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Serum calcium and 25-OH-D_3 in mothers of newborns with craniotabes

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1 Introduction

Craniotabes of newborns, an ossification disturbance of the skull bones, is considered a harmless phenomenon, due to the incoordination between the rapid growth of the brain and the calcification process in the vertex during the last month of gestation [1]. It is manifest most often in premature babies, but is seen often also in fullterm newborns. The incidence of craniotabes varies from 10 to 35 percent of all newborns [1]. The infants with this defect have a normal calcium and phosphorus level and the soft area calcifies spontaneously in a few months.

The exact pathogenetic mechanism of craniotabes in newborns has remained obscure. GRAHAM and SMITH [6] recently supposed that early engagement of the fetal head is essential for its manifestation. The major changes in the mineral metabolism during pregnancy could also play a role in incorrect calcification of the parietal bones [9].

The aim of the present study was to investigate the role of local factors, changes in calcium balance and serum 25-OH-D_3 levels in mother-neonate pairs with the manifestation of craniotabes during the end of gestation.

2 Material and methods

2.1 Definition of craniotabes

Diagnosis was based on the palpation examination of the head of the newborn in the second or third day of life by the same pediatrician (JK). Diffuse softening of the cranial bones around the sagittal suture, or a local smooth (ping-pong) area were used as criteria for craniotabes.

2.2 Patients

The first series consisted of 16 mother-newborn pairs in a consecutive order from the beginning of May 1980 until the end of July 1980 seen in the University Central Hospital of Oulu. The mothers were studied in the third postpartal day for the concentrations of serum calcium (s-Ca), inorganic phosphorus (s-Pi), alkaline phosphatase (s-AFOS) and parathormone (s-PTH) and the parathormone index (PTH_{ind}), calculated as s-Ca x s-Pi/s-AFOS. A 24-hour urine collection was performed for the

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determination of urinary calcium (dU-Ca) and phosphorus (dU-Pi) excretion. The newborns were studied in their third day of life for the concentrations of s-Ca, s-Pi and s-AFOS and PTH_{ind}. A control series consisted of 10 mothers without use of any vitamin D during pregnancy, each with a newborn without craniotabes, delivering at the same time. In these mothers the same investigative procedure was used as in the study group.

For the determination of serum 25-OH-D_3 concentrations another series of 11 mothers and newborns with craniotabes was collected on the third day after the delivery starting on October 1st until the end of January 1981.

A control series for vitamin D_3 studies consisted of 16 mothers of newborns without craniotabes delivering at the same seasonal time.

The course of all 27 pregnancies of both the study groups were analyzed retrospectively from the case-notes of the mothers. Every pregnancy had been followed up by the out-patient maternity care units from the first trimester and thirteen of them had also hospital controls including ultrasonic and biochemical examinations from the second or third trimester.

2.3 Laboratory methods

The concentrations of s-Ca, s-Pi, dU-Ca and dU-Pi were determined by a colorimetric method, s-AFOS by an enzymatic method and PTH by an RIA method with a 12.7 percent intra-assay variation [2]. A specific protein binding method using human carrier protein as a binding protein was used in the determination of s-25-OH-D_3, which was separated from other vitamin D derivatives by gaschromatography [7]. The lowest reliable concentration determined by our method is 3 μg/ml.

Statistical methods: A student's t-test was used in the analysis of calcium studies and a MANN-WHITNEY nonparametric test in the analysis of vitamin D_3 studies.

3 Results

The course of the pregnancy:

Eleven out of 27 mothers with a newborn with craniotabes were primigravida; none had had more than two earlier gestations. 21 of these mothers completed an uneventful pregnancy. Four pregnancies were complicated by pre-eclampsia, one by latent diabetes and one was a twin-pregnancy. Clinical examination revealed engagement of the fetal head within the pelvis before 33 weeks of gestation in four cases, between the 33rd and 36th week in two cases and in the rest thereafter. Two out of thirteen ultrasonically examined fetuses presented a late flattening type of biparietal diameter growth retardation. The symphysis-fundus growth was retarded in three pregnancies. — A spontaneous uncomplicated delivery with cephalic presentation took place in all but two pregnancies, which were delivered by a Cesarean section.

Twelve out of these 27 newborns were females and fifteen were males. The average birth weight of the newborns was 3536 g (range 2800–4440 g), birth height 50.4 cm (range 46.5–53.0 cm) and head circumference 34.8 cm (range 33.0–36.5 cm).

