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Diagnostic errors in vitamin D deficiency rickets

Błędy w rozpoznawaniu krzywicy z niedoboru witaminy D

INTRODUCTION

The real deficiency of the vitamin D in infants is quite rare in Poland now, however rickets was a common illness in the past. The optimal dosing of the vitamin D, calcium and phosphorus in the infant diet has become easy because of increased percentage of breast-fed infants, while the others usually receive formulae adequate to the nutrient requirements. Thanks to numerous semi-scientific publications the mothers have unlimited access to the information on the principles of proper nutrition and infant care. This should be helpful in decreasing the number of infants with the disturbed calcium/phosphate state (Ca/P).

The research carried out in eighties and published in pediatric periodicals [1, 5, 9] undoubtedly showed factors that should be accounted for when ordering the proper prophylactic dose of vitamin D in infants. The criteria helpful to diagnose the deficiency of vitamin D in infants were fixed, too.

The clinical practice still shows the tendency of pediatricians and orthopedists to overestimate the deficiency of the vitamin D in infants. This may result in ordering too large doses neglecting the risk of overdosing [2, 7].

The aim of the study was to verify if the vitamin D deficiency rickets is diagnosed correctly.

MATERIAL

The research covered 35 infants (23 boys and 12 girls) hospitalized in the Department of Neonatal Pathology, Infants and Cardiology in Lublin in 1998. On the base of clinical examination the physicians diagnosed acute respiratory tract infection and the vitamin D deficiency rickets and sent the children to the hospital.

The infants did not suffer chronic illness, including congenital metabolic disorders. Term-born infants were the majority of tested ones — 29 (82.86%), only 6 (17.14%) were preterm infants. The birthweight of 32 infants (91.43%) was over 2500 g (Table 1a). The infants aged 4–6 month belonged to the most numerous group (Table 1b)..

The group of 31 infants (88.57%) were breastfed or received formulae adequate to their nutrient requirements, only 4 infants (11.43%) received solved cow milk (Table 1). Apart from the milk feeding the infants were provided with the additional diet, according to the current orders.

The anamnesis showed that before hospitalization 8 infants (22.86%) received vitamin D according to the average requirements, 18 (51.43%) received large doses exceeding the average requirements, but lower than curative ones, 6 (17.14%) received

Table 1a. Characteristic of tested infants

Birthweight	Number of infants (n)	%
< 2500 g	3	8.57
2500–3000 g	6	17.14
> 3000 g	26	72.29

Table 1b. Characteristic of tested infants

Age	Number of infants (n)	%
1–3 month	6	17.14
4–6 month	23	65.72
7–9 month	3	8.57
10–12 month	3	8.57

Table 1c. Characteristic of tested infants

Nutritional practice	Number of infants (n)	%
Mother's milk	10	28.57
Mother's milk + formulae	7	20.00
Formulae	14	40.00
Cow milk	4	11.43

Table 2. Clinical symptoms diagnosed at first as vitamin D deficiency rickets

Clinical symptom	Number of patients (n)	%
Craniotabes	27	77,14
Sweating	2	5,71
Harrison's groove	2	5,71
Bow-legs	1	2,86
Incorrect eruption of teeth	1	2,86
Psychophysical retardation	2	5,71

the curative doses and 3 infants (8.57%) never received vitamin D as a drug. The time of using the curative doses was 1 to 8 weeks. Water drops (*Vitaminum D₃* — Terpol) were given to 18 (51.42%) infants, the oil solution (*Vigantol* — Merc) in drops to 14 (40.00%) infants.

The symptoms at first recognized as the results of vitamin D deficiency are presented in Table 2.

METHOD

The daily dose and the type of vitamin D₃ received by children till the time of hospitalization were found from anamnesis. Then the thorough clinical examination was carried out together with the laboratory tests evaluating the calcium/phosphate state, i.e. the levels of serum 25-hydroxyvitamin D (25-OH-D), calcium, phosphate and alkaline phosphatase (ALP). Calcium excretion was determined by Sulkowicz test and urinary calcium/creatinine ratio (Ca/Cr) in urine samples. The tests were done using standard laboratory techniques. Five groups of infants were selected on the base of obtained results (Table 3).

