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Hypocalcemic Seizures in Breastfed Infants with Rickets Secondary to Maternal Vitamin D Deficiency

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Abstract:
Objective: *This study was done to evaluate if nursing mothers of infants with rickets have vitamin D deficiency, and to evaluate the relationship between maternal vitamin D levels and Hypocalcemic seisures in infants with rickets.*
Material And Methods: *This study was conducted from July 2014 to December 2014 at G. B Pant Children hospital which is tertiary care hospital and is associated hospital of government medical college Srinagar India. Infants were included in this study if they were breastfed and presented with any of the following criteria: delayed motor milestones or delayed teething, were found to have specific rachitic signs, or presented with Hypocalcemic seisures. We checked serum calcium (Ca), phosphorus (P), alkaline phosphatase, 25 hydroxy vitamin D [25(OH)D] and parathyroid hormone (PTH) levels in both infants and their mothers. Out of 64 infants who met clinical criteria for rickets, 20 (31%) of breastfed infants had vitamin D deficiency while as 32 (50%) of infants had vitamin D insufficiency. Fifty two (81%) mothers had vitamin D deficiency (25(OH) D <20 ng dl^{-1}). Mothers of 18 infants who presented with Hypocalcemic seisures had severe vitamin D deficiency, (P=0.005).*
Conclusion: *We conclude the maternal vitamin D deficiency is common in nursing mothers of infants diagnosed with rickets. Hypocalcemic seisures in rachitic infants are invariably associated with severe vitamin D deficiency in mothers. Hypocalcemic seisures in infancy secondary to maternal vitamin D deficiency might be prevented by supplementation.*

I. Introduction

Vitamin D is essential precursor of 1, 25-hydroxyvitamin D, the steroid hormone required for calcium absorption and growth in children. During the first 6-8 weeks of life, the vitamin D status of infants is determined by the vitamin D levels at birth, which depends on the vitamin D status of the mother[1]. Breast milk concentration of vitamin D is low (<20 IU/L) and is inadequate for the needs of the growing infants[2]. Vitamin D in breast milk relates to mothers vitamin D intake, skin pigmentation and sun exposure[3]. Vitamin D deficiency with a resurgence of rickets is increasingly being reported in infants and toddlers from various parts of world, especially from temperate regions and among African American babies[4-6]. Rickets and hypocalcemic seizures due to vitamin D deficiency in exclusively young infants have been recently reported from southern India[7,8]. There are few reports of vitamin D deficiency among pregnant women and cord blood of their newborns[9,10] and breastfed young infants from India[11,12]. A state of deficiency occurs months before rickets is obvious on physical examination, and the deficiency state may also present with growth failure, lethargy, irritability, and a predisposition to respiratory infections during infancy[13]. Recently, young infants who presented with hypocalcemic seizures, were found to have congenital vitamin D deficiency[14,15]. Several lifestyle and environmental factors including inadequate exposure to sunlight and decrease in the number of physicians who routinely prescribe vitamin D supplements for breastfed infants are partly responsible for high prevalence of Vitamin D deficiency in the developing countries and resurgence in developed countries[16].

Amongst the various etiologies hypocalcemia is major biochemical cause of seizures in infancy in developing countries[17,18]. It constitutes 25.6% of afebrile seizures in children[19]. Hypocalcemia due to vitamin D deficiency constitutes an important cause of infantile seizures in developing countries. Infants are vulnerable population for developing deficiency due to high rate of skeletal growth[20].

II. Material And Methods

This study was conducted at G B Pant children hospital Srinagar between July 2014 to December 2014. Ethical committee of this children hospital approved the study protocol. Sixty four infants with vitamin D deficiency or nutritional rickets were identified in this time period. These patients were diagnosed by clinical presentation, biochemical results and radiological findings. The usual presentation of these patients were in the form of delayed motor milestones, delayed dentition, hypocalcemic seizures or other illnesses.

