

Epidermolytic ichthyosis and rickets. Case report.

Perosa A.*, Sardella L.***, Acquafredda A.***, Mazzotta F., Bonifazi E.

Pediatric Dermatology Unit, University of Bari, Bari (Italy)

*Pediatrician, Bari, ***"Ospedale Di Venere", Bari (Italy)

***Department of Pediatrics "B. Trambusti", University of Bari, Bari (Italy)

Summary

A case of rickets due to vitamin D deficiency in a 3-year-old little girl with epidermolytic ichthyosis is reported. Her mother was also affected by epidermolytic ichthyosis and followed by one of us. To the best of our knowledge, this is the first case of rickets in a subject with epidermolytic ichthyosis.

Key words

Rickets, epidermolytic ichthyosis.

The most frequent rickets of the past, due to deficiency of vitamin D, started in the 19th century in the industrialized countries of North Europe and North America, due to the smog and the concentration of people in big towns with high and close buildings, that significantly decreased ultraviolet radiations (2). This was why rickets was called "the English disease". Nowadays, rickets is exceptional in industrialized countries, because children receive vitamin supplementation early in life. On the other hand, in the developing countries rickets is usually due to a decreased intake of calcium and/or vitamin D (7, 12, 13).

However, in the last decades in the industrialized countries appeared new trends that may favor re-emerging of rickets. The first trend is the very widespread diffusion of true or presu-

med food allergy (4). The latter in children points out to milk and eggs in most cases, being responsible for the decreased intake with the diet of calcium, which is present in the milk, and of vitamin D, which is present in the egg yolk. The second trend is the increasing phobia regarding sun exposure, that may be responsible for a decreased cutaneous photosynthesis of vitamin D. With regard to the first trend, there are already reports in the relevant literature of rickets induced by deficient diets given to atopic infants with true or presumed food allergy (4). With regard to sun exposure, we should remember that before the industrial revolution, when tanning was still an indicator of vulgarity, rickets was a disease of the affluent (2).

A decreased sun exposure due to the esthetical defect was hypothesized to explain shortage

**Vitamin D₃ or cholecalciferol present in the human organism is only partially introduced with diet, particularly with the yolk and at a lesser extent with vegetables, cereals and fruit. To a great extent cholecalciferol is synthesized in the basal and prickly layer of the epidermis through the photoconversion of 7-dehydrocholesterol, thanks to the ultraviolet B (295-310 nanometres) radiations. Later on, both dietary and intrinsically synthesized cholecalciferol undergo 25-hydroxylation in the liver (25-hydroxy-cholecalciferol or 25-OHD₃ or calcifediol), which is the form of vitamin D with highest plasma levels -25 ng/mL- and further hydroxylation in the kidney in 1 position (1,25-dihydroxy-cholecalciferol or 1,25-(OH)₂D₃ or calcitriol). Once activated, vitamin D₃ acts in the intestine and kidney by increasing the absorption of calcium and phosphorus and thus favoring an adequate calcification of the osteoid tissue and a good neuromuscular activity.*

rickets observed in cases of congenital lamellar ichthyosis (6, 12, 14). Shortage rickets was rarely reported even in other types of ichthyosis, such as congenital erythrodermal ichthyosis and X-linked ichthyosis (10).

Here is reported a case of rickets due to vitamin D shortage in a 3-year-old little girl affected by congenital ichthyosis bullosa. She was born to a woman with the same inherited disorder followed up for more than 20 years by one of us (B). To the best of our knowledge this is the first case of rickets in a subject with ichthyosis bullosa.