The infants with biochemical disorders found as the result of the vitamin D overdosing, which was contrary to the preliminary diagnosis, had USG of abdomen. All tested infants had clinical control examination to verify the diagnosis.

RESULTS

The results of the study were surprising. The results of all tests evaluating the Ca/P state were within normal ranges in the group of 9 infants (25.71%), in the rest 26 infants (74.29%) the results were outside the normal ranges. Only 5 infants, i.e. 14.29% of all tested confirmed vitamin D deficiency. The most numerous group — 13 infants (37.14%) had laboratory evidence of vitamin D overdosing, while the groups of 4 infants (11.43%) had results of biochemical tests suggesting insufficient supply of calcium or the excess of phosphorus in the diet, which confirmed the earlier anamnesis. The average values of tested parameters in individual groups of infants are presented in Table 3.

Table 3. Values of tested parameters (mean \pm SD) in the five groups

Group of infants	n	Serum test				Urine tests	
		Ca mmol/l	PO ₄ mmol/l	ALP IU/l	25(OH)D ng/ml	Sulkowicz test	Ca/Cr ratio
Without biochemical abnormalities	9	2.39 \pm 0.09	1.72 \pm 0.18	145 \pm 22	32 \pm 14	(+) 5 (++) 4	0.86 \pm 0.19
With vitamin D deficiency	5	2.23 \pm 0.12	1.11 \pm 0.24	389 \pm 27	9 \pm 5	(-) 2 (+) 3	0.32 \pm 0.17
With vitamin D overdosing	13	2.73 \pm 0.29	2.19 \pm 0.15	177 \pm 32	83 \pm 11	(+++) 13	1.53 \pm 0.37
With calcium deficiency in diet	4	2.17 \pm 0.11	1.82 \pm 0.11	245 \pm 32	31 \pm 8	(-) 4	0.11 \pm 0.11
With excess of phosphorus in diet	4	2.21 \pm 0.17	2.41 \pm 0.13	270 \pm 29	41 \pm 10	(+) 2 (-) 2	0.61 \pm 0.28

From the practical point of view the most alarming is to find so numerous group of infants with preliminary diagnosed vitamin D deficiency rickets and in fact these infants suffered from vitamin D overdosing.

The blood tension above 90th centile was found in 10% of infants with vitamin D overdosing. It gradually decreased as the result of terminating vitamin D dosage. Despite of hypercalciuria renal ultrasonography was correct in all infants. In the group of children with hypercalcemia on the base of anamnesis, biochemical tests and results of treatment the idiopathic infantile hypercalcemia was excluded.

All the infants had control clinical examinations. The long-term observation confirmed that the final diagnosis was correct.

DISCUSSION

The variety of ordered doses and specimens of vitamin D₃ by physicians in similar clinical cases, which is found from this study too, proves that they disregard the current recommendations concerning prophylactics and rickets treatment. Many physicians have the tendency to diagnose vitamin D deficiency rickets only from non-specific bone symptoms. However, according to the numerous researches the mineralization of bones in infants is generally caused not only by the lack of vitamin D, but also the inadequate intake of calcium and phosphorus in the diet [3, 4, 6, 7].

The use of low calcium diet is a frequent problem. Mothers having the negative calcium balance provide the infant with milk of small calcium content. The intolerance for cow milk protein, commonly diagnosed at present, make the mothers not to drink milk and having nothing as a substitute of calcium rich product. This results in the deficiency of calcium in the mother and consequently in the breast-fed infant. The increase of vitamin D doses in infants with hypocalcaemia and insufficient calcium supply is an error.