The study included 64 infants with nutritional rickets and their mothers. Consent was given by all mothers for study. Clinical information were obtained regarding the following: infants age, infants dietetic history, history of calcium or vitamin D supplementation to the infant or his mother and history of regular sun exposure. Motor milestones and dentition were assessed history and physical examination. Radiological examination of the wrists, ankles and knees was done for all cases. CT scan of the head was done for infants who presented with seizures. CSF examination was also done in all cases of seizures. None of the infants nor any mothers suffered from renal or liver disease, or was on anticonvulsant therapy. Neither the infants nor the mothers were receiving calcium or vitamin D supplementation. Social class of mother was not included as a risk factor for developing vitamin D deficiency among nursing mothers of rachitic infants. Mothers living in urban and rural were not compared as per their vitamin D status. Maternal education and work was also not included too. Blood (4ml) was drawn for estimation of serum calcium, phosphate, alkaline phosphate (ALP), 25(OH) D and parathyroid hormone (PTH) for both infant and mother. Serum calcium was measured by calorimetric, o-cresolphtalein (CPC). Reference value 8.6-10.3 mg dl^{-1} (2.15-2.57 $mmol^{-1}$). Serum phosphorus was measured using phosphomolybate UV, End point. Reference values for infants: 1-30 days 3.9-7.7 mg dl^{-1} ,1-2 months 3.5-6.6 mg dl^{-1} and 1-3 years 3. 1-6 mg dl^{-1}. For mothers: 2.6-4.5 mg dl^{-1}. Serum alkaline phosphatase was measured by using enzymatic kinetic method. Reference values for infants: Age 1 day -30 days 48-406 IU L^{-1} for females while males 75-310 IU L^{-1}. Age 1 month – 1 year: 124-341 IU L^{-1} for females while 82-319 IU L^{-1} for males. Age 1-3 years: 108-317 IU L^{-1} for females while 104-345 IU L^{-1} for males. Vitamin D was measured using 25-hydroxyvitamin D ^{125}I RIA Kit. Intact PTH were measured with the intact PTH using ELISA. Reference range used was between 13.9-75.1 pg ml^{-1}.

Defnitions: For infants vitamin D insufficiency was considered when 25(OH) D <20 ng ml^{-1} which equals <50 nmol L^{-1} while vitamin D deficiency was considered when 25(OH) D < 10 ng ml^{-1} which equals <25 $nmol^{-1}$. For mothers: vitamin D insufficiency when 25(OH) D was between 20-32 ng ml^{-1} which equals 50-80 $nmol^{-1}$. Vitamin D deficiency when 25(OH) D was < 20ng ml^{-1} which equals 50 $nmol^{-1}$.

Radiographic Evauation: All infants were subjected to radiography of bilateral wrists to detect feactures of rickets. The radiographs were interpreted by a single radiologist, experienced in reporting of pediatric radiographs, who was blinded to the biochemical vitamin D status of infants.

III. Results

The results of this study showed total of 64 rachitic infants. Among 64 infants 45 (70%) presented with delayed closure of anterior fontanelles, 58 (90%) patients had frontal and parietal bossing, rachitic rosary was found in 35 (54%) of patients and Thirty infants (46%) presented with delayed development or delayed dentition. Eighteen infants (28%) had hypocalcemic seizures. Signs of rickets were found on physical examination of other infants who presented with chest infections 10 (16%), gastroenteritis 4 (6%) or dietetic counseling 4 (6%). Seven (10%) patients presented with Harrisons groove and only 2 (3%) patients had inspiratory stri

Table-1Clinical presentation of rachitic breastfed infants

Clinical presentation	NO.	%
Delayed closure of anterior fontanelles	45	70
Parietal and frontal bossing	58	90
Rachitic rosary	35	54
Delayed motor milestones or delayed dentition	30	46
Hypocalcemic seisures	18	28
Chest infections	10	16
Gastroenteritis	4	6

There were 38 males (59%) and 26 females (41%). All 64 infants were breastfed with 45 (70%) exclusively breastfed, 10 (15%) were given both cows milk and breast milk and rest 9 (14%) were receiving formula feeding and breast milk. Thirty five (54%) infants generally remained indoors at home. The rest of infants went outside occasionally without any purpose to get sunlight. Infants with dark skin were 25 (39%) out of rachitic infants in the study. All the infants and their mothers had limited sun exposure. Some of mothers wore covered dress (exposing the face and hands only) while others were veiled (covering their faces).

Table-2 Demographic characteristic of rachitic infants in this study

Studied parameter	No.	%
Sex: Males	38	59

Females	26	41
First birth order	15	23
Exclusively breastfed	45	70
Prevalance of dark skin	25	39

Infants who presented with Hypocalcemic seisures were younger than other rachitic infants (p=0.005). Their mothers were more vitamin D deficient (p=0.005). Our study demonstrated severe maternal vitamin D deficiency as a cause of rickets and Hypocalcemic seisures in breastfed infants.