Case report

L.G., first-born, was born by natural child-birth after a gestation of 36 weeks and 4 days with a weight of 2,770 g and height of 45 cm. At birth she was visited by one of us (B) due to erythroderma and blisters on the back. The diagnosis of ichthyosis bullosa was easy even

thanks to the familial history. Her mother was indeed affected by the same disease and 20 years before underwent at the age of 9 months primary Herpes Simplex infection (Kaposi-Juliusberg eruption -see Fig. 2-). The little girl was bottle-fed because her mother was even affected by hepatitis C. In spite of her disease, the patient always showed a normal weight and height for age (25° percentile). In the first year of age she underwent recurrent episodes of wheezing sometimes requiring hospitalization. When aged three years she complained of evening and sometimes night pain in the lower limbs. At the moment of the visit she presented uniformly reddening of the skin with areas of thinned skin level with the diaper area due to the peeling of superficial skin layers. Her limbs were normally lined up. There were no signs of inflammation level with her joints and the podoscopic examination was normal.

The laboratory examinations showed markedly increased alkaline phosphatase (1,716 U/L, n.v. 270-850), calcium and phosphorus at



Fig. 1

Fig. 1, 2: Mother and daughter affected by epidermolytic ichthyosis (Fig. 1). In Fig. 2 the mother, when aged 10 months, with primary herpetic eruption evident on the right thigh. In Fig. 3 you can see the radiographic signs of rickets in the daughter at the age of 3 on the knees.



Fig. 2

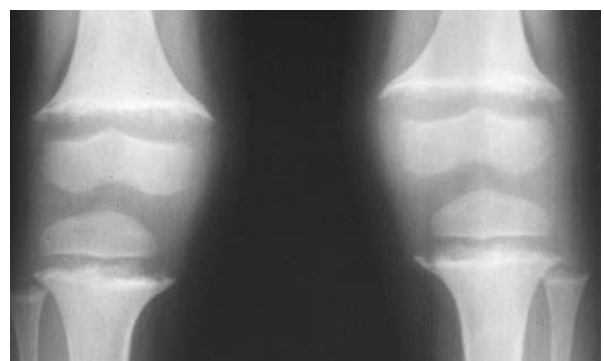


Fig. 3

the low limit of the normal values and finally normal indexes of inflammation and liver and renal function.

The radiological examination of the left hand, pelvis and lower limbs (Fig. 3) showed the typical findings of the shortage osteodystrophy vitamin D dependent, with cupping of the metaphyses of the long bones, irregular thickening of the line of temporary calcification, thickening of the growing cartilage and osteopenia. In order to be sure of the diagnosis, the calcium-phosphorus metabolism was deeply investigated. After two weeks of sun exposure for several minutes, the laboratory examinations showed increased parathyroid hormone (751.3 pg/ml, n.v. 10-65), decreased 25-OH-vitamin D₃ (5.70 ng/ml, n.v. 10-68), decreased total calcium (7.6 mg/dl, n.v. 8-10.5) and ionized calcium (3.5 mg/dl, n.v. 4.6-5.3), decreased inorganic S-phosphate (2.90 mg/dl, n.v. 3.60-5.90), calciuria 2 mg/dl (n.v. 2-17.5) and increased renal excretion of phosphates (74.9, n.v. 20-60). These results confirmed the diagnosis of rickets. Therefore, the little girl received 600 U/per day of vitamin D₃ for 1 month.

Ten days after the onset of treatment with vitamin D₃ the little patient reported significant improvement of the osteo-articular pain. After one month of treatment, the results of laboratory investigations turned to normal values as follows: vitamin D₃ 79.50 ng/ml, S-alkaline phosphatase 428 u/L, total S-calcium 9 mg/dl, inorganic S-phosphate 5.60, S-parathyroid hormone 68.5 pg/ml, phosphaturia 24.4 and calciuria 9.1 mg/dl.

The little patient was advised to go on with vitamin D₃ and to repeat the radiological examination after 6 months from the onset of treatment.

