Craniotabes in Normal Newborns: The Earliest Sign of Subclinical Vitamin D Deficiency

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Context: Craniotabes in otherwise normal neonates has been regarded as physiological and left untreated.

Objective: Our objective was to investigate the role of vitamin D deficiency in the development of craniotabes in normal neonates.

Design and Setting: Newborn screening of craniotabes was conducted at the single largest obstetrical facility in Kyoto, Japan. Follow-up study at 1 month was conducted at Kyoto University Hospital.

Subjects: A total of 1120 consecutive normal Japanese neonates born in May, 2006, through April, 2007, were included in the study.

Main Outcome Measures: The incidence of craniotabes was scored each month. Neonates with craniotabes were followed up at 1 month with measurements of serum calcium, phosphorus, alkaline phosphatase (ALP), intact PTH, 25-OH vitamin D (25-OHD), urinary calcium, phosphorus, creatinine, and hand x-rays.

Results: Craniotabes was present in 246 (22.0%) neonates, and the incidence had obvious seasonal variations, highest in April-May and lowest in November. At 1 month, infants with craniotabes had significantly higher serum ALP compared with normal neonates; 6.9% of them had elevated intact PTH over 60 pg/ml, and 37.3% had 25-OHD less than 10 ng/ml. When separately analyzed according to the method of feeding, 56.9% of breast-fed infants showed 25-OHD less than 10 ng/ml, whereas none of formula/mixed-fed infants did, and breast-fed infants had significantly higher serum PTH and ALP compared with formula/mixed-fed infants.

Summary: These results suggest that craniotabes in normal neonates is associated with vitamin D deficiency *in utero*, and the deficiency persists at 1 month in many of them, especially when breast-fed. **(*J Clin Endocrinol Metab* 93: 1784–1788, 2008)**

Craniotabes is a softening of skull bones that is known to be associated with a variety of pathological conditions, including rickets, hypervitaminosis A, osteogenesis imperfecta, hydrocephalus, or congenital syphilis. On the other hand, craniotabes in otherwise normal newborns has largely been regarded as a physiological condition without the need for treatment (1, 2). In fact, Medline Plus of the U.S. National Library of Medicine and the National Institute of Health recommends no tests or treatment for craniotabes in normal neonates (http://www.nlm.nih.gov/medlineplus/ency/article/001591.htm). This is partly because the condition is found in a considerable percentage of otherwise normal neonates, up to 30%, and is usually self-limited, healing within 2–3 months (1). In addition, previous small-scale studies failed to show lower serum 25-OH vitamin D (25-

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Abbreviations: ALP, Alkaline phosphatase; 25-OHD, 25-OH vitamin D.

OHD) in mothers of newborns with craniotabes as compared with that of mothers of newborns without craniotabes (3). At present, subtle alteration of calcium metabolism or physical compression due to early engagement has been postulated as causes of this "benign" craniotabes (1).

However, given the results of recent reports showing the high incidence of vitamin D deficiency in pregnant women (4–8), a higher incidence of craniotabes among normal neonates does not necessarily mean that the condition is physiological. In addition, there is now compelling evidence that transient vitamin D deficiency *in utero* or in infancy could lead to an increased risk of childhood type 1 diabetes or decreased bone mass later in life (9, 10). Increased risks are also suggested for other disorders such as childhood asthma (11), lower respiratory tract infections in infancy (12), or even schizophrenia (13). If craniotabes in normal neonates reflects mild vitamin D deficiency *in utero*, and if the condition persists longer in infancy, it might lead to a variety of health problems later in life.

In this study, to address the question of whether craniotabes in normal neonates really is a benign condition requiring no attention, we systematically screened 1120 consecutive normal neonates born at a single hospital in Kyoto, Japan, for signs of craniotabes. Japan is a country in which systematic vitamin D supplementation is not performed either for pregnant women or for breast-fed infants. Most food products are not fortified with vitamin D, except for a few items, including infant formulas. We hypothesized that if craniotabes in normal newborns really reflects vitamin D deficiency *in utero*, the incidence should be affected by the month of birth, as in other symptoms caused by vitamin D deficiency; therefore, we first analyzed seasonal variation in the incidence of craniotabes. The effects of a variety of other maternal and fetal conditions were also analyzed. Newborns with craniotabes were then followed up at 1 month to examine their postnatal vitamin D and calcium metabolism status with special emphasis on the relationship with the method of feeding: breast-feeding or formula/mixed feeding.