Table-3 Infants age and biochemical test in infants presented with or without Hypocalcemic seisures and their maternal values

	Infant values			Maternal values		
	Group-A	Group- B	p-value	Group-A	Group-B	p-value
Infants age(months) Mean±SD Median(IQR)	3.67±1.6 (3)	12.35±4.3 (0.335)	0.001*			
S.ca(mg dl^{-1}) Mean±SD Median(IQR)	6.5±1.48 6.8 (2.8)	8.5±1.5 8.7 (1.530)	0.004*	8.3±1.1 8.8 (1.8)	8.8±1.7 8.7(9)	0.464
S.P (mg dl^{-1}) Mean±SD Median(IQR)	3.3±0.88 3.5(1.8)	3.88±1.19 4(1.9)	0.184	3.7±0.9 4(1.8)	4.2±1.1 4.2(1.9)	0.297
S.Alkaline Phosphatase(IU L^{-1}) Mean±SD Median(IQR)	286±144 277(221)	189±248 175(201)	0.69	119±48 117(55)	102±55 89(35)	0.154
S.25(OH)D($ngml^{-1}$) Mean±SD Median(IQR)	9.73±5.9 6.79 (10)	17.4±8.23 18 (10)	0.016*	10.5± 5.5 8.9 (11)	26±17.4 18(18)	0.005*
S.PTH(pg ml^{-1}) Mean±SD Median(IQR)	3.3±0.88 3.5(1.8)	3.88±1.19 4(1.9)	0.125	103±64 88(184)	69 ± 45 50(50)	0.208

Group A: Infants presented with Hypocalcemic seisures. Group B: Infants who do not present with Hypocalcemic seisures. S 25 (OH)D: 25 hydoxy vitamin D, PTH: Parathyroid hormone. *Significant, IQR: Interquartile. S. P: Serum phosphorus

Table-4 Biochemical results of breastfed infants with vitamin D deficiency and/ or nutritional rickets and their mothers

Results	Infants	Mothers	Correlation r	P-value
S.Ca (mg dl^{-1}) Range Mean±SD Median (IQR)	4.5-10.9 7.9±1.7 8.1 (1.6)	5.6-14.7 8.7 ±1.6 8.6 (1.90)	0.392*	0.026
S. P(mg dl^{-1}) Range Mean±SD Median (IQR)	1.6-6 3.73±1.27 4(1.6)	2.5-6.1 4.1± 1.07 4.1(1.8)	\\ 0.443*	0.011
S.ALP(IU L^{-1}. Range Mean±SD Median (IQR)	77-1250 293.6±221 229(211)	43-277 107.4±54.4 90(50)	0.054	0.769
S.25(OH)D(ng ml^{-1}). Range Mean±SD Median (IQR)	3-38 15.29±8.3 15(13)	4-70 21±16 16(18)	0.326	0.069
S. PTH (pg ml^{-1}) Range Mean±SD Media (IQR)	10-252 98±65 77(56)	18-222 78.9±52 57(73)	0.295	0.101

S: Serum, Ca: calcium, P: Phosphorus, 25(OH) D: 25 hydroxy vitamin D, PTH: Parathyroid hormone. S.ALP: Serum Alkaline phosphatase.*Significant Correlation

Most of our patients were from middle and lower classes of nonworking mothers. Forty five (70%) of the mothers of rachitic infants had vitamin D deficiency while an additional seven (11%) had vitamin D insufficiency. In this study 30% of breastfed rachitic infants had Vitamin D deficiency while as 50% of rachitic infants had vitamin D insufficiency. In others 20% of cases insufficient intake of calcium is suggested as a cause of rickets (Hypocalcemic rickets) Present study showed positive correlation between rachitic infants and their mothers but P value was insignificant (r=0.326. p=0.069). Serum PTH levels in rachitic infants showed negative correlation with serum 25(OH) D (r=-0.365, P=040), also this negative correlation was in their mothers (r=-0.343, P=0.055).

Infants with Hypocalcemic seisures had lower serum calcium than infants who did have seisures (P=0.004). They also had lower 25(OH) D levels than those who did not have seisures (P=0.016). The mothers of those infants had less 25(OH) D levels than mothers of infants who did not have seisures (P=0.OO5). Our data suggests that infants with Hypocalcemic seisures were born with less vitamin D stores because their mothers were severely deficient in vitamin D. Our study showed that the younger infants presented with Hypocalcemic seisures while the older presented with manifestations of bony affection or delayed motor milestones.