Discussion

With regard to the differential diagnosis from other types of rickets, causes responsible for a defective intestinal absorption such as celiac disease, cystic fibrosis, continuous intake of corticosteroids, etc. were ruled out. The little patient did not intake drugs such as anticonvul-

sive drugs, which are able to hasten the metabolism of vitamin D. Rachitogenic tetania was ruled out thanks to the lack of convulsion and tetania and vitamin D₃-dependent rickets due to the late onset -3 years- of the clinical symptoms. Finally, renal and liver disorders possibly responsible for lacking activation of cholecalciferol or for increased renal reabsorption of phosphates were ruled out thanks to the lack of clinical features -varus condition, tooth disorders- and to the normal renal and liver function.

The lack of other causes responsible for shortage rickets supported the hypothesis that the disorder of our little patient was linked to her dermatological condition.

We first hypothesized a deficient sun exposure, possibly due to the worsening of ichthyosis bullosa with sun and hot climate and to the esthetical problem. Due to the latter, the mother could not undress her daughter in order to hide her cutaneous conditions. However, this hypothesis was not supported by an improvement of the biological parameters after the patient had been voluntarily exposed to the sun for about two weeks.

Moreover, the reports of the relevant literature regarding rickets occurring in other types of ichthyosis such as X-linked ichthyosis (10, 12) significantly improving with sun exposure -the latter being thus advised in such condition- do not support the hypothesis that a defective sun exposure can be responsible for this type of rickets. Neither we believe that an exaggerate use of sunscreens could be responsible for rickets associated with ichthyosis, because most cases were reported in countries (6, 11, 12) where a large use of sunscreens is actually unlikely.

Therefore, we considered other conditions associated to ichthyosis that could be responsible for a defective synthesis of vitamin D in the skin. Natural tanning, which is aimed at preventing sun radiations to reach the epidermal cells, is a very complex phenomenon. However, two factors of this phenomenon are over expressed in the cases of rickets associated to ichthyosis. The first factor is the hyperkeratosis of the horny layer. The latter is indeed present in all types of ichthyosis. The second factor is the

increased amount of melanic pigment within the epidermis. The latter is surely present in the cases of rickets associated to ichthyosis reported in the relevant literature, because we are dealing with Nigerian, South African (12, 13), Sudanese (6) or Indian (5) children. The phototype of our little patient is indeed dark. These two factors, which are present both in natural tanning and rickets associated to ichthyosis, could be responsible, at least partially, for a decreased synthesis of vitamin D.

Finally, we should consider the relationship between ichthyosis and lipids, being vitamin D liposoluble and deriving from cholesterol. We know that the lack of steroid sulfatase enzyme in X-linked ichthyosis favors the accumulation of cholesterol sulfate within the intercellular lipid matrix of the epidermis, increasing the cohesion between the single corneocytes. Moreover, the lipid metabolism is affected in other ichthyosis conditions, both congenital (8) and acquired. In Refsum's syndrome the deficiency of phytanoloA hydroxylase prevents the physiological synthesis of ceramides. In Sjögren-Larsson syndrome the deficiency of aldehyde-dehydrogenase decreases the synthesis of fatty acids. In lamellar and erythrodermic congenital ichthyosis the deficiency of transglutaminase 1 alters

the lipid involucre of corneocytes. Due to these reasons, it is possible that the metabolism of a liposoluble vitamin derived from cholesterol could be affected by the ichthyosis condition of the skin.

These considerations and the pain of the lower limbs reported in her childhood also by the mother of the little patient, which is also affected by epidermolytic ichthyosis, suggest a deep investigation to unveil subclinical rickets in children with whatever type of ichthyosis, especially when dark skinned.

In conclusion we reported a case of shortage rickets in a little girl affected by epidermolytic ichthyosis. We were not able to unveil extracutaneous causes possibly responsible for her rickets. This is why, even taking into account the data of the literature, we believe that epidermolytic ichthyosis could favor the appearance of rickets. To the best of our knowledge, this is the first report regarding an association of rickets to epidermolytic ichthyosis.

Address to:

Prof. Ernesto Bonifazi
Pediatric Dermatology Unit
University of Bari - Policlinico
Piazza G. Cesare, 11 - 70100 Bari (Italy)

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