Subjects and Methods

Study subjects

With informed consent, 1120 consecutive, normal Japanese neonates born at Adachi Hospital from May, 2006, to April, 2007, were enrolled in the study. The hospital is located in Kyoto (latitude 35.018° north, population ~1,470,000) in mainland Japan, which has 4,446.9-h daylight per year. The hospital is the largest obstetrical facility in the city, dealing with the deliveries of mostly middle-class Japanese women. Premature neonates with birth weights less than 2000 g, or those who required any medical assistance such as iv fluid administration or use of any extra medications to sustain their homeostasis were excluded from the study. The study protocol was approved by the institutional review board at Adachi Hospital.

Methods

Neonates were checked for the presence of craniotabes by a single, expert pediatrician (J.Y.) at 5–7 d of age as a part of routine discharge examinations. Craniotabes was scored positive when the skull bones reversibly bended by application of pressure by the examiner's fingers ("ping-pong ball skull"). The incidence of craniotabes was then correlated with the month of birth to examine the seasonal variation. The influence of additional factors, maternal age at delivery, number of pregnancies, birth weight, and weeks of pregnancy, were also analyzed. Neonates with craniotabes were then followed up at 1 month of age with physical examination by the same pediatrician (J.Y.), and blood chemistry, including serum calcium, phosphorus, alkaline phosphatase (ALP), intact PTH, 25-OHD, spot urinary chemistry for calcium, phosphorus, creatinine, and hand x-ray for signs of rickets. Serum concentration of 25-OHD was measured by the RIA assay (25-hydroxyvitamin D 215I-RIA kit; DiaSorin Inc., Stillwater, MN), and serum intact PTH was measured by the immunochemiluminometric assay (ECLusys PTH; Roche Diagnostics Corp., Basel, Switzerland). All laboratory and radiological data were obtained at Kyoto University Hospital. Cupping of the distal end of ulna was taken as the earliest sign of rickets. The x-rays were blindly assessed by two examiners (J.Y. and T.Y.) and considered positive only when both reached the same conclusion. The results were then separately analyzed according to the method of feeding, *i.e.* breast feeding or formula/mixed feeding. When the mean formula intake exceeded 40 ml/d, it was classified as mixed feeding. Because it is ethically difficult to draw blood samples from normal infants for this particular project, contemporaneously accumulated serum calcium, phosphorus, and ALP values obtained from 174 normal infants aged 25–45 d were used as normal controls. Briefly, the data were extracted from the total record of blood chemistry obtained at Kyoto University Hospital, from September 1, 2005, through August 31, 2007. The reagents and analyzer were the same as those used for the current study. Inclusion criteria as normal infants were the same as those for the study. In addition, infants were excluded when they were known to have conditions such as major congenital anomalies, abnormal calcium metabolism, acute illnesses, abnormal liver function tests, or hypoalbuminemia that might affect the serum calcium, phosphorus, or ALP.

TABLE 1. Profiles of newborns enrolled in the study

	Male	Female
No.	547	573
Mean birth weight (range)	3115 g (2078–4384)	3018 g (2238–4316)
Gestational wk	35 wk 6 d to 42 wk 2 d	36 wk 4 d to 42 wk 0 d

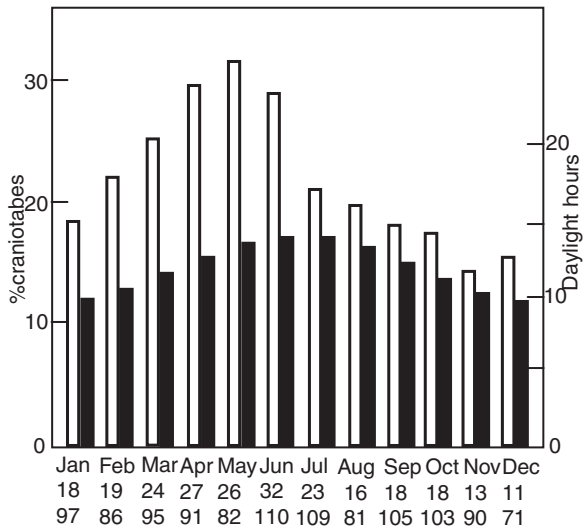

FIG. 1. Incidence of neonatal craniotabes and daylight hours in Kyoto sorted by the months of birth. *Open bars* show the incidence of craniotabes, and *filled bars* show the daylight hours in each month. Actual numbers of deliveries (*lower row*) and the numbers of neonates with craniotabes (*upper row*) are shown at the *bottom*. Apr, April; Aug, August; Dec, December; Feb, February; Jan, January; Jul, July; Jun, June; Mar, March; Nov, November; Oct, October; Sep, September.