Radiological evidence of rickets was seen 50% of patients as metaphyseal widening and healing line. The infants with radiological rickets had lower levels of serum 25(OH) D, Calcium and phosphate and higher ALP.

IV. Discussion

Our study has revealed that boys were more involved than girls which is quite similar to the earlier studies[21,22]. On sub-analysis of our confirmed case non of our rachitic infants had received vitamin D supplementation and this is consisted with some studies[23,24]. In our study 31% of rachitic infants had vitamin D deficiency while as 50% of rachitic infants had vitamin D insufficiency. This is supported by some studies[25,26]. In our study dark skin was risk factor developing rickets in breastfed infants. In our study 39% patients had dark skin. This finding is supported by some literature[27].Our study revealed that 45 (70%) of nursing mothers had vitamin D deficiency while as an additional 11% had vitamin D insufficiency. This is in agreement with Dawodu et al. (2005)[28]. We found positive correlation between rachitic infants and their mothers but P was insignificant (r=0.326, P=0.040). This is in contrast to one study[28] who found positive correlation between serum 25 (OH)D in mothers and their children (r=0.39, p=0.012). This might be because in their study they included rachitic and non-rachitic children and their mothers while all our infants had nutritional rickets. Serum PTH levels in rachitic infants showed negative correlation with serum 25(OH) D (r=-0.365, p=0.040), also this negative correlation was in their mothers (r=-0.343, p=0.055). In Dawodu et al (2005) study[28], serum PTH was available only in rachitic children and their mothers which showed trend towards negative correlation with serum 25(OH)D.

In our study infants with Hypocalcemic seisures had lower serum calcium than infants who did not (P=0.004). They also had lower 25 (OH)D than those who did not have seisures with (p=0.016). The mother of those infants had less 25(OH)D than mothers of infants who did not have seisures,(p=0.005). This finding is supported by Balasubramanian and Ganesh (2008)[29] observation during the study of hypocalcemia in infants and children. We found in our study that the younger infants presented with Hypocalcemic seisures while the older infants presented with manifestatipon of bony affection or delayed motor milestones. This is in agreement with study conducted by Ladhani et al. (2004)[30]. In this study 31% of breastfed infants have vitamin d deficiency and 50% of infants had vitamin D insufficiency and 19% of patients may be having Hypocalcemic rickets due to insufficient calcium intake[31].

Bibliography

[1]. Holicks MF, Mac Laughlin JA, Doppelt SH. Regulation of cutaneous previtamin D3 photosynthesis in man. Skin pigment is not an essential regulator. Science. 1998;211:590-3.
[2]. Kamno M, Tsugawa N, Suhara Y, Wada A, Mori T, Murata K, et al. Quantification of fat-soluble vitamins in human breast milk by liquid chromatography-tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 2007;859:192-200.
[3]. Specker BL. Do North American women need supplemental vitamin D during pregnancy or lactation? Am J Clin Nutr. 1994;59:484S.
[4]. Wagner C. Rickets: emerging from obscurity. Am Fam Physician. 2006;74:561–2.
[5]. Ward LM, Gaboury I, Ladhani M, Zlotkin S. Vitamin D-deficiency rickets among children in Canada. CMAJ. 2007;177:161–6.
[6]. Kreiter SR, Schwartz RP, Kirkman HN, Charlton PA, Calikoglu AS, Davenport ML. Nutritional rickets in African American breast-fed infants. J Pediatr. 2000;137:153–7.
[7]. Girish M, Subramaniam G. Rickets in exclusively breast fed babies. Indian J Pediatr. 2008;75:641–3.
[8]. Balasubramanian S, Shivbalan S, Kumar PS. Hypocalcemia due to vitamin D deficiency in exclusively breastfed infants. Indian Pediatr. 2006;43:247–51.
[9]. Sachan A, Gupta R, Das V, Agarwal A, Awasthi PK, Bhatia V. High prevalence of vitamin D deficiency among pregnant women and their newborns in northern India. Am J Clin Nutr. 2005;81:1060–4.
[10]. Goswami R, Gupta N, Goswami D, Marwaha RK, Tandon N, Kochupillai N. Prevalence and significance of low 25-hydroxyvitamin D concentrations in healthy subjects in Delhi. Am J Clin Nutr. 2000;72:472–5.
[11]. Bhalala U, Desai M, Parekh P, Mokal R, Chheda B. Subclinical hypovitaminosis D among exclusively breastfed young infants. Indian Pediatr. 2007;44:897–901.
[12]. Seth A, Marwaha RK, Singla B, Aneja S, Mehrotra P, Sastry A, et al. Vitamin D nutritional status of exclusively breast fed infants and their mothers. J Pediatr Endocrinol Metab. 2009;22:241–6.
[13]. Papandreou, D, P. Malindretos, Z. Karaboulta and I. Rousso, 2010. Possible health implications and low vitamin D status during childhood and adolesence: An updated mini review. Int. J. Endocrinol., 2010: 472173-472173.
[14]. Holicks, M. F., R. Lim and A.S. Dighe, 2009. Case records of the Massachusetts General Ho seisuresspital. Case 3-2009. A 9-month old boy with seisures. N. Engl. J. Med., 360: 398-407.
[15]. Orbak, Z., M. Karacan, H. Doneray and C. Karakelleoglu, 2007. Congenital rickets presenting with hypocalcemic seisures. West India Med. J., 56: 364-367.

