Partial Correlation	Collinearity Statistics
					Tolerance
Age	-.171[a]	-1.164	.251	-.183	.993
Sex	-.153[a]	-1.010	.319	-.160	.941
Diet(Kcal/Day)	-.190[a]	-1.028	.310	-.162	.630
Calcium(Mg/Day)	.077[a]	.442	.661	.071	.722
Medication	-.215[a]	-1.476	.148	-.230	.992
Physiotherapy	.123[a]	.818	.419	.130	.967
S.Calcium(Mg/Dl)	.081[a]	.545	.589	.087	.991
S.Phosphorus(MG/DL)	.075[a]	.498	.621	.080	.964
S.ALP(IU/L)	-.219[a]	-1.504	.141	-.234	.995
S.PTH(PG/ML)	-.201[a]	-1.334	.190	-.209	.936
S.VIT.D(NMOL/L)	-.198[a]	-1.292	.204	-.203	.911

a. Predictors in the Model: (Constant), PEM GRADE

b. Dependent Variable: Z-SCORE

[Table/Fig-5]: Regression.

DISCUSSION

The present study shows that spastic quadriplegic children have significantly lower values of S. Calcium, S. Alkaline phosphatase, while no significant difference in between S. Phosphorus, S. PTH and S. Vit D levels as compared to controls. BMD values were lower in cases and it was found that nutritional status independently contributes to lower BMD values, while physiotherapy and use of anticonvulsant drugs did not correlate significantly with BMD values. Bone age was lower than chronological age in most of the subjects.

In our study, we aimed to identify factors that may affect bone mineralization and to assess their association with BMD. Results of the present study demonstrates that decrease in BMD is significant in children with spastic quadriplegia. The suggested mechanisms responsible for the reduction in bone density in these children are poor nutritional status, insufficient calcium intake, immobilization and anticonvulsant use [17]. Reduced BMD values (measured by Dual-Energy X-ray Absorptiometry) in the spastic quadriplegic group as compared to the healthy controls in the study, further confirmed the presence of inadequate mineralization in children with cerebral palsy. King and colleagues also found that Lumbar spine BMD was markedly reduced in children with spastic quadriplegia [18]. In another series, Coppola G and colleagues confirmed that a severe mental retardation and spastic quadriplegia are significantly correlated to an abnormal bone mineral density with or without epilepsy [19].

Antiepileptic drug use may affect skeletal mineralisation adversely. Sato et al., and Tsukahara et al., found that long term antiepileptic treatment induces a state of decreased bone turn over and low bone mineral density [20,21]. In our study, mean BMD was lower in the subjects taking anticonvulsants but this difference

was statistically insignificant (t-test 0.155 and 0.206 in male and female respectively, & Partial correlation = -0.230). Demet Yardimci et al., found no statistical correlation between the duration of anticonvulsant and bone mineral density and bone mineral content values in both sexes [16].

Poor feeding skills may lead to inadequate caloric, protein and calcium intake. In our study, mean calorie and calcium intake was significantly lower in study population as compared to controls (p 0.0001). 92.6% cases and 85.4% of controls in present study had subnormal vitamin D levels. Vitamin D deficiency has been associated with inadequate exposure to sun, vegetarian diet and absence of Vitamin D fortification in milk and food. A study comparing the outcomes of treatment with Vitamin D and bisphosphonate therapy on BMD values showed that bisphosphonate therapy was effective for patients who presented with secondary osteoporosis due to cerebral palsy [22]. Stallings et al., reported that malnutrition and growth failure were common in children with quadriplegic cerebral palsy [23]. Tandon et al., reported that a greater body mass index gain in childhood and adolescence is associated with higher peak bone density [24]. Another study by Henderson et al., showed that BMD z score was low in subjects with feeding problems [25]. Our data showed that, mean BMD z-score in severe malnutrition group was lower than non severe malnutrition group. Linear significance was 0.018 and significance of quadratic regression was 0.006.