TABLE 2. Correlation between the incidence of neonatal craniotabes and various perinatal factors

Gestational wk	35	36	37	38	39	40	41	42
Total delivery	1	18	71	213	321	349	142	5
No craniotabes	1	7	10	42	87	74	24	1
% craniotabes	100	38.9	14.1	19.7	27.1	21.2	16.9	20.0
$P = 0.1997$ (ns)								
Birth weight (g)	2000–2499	2500–2999		3000–3499		3500–3999		4000–4499
Total delivery	61	457		470		123		9
No craniotabes	17	98		109		20		2
% craniotabes	27.9	21.4		23.2		16.3		22.2
$P = 0.2776$ (ns)								
No. of deliveries		1	2	3	4≦			
Total delivery		593	419	98	10			
No craniotabes		140	89	14	3			
% craniotabes		23.6	21.2	14.2	30.0			
$P = 0.1000$ (ns)								
Maternal age		<30	30–34	35–39	40≦			
Total delivery		265	535	277	43			
No craniotabes		61	126	53	6			
% craniotabes		21.7	23.6	19.1	14.0			
$P = 0.1110$ (ns)								

Distributions of the incidence of craniotabes are shown in correlation with gestational weeks, birth weight, number of deliveries, and maternal age at delivery. *P* values obtained with the χ^2 tests for trend are shown. ns, Not significant.

Statistical analyses for comparison of the means were performed by the unpaired *t* test, and frequency tables were analyzed by the χ^2 test for trend, with *P* values less than 0.05 considered significant.

Results

Table 1 shows the profiles of the newborns enrolled in the study. At 5–7 d of age, 246 neonates (22.0%) were found to have craniotabes, which was typically found in parietal bones surrounding the sagittal suture. Figure 1 shows the incidence of craniotabes sorted by the month of birth. The incidence was highest in neonates born in April-May and lowest in those born in November. Otherwise, the incidence of craniotabes was not significantly related with the maternal age, number of pregnancies, birth weight, or weeks of pregnancies, although neonates of earlier gestational age and lower birth weight tended to have a higher incidence (Table 2).

Of 246 neonates with craniotabes, 233 underwent a checkup at 1 month. Craniotabes persisted in 63 (27.0%) of the neonates. Hand x-ray revealed the earliest signs of rickets in 68 (29.2%). Of the 63 infants with craniotabes, 24 also had radiological signs of rickets. Mean serum ALP was significantly higher in the craniotabes group as compared with normal controls, whereas there were no significant differences in serum calcium and phosphorus between these groups (Table 3). Although there were no data of normal controls for serum intact PTH at 1 month, 16 (6.9%) of the craniotabes group showed intact PTH levels higher than the conventional normal upper limit of 60 pg/ml (60 ng/liter). In addition, 87 (37.3%) of the craniotabes group had serum 25-OHD less than 10 ng/ml (25 nmol/liter). These results suggest that the metabolic abnormalities caused by vitamin D deficiency *in utero* persisted at 1 month in many of the infants found to have craniotabes at birth.

When the results were separately analyzed according to the method of feeding, the differences in serum 25-OHD and intact PTH were remarkable (Fig. 2). Of breast-fed infants, 56.9% showed serum 25-OHD less than 10 ng/ml (25 nmol/liter), and 17.0% had an extremely low 25-OHD less than 5 ng/ml (12.5 nmol/liter). Serum intact PTH was elevated over 60 pg/ml (60 ng/liter) in 15 (9.8%) of the breast-fed infants. In contrast, none of formula/mixed-fed infants showed 25-OHD less than10 ng/ml (25 nmol/liter), although even in this group, only a few infants showed proposed optimal serum 25-OHD of 30 ng/ml (75 nmol/liter) (14, 15). Elevated intact PTH over 60 pg/ml (60 ng/liter) was observed in only one (1.25%) of the infants in this group. When these two groups were compared, serum ALP was significantly higher in breast-fed infants ($P = 0.0004$), whereas serum phosphate and the urinary calcium to creatinine ratio were significantly higher in the formula/mixed-feeding group ($P = 0.0026$ and 0.0043, respectively) (Table 4). There was no statistically significant difference in serum calcium levels between these two groups ($P = 0.74$) or in the percentage of infants with remaining craniotabes or x-ray changes.