[16]. Davenport, M.L.,A. Uckun and A.S. Calikoglu, 2004. Pediatrician patterns of prescribing vitamin supplementation for infants: Do they contribute to rickets? Pediatrics, 113: 179-180.
[17]. Ahmed I, Attiq M, Iqbal J, Khurshid M, Whittaker P (1995) Vitamin D defciency rickets in breast-fed infants presenting with hypocalcemic seisures. Acta Paediatr 84: 941-942.
[18]. Balasubramanian S, Shivbalan S, Kumar PS (2006) Hypocalcemia due to vitamin D deficiency in exclusively breastfed infants . Indian Pediatr 43: 247-251.
[19]. Cetinkaya F, Sennaroglu E, Comu S (2008) Etiologies of seisures in young children admitted to an inner city hospital in a developing country. Pediatr Emerg Care 24: 761-763.
[20]. Garcion E, Wion-Barbot N, Montero-Menei CN, Beger F, Wion D (2002)New clues about vitamin D functions in central nervous system. Trends Endocrinol Metab 13:100-105.
[21]. Laditan AA, Adeniyi A.Rickets in Nigerian children- response to vitamin D.J Trops Med Hyg 1975;78:206-209.
[22]. Salimpour R. Richets in Tehran, Study of 200 cases. Arch Dis Child 1975; 50: 63-66.
[23]. Daaboul, J., S.Sanderson, K. Kristensen and H. Kitson, 1997. Vitamin D deficiency in pregnant breast feeding women and their infants. J. Perinatol., 17: 10-14.
[24]. Taylor, J.A., W. Geyer and K.W. Feldman, 2010. Use of supplemented vitamin D among infants breastfed for prolonged period. Pediatrics, 125: 105-111.
[25]. Hatun, S., B. Ozkan, H. Doneray, F. Cizmecioglu, D. Toprak and A.S. Calikonglu, 2005. Vitamin D deficiency in early infancy. J. Nutr., 135; 279-282.
[26]. Baroncelli, G.I., A. Bereket, M.El-Kholy, L. Audi and Y. Cesur et al., 2008. Rickets in the Middle east: Rle of environmental and genetic predisposition. J. C;lin. Endocrinol. Metab., 93: 1743-17509.
[27]. Kreiter, S.A., P.P. Schwarts, H.N. Jr. Kirkman, P.A. Charton, A.S. Calikoglu and M.L. Davenport, 2000. Nutritional rickets in African American breastfed infants.J. Pediatr., 137: 153-157.
[28]. Dawodu, A., M. Agarwal, M. Sankarankutty, D. Hardy, J. Kochiyil and P. Badrinath, 2005. Higher prevalance of vitamin D deficiency in mothers of rachitic than non-rachitic children. J. Pediatr., 147: 109-111.
[29]. Balasubramanian, S. and R. Ganesh, 2008. Vitamin D deficiency in exclusively breastfed infants. Indian J. Med. Res., 127: 970-973.
[30]. Ladhani, S., L Srinivasan, C. Buchanan and J. Allgrove, 2004. Presentation of vitamin D deficiency .Arch. Dis. Child., 89: 781-784.
[31]. Pfitzner, M.A., T.D Thacher, J.M. Pettifor, A.I. Zoakah, J.O.. Lawson, C.O. Isichei and P.R. Fischer, 1998. Absence of vitamin D deficiency in young Nigerian children. J. Pediatr., 133: 740-744.