For laboratory findings, i.e. calcium and phosphorus metabolism see (Tab. I).

Tab. I. Laboratory findings (mean ± SD) in 16 mothers with a newborn with craniotabes.

Subjects	N	S-Ca mmol/l	S-Pi mmol/l	dU-Ca mmol/24-h	dU-Pi mmol/24-h	S-AFOS U/l	S-PTH	PTH_{ind}
Mothers with a newborn with craniotabes	16	2.19* ± 0.10	1.19 ± 0.12	3.22 ± 2.80	30.6* ± 8.9	290 ± 83	1.4 ± 0.3	9.6 ± 3.0
Controls	10	2.28 ± 0.09	1.19 ± 0.15	3.79 ± 2.49	39.9 ± 7.7	250 ± 50	1.6 ± 0.6	10.6 ± 2.5

* $p < 0.05$ as compared with controls

Tab. II. S-Ca, S-Pi and S-AFOS (mean ± SD) in 16 newborns with craniotabes and in normal newborns

	Newborns with craniotabes	Normal newborns
N	16	16
S-Ca mmol/l	2.30 ± 0.14	2.28 ± 0.13
S-Pi mmol/l	2.02 ± 0.31	1.98 ± 0.24
S-AFOS U/l	435 ± 115	372 ± 76
PTH_{ind}	11.4 ± 3.6	12.3 ± 2.9

3.1 Mothers

The level of s-Ca in the mothers of newborns with craniotabes was lower than in controls ($p < 0.05$). The phosphate excretion in urine was also decreased ($p < 0.05$). No significant difference was found in the level of s-Pi, s-AFOS or s-PTH between the study group and controls (Tab. I).

3.2 Serum 25-OH-D_3 (Fig. 1)

As expressed in Fig. 1 the levels of s-25-OH-D_3 in mothers of newborns with craniotabes and also in the infants themselves were both low without difference as compared with controls. In the study group seven mothers out of 11, and in the control group ten out of sixteen showed values below the limit (10 µg/ml) considered to cause osteomalacia. The values of 25-OH-D_3 in non-pregnant controls were higher ($p < 0.001$) than in mothers of both study and control groups. A good correlation was found between the serum levels of s-25-OH-D_3 in the mothers and their newborns.

3.3 Newborns

The mean concentrations of s-Ca (2.30 versus 2.28), phosphorus (2.02 versus 1.98) and s-AFOS (435 versus 323) in newborns showed no significant difference as compared to the controls.

4 Discussion

The clinical findings in the retrospective analysis of 27 pregnancies of newborns with craniotabes did not show any remarkable alterations that would illuminate the aetiology of craniotabes. Only in six cases the head of the fetus was engaged before the 36th week of gestation, which is only a little more than normal. In this light local factors