TABLE 3. Mean serum calcium, phosphorus, and ALP of normal controls and infants with craniotabes at 1 month

	Normal controls	Total craniotabes	*P* value
Serum calcium (mg/dl)	9.97 (0.39)	9.90 (0.36)	0.0887 (ns)
Serum phosphorus (mg/dl)	6.74 (0.61)	6.74 (0.39)	0.9748 (ns)
Serum ALP (IU/liter)	925.9 (197.64)	1062.5 (253.9)	<0.0001

Numbers in parentheses show SD. ns, Not significant.

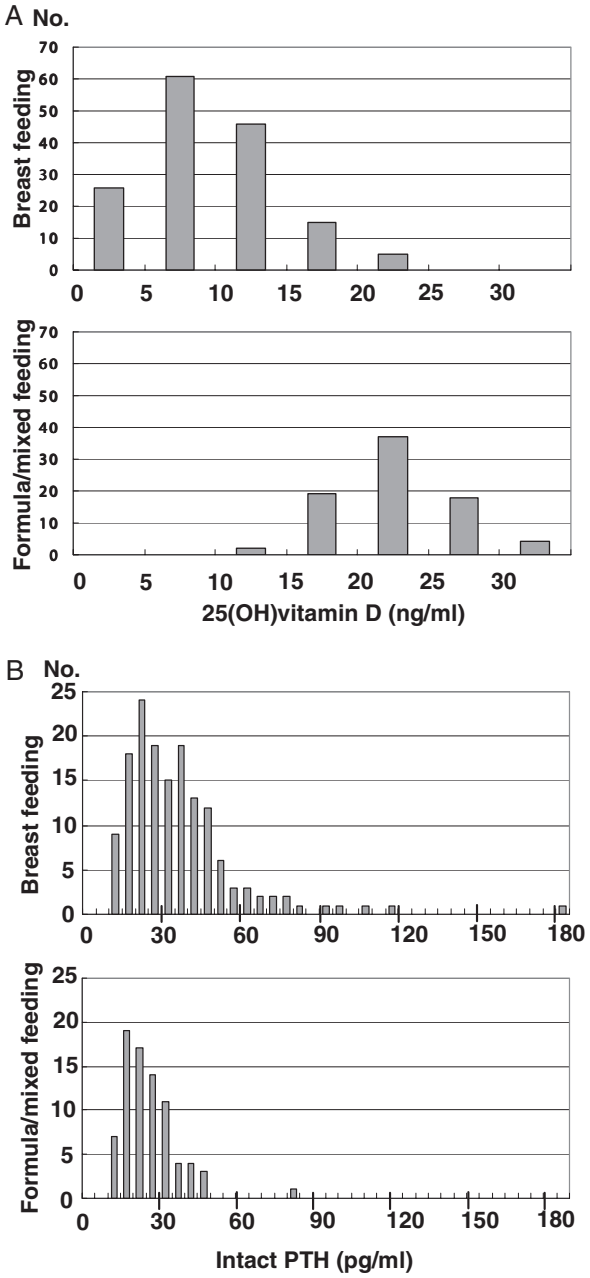

FIG. 2. Distribution of serum 25-OHD and intact PTH at 1 month. A, 25-OHD of infants with craniotabes at birth. *Upper panel*, The results for breast-fed infants. *Lower panel*, Formula/mixed-fed infants with craniotabes. B, Serum intact PTH at 1 month. *Upper panel*, Breast-fed infants with craniotabes. *Lower panel*, Formula/mixed-fed infants with craniotabes.

All infants with serum 25-OHD less than 10 ng/ml (25 nmol/liter) were then treated with 0.25 μg/d oral alphacalcidol. Craniotabes was undetectable in all of them after 3–4 wk.