Another important correlate of low BMD in children with CP is physiotherapy. Our data indicate that BMD values in the subjects with regular physiotherapy were higher compared to those without physiotherapy but this difference was statistically insignificant in males (Anova=0.448), while in females it was significant (Anova=0.002). {Correlation coefficient was 0.130 for physiotherapy and BMD}. The significant difference found in females was probably because of co-existing severe malnutrition. Bülent Ünay et al., found no significant difference in the bone mineral density values of children on regular physiotherapy or who were not on physiotherapy [26]. Many similar studies had been conducted to assess the relation of BMD with other parameters and various therapeutic interventions and had shown almost similar conclusion which suggest that BMD values were much lower in children with CP due to the various underlying problems mentioned in their studies [27-33] [Table/Fig-6].

Our data indicate that bone age was delayed in 35 (83.33%) subjects (75% in non severe malnutrition and 100% in severe malnutrition). Seven children had normal bone age compared to chronological age, all of them belonged to non severe malnutrition group. Our results shows that nutritional inadequacies is one of the important factors for skeletal maturation, other factors like negative neuropathic effect, severity, type of the cerebral palsy and low bone mineral density may shows additive effect. Study by Demet Yardimci et al., showed that skeletal maturation is frequently delayed in children with spastic cerebral palsy [16].

LIMITATIONS

We did not follow up our patients to compare the results of various medical and physical interventions they received.

CONCLUSION

Skeletal maturation and mineralisation are significantly influenced by nutritional status in children with cerebral palsy and adequate steps should be taken to maintain appropriate nutrition in these children.

Abbreviations: BMD, bone mineral density; CP, cerebral palsy; DEXA, dual energy X ray absorpsiometry; GMFC, gross motor functional classification; IAP, Indian academy of paediatrics; PEM, protein energy malnutrition; PTH, parathyroid hormone; SD, standard deviation; SMS, sawai man singh.

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Study (year)	Subject [n]	Age group (years)	Parameter evaluated	Observations
Henderson et al., (2005) [27]	80	2.6 – 21.1	BMD, Bone age, Tanner staging and anthropometric assessment	Diminished linear growth (height), low lumbar spine bone density, and low body fat are independently associated with delay in skeletal maturation.
Gollapudi et al., (2007) [28]	51	Mean age Boys – 7.1 Girls – 8.6	Bone age	Ambulatory cerebral palsy patients had advanced bone age as compared with chronological age.
Iwasaki et al., (2008) [22]	20	1 – 16	BMD, treatment with Vitamin D and Bisphosphonate	Bisphosphonate therapy is effective for patients presenting with secondary osteoporosis with cerebral palsy.
Van Eck et al., (2008) [29]	100	9 – 16	Skeletal age by X-ray of the hand	Skeletal age of females with cerebral palsy was significantly higher than their chronological age, but this did not apply to males.
Henderson et al., (2010) [30]	619	6 – 18	BMD and fracture	Strong correlation between fracture history and BMD z-scores in the distal femur.
Coppola et al., (2012) [19]	113	3 – 25	BMD	A significantly lower BMD z-score value was found in patients with CP, mental retardation, and epilepsy compared with those without epilepsy.
Tatay et al., (2012) [31]	69	2-18	BMD	BMD were much lower thn the reference levels.
Rezende et al., (2015) [32]	31	10-20	BMD and anthropometric data	High incidence of osteoporosis in patients with neuromotor scoliosis secondary to quadriplegic CP.
Grossbergetal et al., (2015) [33]	40	6-26	BMD	Age and change in body weight were relevant factors.
Our study	42	2-5	BMD, Nutritional assessment, Bone age, Serum Calcium, phosphate, alkaline phosphatase, PTH and Vitamin D	Decreased BMD and delayed bone age is prevalent in children with spastic quadriplegia and nutritional status is an important contributing factor.

[Table/Fig-6]: Comparison of various studies.

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