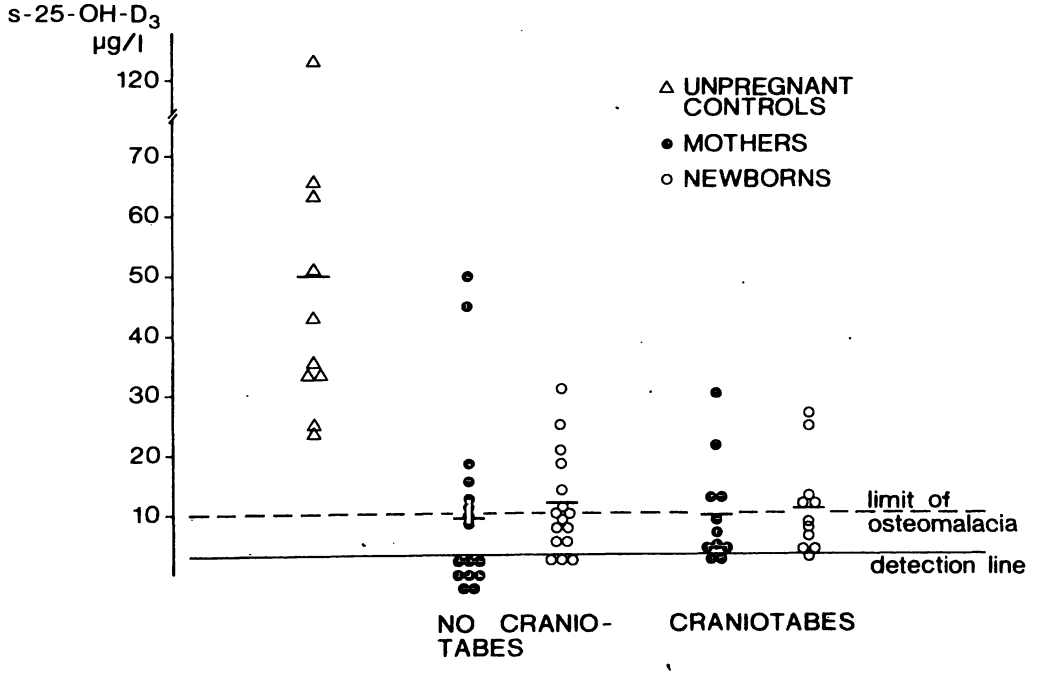

Fig. 1. Serum 25-OH-D_3 in unpregnant controls, in healthy mothers and newborns and in mothers with a newborn with craniotabes. All groups have been studied in the same season.

e.g. compression as suggested by GRAHAM and SMITH [6] can not be considered as the only factor for craniotabes, but they may have influence in some cases.

We found a minor decrease in serum Ca concentrations in mothers of newborns with craniotabes and the dU-Pi excretion in urine was also decreased as compared with controls. This might refer to insufficient dietary intake of Ca and Pi or vitamin D deficiency. The former was not possible to evaluate retrospectively. Most mothers exhibited also low values of vitamin D_3 but the mean level remained at the same level as compared with the values in mothers of newborns without craniotabes but significantly lower than in non-pregnant controls. The lack of vitamin D_3 is known to cause demineralization of bones and craniotabes in older infants and children [8] and it may be that slightly more altered Ca-metabolism than normally [9] in association with low s-25-OH-D_3 concentrations in the mothers during pregnancy could play some role in the etiology of craniotabes in newborns.

In infants the mean level of vitamin D_3 was the same as in their mothers, but very low values were not seen as often in newborns perhaps indicating active transport in cases with lack of 25-OH-D_3, which usually shows equilibrium between the mother and her child [4, 5]. The results clearly indicate that vitamin D substitution during pregnancy is necessary also in this latitude [3] as most mothers studied for s-25-OH-D_3 concentrations after the delivery showed values below the limit considered to cause osteomalacia.

In conclusion we consider that the manifestation of craniotabes during pregnancy is associated in most cases with a minor alteration in the maternal Ca and vitamin D metabolism but their final value in its pathogenesis remains obscure.

Summary

Serum calcium and 25-OH-D_3 in mothers of newborns with craniotabes. The aim of this study was to investigate whether calcium or vitamin D balance during late pregnancy have influence on the outcome of newborn craniotabes. 27 mothers and their fullterm newborns with craniotabes in two series were studied for clinical findings, course of pregnancy and calcium and vitamin D metabolism after the pregnancy. Calcium and phosphorus balance were studied in the first 16 mother-newborn pairs and compared to a control group. Serum 25-OH-D_3 concentrations were determined in the next 11 pairs and compared to a control group delivering in the same season and also to unpregnant women. The course of pregnancy did not show retrospectively any significant alterations and the clinical findings except craniotabes of the newborns were normal. In four cases the fetal head was engaged before 33th of gestation. In mothers serum calcium level was lower ($p < 0.05$) and the excretion of phosphorus decreased ($p < 0.05$) after the pregnancy as compared to controls. The values of serum 25-OH-D_3 were at the same level in mothers and newborns with craniotabes as compared to controls but the values of mothers were lower ($p < 0.001$) as compared to unpregnant controls.

In conclusion, craniotabes of the newborns seems to have no unique etiologic factor. The changes of calcium and vitamin D metabolism during pregnancy may be considered as predisposing factors in some cases and early engagement in some other. Perhaps also other reasons can be found.

Keywords: Alkaline phosphatase, craniotabes of newborns, parathormone, serum calcium, serum phosphate, s-25-OH-D_3.