The premature infants, particularly rapidly growing and breast-fed suffer from the rickets as a result not only from the calcium deficiency but also from the deficiency of phosphorus. The excess of phosphorus in the diet may be dangerous, too. Hyperphosphataemia can occur as a consequence of increased exogenous phosphorus load. Craniotabes and other rickets similar symptoms observed in rapidly growing term and artificially-fed infant between 3 and 8 month of life, is mainly caused by supplying too much phosphorus in the diet [7]. The similar mechanism may lead to craniotabes in fast growing breast-fed infants, which mothers drink too much cow milk. In these cases the increase of vitamin D doses is not advisable and is not effective. The effective treatment should limit the absorption of phosphorus.

Rickets is not only the bone illness. The isolated bone symptoms (craniotabes, bow-legs, incorrect eruption of teeth) although resembling rickets, they cannot be the base for the diagnosis [8]. The especially frequent error is to treat the physiological bow-legs in infants as the symptom of vitamin D deficiency. Meanwhile the bow-legs in infants occurs temporarily as an physiological stage of bone growing process or it is the pathological process showing the tendency of increase and consolidation. The essential is to diagnose the observed bow-legs as the physiological or ill state. Hasty diagnosis of vitamin D deficiency and ordering treatment with large dose of vitamin D may result in dangerous consequences. From the other side, overlooking the genetically conditioned rickets may cause strong bone deformations.

Each infant needs individual diagnosis of optimal supplementation of vitamin D. The prophylactic dose must be modified according to the current demand. Vitamin D₃ included in the available in Poland vitamin and the infant formula is biologically active and should be accounted for in the calculation of daily prophylactic dose.

Vitamin D is the essential precursor of 1,25-dihydroxy-vitamin D, strong and biologically long lasting steroid hormone required for calcium absorption, bone development and growth in children. Vitamin D should be applied consciously. Vitamin D is not a panacea on all disorders of the bone mineralization. The active metabolites of vitamin D, the parathyroid hormone and calcitonin are the group of substances, watching over the calcium/phosphate homeostasis. Hypervitaminosis D stimulates osteolysis.

The most practice information is given by serum 25(OH)D levels, considered to be a direct reflection of the body vitamin D stores.

The easiest way to diagnose vitamin D deficiency rickets is to prove the difference between the requirement estimated according to the current state of the infant and the real supply of vitamin D from all the sources. Therefore the anamnesis should be the most important in diagnosing vitamin D deficiency rickets.

Considering the increase of vitamin D dose in the infant the following should be taken into account:

- Is the supply of calcium, phosphorus and magnesium sufficient in the diet?
- Is the proportion between calcium and phosphorus appropriate?
- Does the diet contain ingredients decreasing intestinal absorption of calcium, phosphorus and magnesium?

- Is the applied specimen of the vitamin D properly stored and dosed?
- Are there any additional circumstances influencing the increase of calcium requirements?

Several symptoms characteristic to the vitamin D deficit, like the psychophysical retardation, no appetite, vomiting, obstruction may occur from its overdosing.

There is a difference between of the vitamin D overdosing and oversensitiveness, when the normal doses are cause abnormalities in Ca/P metabolism. Too large doses of vitamin D may not result in visible negative clinical effects for the long time. Some children tolerate even large intake, however the results of vitamin D overdosing may become visible sooner or later in the form of severe renal lesions or arteriosclerosis. Hypercalcemia is a very serious clinical state regardless of the reason and it requires precise diagnosis and treatment.

Vitamin D specimens in the form of drops are used traditionally in Poland in the prophylactic and vitamin D deficiency rickets treatment. There is no reason to change this tradition. The specimen in the form of drops has the advantage of precise dosing. The use of only water solution of vitamin D is advisable. The opinion that vitamin D water solution produced in Poland does not have adequate biological activity has been univocally proven false [1]. The vitamin D included in infant formula is biologically active, too. The oil solutions are particularly contraindicated in the youngest infants because of their individually ability to fat absorption. The use of concentrated oil solutions most frequently leads to vitamin D intoxication.