Discussion

Craniotabes in otherwise normal newborns has long been regarded as a physiological condition based on small-scale studies conducted in the 1980s (1–3); however, the clear seasonal variation in incidence strongly suggests that the condition is associated with vitamin D deficiency *in utero*, and the seasonal variation most likely reflects the sun exposure time of pregnant women because the UVB intensity in Kyoto was reported to fluctuate in parallel with the daylight hours (16). Comparing monthly daylight hours, the incidence of craniotabes was influenced by the daylight hours approximately 4 months before delivery. At 1 month, infants with neonatal craniotabes showed statistically significant elevation of serum ALP compared with normal controls, and some had radiological signs of mild rickets, further supporting the notion that craniotabes in normal neonates reflect a mild form of rickets *in utero*. Unfortunately, from the ethical reasons, the data of normal controls are not from the noncraniotabes group in the current study. Although the "normal" controls were carefully selected from the total records of the same clinical laboratory and the sampling seasons distributed evenly throughout the year, this control group might actually include infants with undetected craniotabes at birth. Therefore, if noncraniotabes infants were strictly selected, the difference in ALP could have been even greater. Although we do not have the actual data on calcium intake of the mothers during pregnancy, total calcium intake of young Japanese women is reported to be relatively low in spring-summer (17). Therefore, the observed data do not seem to support the idea that maternal calcium intake during pregnancy might be responsible for neonatal craniotabes. Likewise, although we do not have data on the difference in the timing of engagement, it is unlikely that these mechanical factors have such a seasonal variation.

Most importantly, vitamin D deficiency could persist, especially in breast-fed infants without vitamin D supplementation. More than half the breast-fed infants with craniotabes showed serum 25-OHD levels of less than 10 ng/ml (25 nmol/liter) at 1 month. Some of those infants showed overt secondary hyperparathyroidism. Serum ALP levels of infants with craniotabes were elevated compared with normal controls, and on average, breast-fed infants showed a statistically significant increase in ALP and intact PTH compared with formula/mixed fed infants. The reason why we could not detect a difference in the percentage of infants with remaining craniotabes between these groups is currently unknown. One possible explanation is that the difference in the vitamin D status between these groups was not large enough to detect the difference in the healing time. In fact, although we took the conventional 10 ng/ml as a cutoff for serum vitamin D, there have been reports suggesting that the full action of vitamin D needs the serum concentration higher than 30 ng/ml (75 nmol/liter) (14, 15). In that case, most of the infants with formula/mixed-fed groups are still deficient in their vitamin D.

Vitamin D deficiency has long been thought of as the disease of the past; however, recently, several studies reported a resurgence of vitamin D deficiency, even in developed countries (18, 19). Pregnant women are reported to be at risk for vitamin D deficiency (4–8) as are neonates, especially when exclusively breast-fed (8, 20).

Vitamin D deficiency classically presents with skeletal manifestations such as rickets in childhood or osteomalacia in adults. In addition, extraskeletal manifestations of vitamin D deficiency, such as muscular hypotonia, disturbances in immunomodulation leading to an increased incidence of immunological disease such as multiple sclerosis, type 1 diabetes, or even certain types

TABLE 4. Mean serum calcium, phosphorus, ALP, and urinary calcium to creatinine ratio of breast-fed and formula/mixed-fed infants with craniotabes at birth

	Breast-feeding	Formula/mixed feeding	*P* value
Serum calcium (mg/dl)	9.90 (0.37)	9.89 (0.34)	0.74 (ns)
Serum phosphorus (mg/dl)	6.68 (0.39)	6.85 (0.38)	0.0026
Serum ALP (IU/liter)	1104.5 (263.1)	982.3 (214.8)	0.0004
Urinary calcium/creatinine	0.484 (0.36)	0.633 (0.38)	0.0043

Numbers in parentheses show SD. ns, Not significant.

of malignancies such as colorectal cancer have been increasingly reported in adults with vitamin D deficiency (21–24). Transient vitamin D deficiency in infancy has also been reported to lead to a variety of postnatal morbidities. Hyppönen *et al.* (9) retrospectively compared the incidence of childhood type 1 diabetes in infants with or without vitamin D supplementation in infancy and reported that the incidence is elevated, up to 3-fold, in infants without vitamin D supplementation. Javaid *et al.* (10) also reported that bone mass at age 9 yr is significantly reduced in children whose mothers had lower serum 25-OHD during pregnancy. Vitamin D-deficient infants are also supposed to be at risk for a variety of microbial infections (12). In this regard, Liu *et al.* (25) recently reported that Toll-like receptors trigger a vitamin D-mediated human antimicrobial response and that sera from African-American individuals contained low 25-OHD with inefficient cathelicidin-mediated antimicrobial activities. These results further support the importance of vitamin D in innate responses against intracellular bacteria, such as *Mycobacterium tuberculosis*. Large-scale, prospective epidemiological studies are necessary to elucidate the effects of early-life vitamin D deficiency on the later health status of otherwise normal neonates. Until the whole picture of perinatal vitamin D deficiency is elucidated, for safety, we suggest treating breast-fed infants with craniotabes with vitamin D, or preferably, treating all pregnant women with vitamin D.

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