Zusammenfassung

Serumkonzentrationen von Calcium und 25-OH-D_3 bei Müttern von Neugeborenen mit Kraniotabes

Die Fragestellung unserer Studie war, ob der Calcium- bzw. Vitamin-D-Spiegel in der Spätschwangerschaft einen Einfluß auf die Entstehung eines Kraniotabes hat. Wir untersuchten 27 Mütter und ihre reifen Neugeborenen mit Kraniotabes unter Berücksichtigung klinischer Parameter, des Schwangerschaftsverlaufs sowie des Calcium- und Vitamin-D-Metabolismus nach der Schwangerschaft, wobei wir 2 Gruppen bildeten. In der ersten Gruppe, die 16 Mütter mit ihren Neugeborenen umfaßte, bestimmten wir Calcium und Phosphat und verglichen die Werte mit einer Kontrollgruppe. Bei den übrigen 11 Paaren bestimmten wir die 25-OH-D_3-Konzentrationen im Serum und verglichen sie mit einer Kontrollgruppe, die in derselben Jahreszeit entbunden hatte sowie auch mit Werten nichtschwangerer Frauen. Der Schwangerschaftsverlauf zeigte rückblickend keine Besonderheiten. Auch die klinischen Befunde bei den Neugeborenen waren, mit Ausnahme des Kraniotabes, normal. In 4 Fällen war der kindliche Kopf bereits vor der 33. Schwangerschaftswoche im Becken eingestellt. Bei diesen Müttern war im Vergleich zur

Kontrolle nach der Schwangerschaft der Serumcalciumspiegel geringer ($p < 0,05$) und die Phosphatausscheidung erniedrigt ($p < 0,05$). Die 25-OH-D_3-Spiegel im Serum von Müttern und deren Neugeborenen mit Kraniotabes waren mit der Kontrollgruppe vergleichbar, die mütterlichen Spiegel jedoch erniedrigt, wenn man sie mit denen von nichtschwangeren Frauen verglich ($p < 0.001$).

Zusammenfassend meinen wir, daß sich der Kraniotabes beim Neugeborenen nicht auf einen einzigen ätiologischen Faktor zurückführen läßt. Abweichungen im Calcium- und Vitamin-D-Metabolismus können in einigen Fällen als prädisponierende Faktoren angesehen werden; in anderen Fällen mag die frühe Einstellung im Becken der Grund sein. Darüber hinaus lassen sich vielleicht noch andere Ursachen finden.

Schlüsselwörter: Alkalische Phosphatase, Calcium im Serum, Kraniotabes beim Neugeborenen, Parathormon, Phosphat im Serum, 25-OH-D_3 im Serum.

Résumé

Calcémie et 25-OH-D_3 sérique chez les mères de nouveaux-nés présentant un cranio-tabès

Le but de cette étude est de déterminer si l'équilibre calcique et de la vitamine D en fin de grossesse influe sur le devenir du cranio-tabès du nouveau-né. 27 mères et leurs nouveaux-nés bien à terme ayant un cranio-tabès, en deux séries, ont été étudiés quant aux données cliniques, au déroulement de la grossesse, et au métabolisme calcique et de la vitamine D après la grossesse. L'équilibre phospho-calcique a été étudié chez les 16 premières paires mère-enfant et comparé au groupe témoin. Les concentrations en 25-OH-D_3 sérique ont été mesurées chez les 11 paires suivantes et comparées au groupe témoin accouché à la même saison et également à des femmes non enceintes. Rétrospectivement, le déroulement de la grossesse n'a pas montré d'anomalies significatives et les données cliniques des enfants, à l'exception du cranio-tabès, étaient normales. La tête foetale était engagée avant la 33ème semaine de gestation dans 4 cas. Chez les mères, la calcémie est plus basse ($p < 0,05$) et l'excrétion du phosphore diminuée ($p < 0,05$) après la grossesse en comparaison avec les témoins. Les valeurs de la 25-OH-D_3 sérique sont au même niveau chez les mères et les nouveaux-nés avec cranio-tabès que chez les témoins, mais les valeurs des femmes enceintes sont inférieures ($p < 0,001$) à celles des femmes témoins non enceintes.

En conclusion, le cranio-tabès du nouveau-né ne semble pas avoir un facteur étiologique unique. Les modifications du calcium et du métabolisme de la vitamine D peuvent être considérées comme des facteurs prédisposants dans certains cas et l'engagement précoce dans quelques autres. D'autres raisons peuvent peut-être aussi être trouvées.

Mot-clés: Calcium sérique, cranio-tabès des nouveaux-nés, parathormone, phosphatases alcalines, phosphate sérique, 25-OH-D_3 sérique.

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