The prophylactics and the treatment of vitamin D deficiency rickets with the use of vitamin D metabolites is also incorrect in medical practice. These specimens are reserved only for the patients with liver and renal diseases.

The vitamin D tolerance is individually differentiated. In our study the group of 18 infants (51.43% of tested infants) received doses exceeding the average requirements but lower than curative, and only in 6 infants the laboratory tests showed the vitamin D overdosing. From the group of 6 infants (17.14% of tested infants) receiving the curative doses, different laboratory evidence of overdosing were found in 5 ones. If the deficit of vitamin D in these infants had been real before the beginning of treatment, then the tests performed in the hospital proved that the selected dose was too large or the time of treatment was too long. The small number of patients does not allow to find detailed conclusions, but the tests performed in the hospital undoubtedly suggest the necessity of precise diagnosis of Ca/P disturbances in infants.

The data from anamnesis show that the orthopedists increase the vitamin D dosage and they often do it arbitrary, denying the orders from the pediatrician. It seems that vitamin D dose should be decided by the pediatrician controlling the infant state, not the orthopedist analyzing only its bone system. The opinion of the orthopedist should be consultative only.

CONCLUSIONS

1. The results of the study suggested that some pediatricians diagnosed the vitamin D deficiency rickets incorrectly.

2. In doubtful cases, before ordering the vitamin D dose increase it is necessary to carry out the additional examinations to evaluate the calcium/phosphate state.

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STRESZCZENIE

Rzeczywisty niedobór witaminsy D u niemowląt w Polsce występuje obecnie rzadko. W przeszłości krzywica była schorzeniem spotykanym powszechnie. Praktyka kliniczna wskazuje jednak na wciąż istniejącą skłonność wśród pediatrów i ortopedów dziecięcych do zbyt pochopnego rozpoznawania stanów niedoboru witaminsy D i zalecania jej w wysokich dawkach, bagatelizując następstwa przedawkowania.

Celem pracy była ocena poprawności rozpoznawania krzywicy z niedoboru witaminsy D u niemowląt. Badaniami objęto 35 niemowląt leczonych w Klinice Patologii Noworodków, Niemowląt i Kardiologii AM w Lublinie, u których lekarze kierujący do szpitala stwierdzili ostre zakażenie układu oddechowego wymagające hospitalizacji oraz krzywicę z niedoboru witaminsy D, rozpoznaną na podstawie badania fizykalnego. Na podstawie wywiadu ustalono dotychczas stosowaną dawkę i preparat witaminsy D₃, przeprowadzono wnikliwe badanie fizykalne oraz wykonywano badania dodatkowe pozwalające ocenić stan gospodarki wapniowo-fosforanowej. Oznaczano we krwi stężenie wapnia całkowitego, fosforanów, 25-hydroksywitaminsy D (25-OH-D) i aktywność fosfatazy alkalicznej (ALP). Wydalanie wapnia z moczem oceniano próbą Sułkowicza i wskaźnikiem wapniowo-kreatyninowym.

Wyniki badań były zaskakujące. U 25.71% dzieci wszystkie wyniki przeprowadzonych badań, oceniających stan gospodarki wapniowo-fosforanowej, mieściły się w granicach normy, tylko u 14.29% ogółu badanych potwierdzono rzeczywisty niedobór witaminsy D. Najliczniejszą grupę — 37.14% stanowiły niemowlęta z laboratoryjnymi wykładnikami przedawkowania witaminsy D, natomiast po 11.43% dzieci miało wyniki badań dodatkowych sugerujące w połączeniu z wywiadem, niedostateczną podaż wapnia lub nadmiar fosforu w diecie.

Wnioski

1. Wyniki badań wskazują na zbyt pochopne rozpoznawanie wśród niemowląt krzywicy z niedoboru witaminsy D.

2. W przypadkach wątpliwych diagnostycznie, przed podjęciem decyzji o zwiększeniu dawki witaminsy D, konieczne jest wykonywanie badań dodatkowych pozwalających ocenić stan gospodarki wapniowo-fosforanowej.

