Common Vitamin D-Deficiency Rickets

Louis David

Service de Pédiatrie, Hôpital Edouard-Herriot, Place d’Arsonval, 69437 Lyon, Cédex, France

In many countries the "common" denomination given to vitamin D-deficient rickets only has an historical meaning as the affection has become rare. However, it reminds us that for centuries it has been a frequent and debilitating disease among infants and children. Its frequency was particularly high in the industrial cities of the nineteenth and early twentieth centuries. For example, in 1909 Schmorl reported over 80% of rickets on autopsy findings in German children (1). Following the discovery in the 1920s that vitamin D was the antirachitic substance lacking in common rickets, it became possible to prevent rickets by adding vitamin D to infant diets and this resulted in a considerable decrease in its frequency.

In recent years, following the unraveling of vitamin D metabolism and the development of sensitive assays for determination of the circulating levels of vitamin D metabolites, great progress has been made in the understanding of the pathophysiology of the disease. Nevertheless common rickets remains a major problem of public health in many countries. In the countries where vitamin D supplementation of milk is systematic, the frequency of the disease is very low but cases are still observed in breast-fed infants and among infants from families with special dietary habits (2–6). In the countries where prevention is performed using oral vitamin D preparations, many infants and children escape the prevention so that common rickets remains relatively frequent (7,8). On the other hand, excessive doses of vitamin D are still given to many infants and children over the world exposing them to the risk of hypervitaminosis D.

PATHOPHYSIOLOGY

There are three physiological sources of vitamin D for young infants: (i) maternal reserves built during fetal life, (ii) maternal milk, and (iii) endogenous synthesis from sun exposure. By contrast the vitamin D content of the diet is usually very low, almost negligible. The high frequency of vitamin D deficiency among infants is due to the fact that these three potential sources are easily defective:

1. As shown by the strong positive correlation between plasma maternal and cord
25(OH) vitamin D [25(OH)D] levels (9–11) the vitamin D reserve of the neonate depends upon the vitamin D status of the mother. Thus infants born from vitamin D-deficient mothers present with early vitamin D depletion, possibly starting during fetal life in severe maternal deficiency.

2. The vitamin D content of maternal milk is very low unless the mother has optimal vitamin D stores from regular sun exposure or dietary vitamin D supplementation (12,13). As a consequence a majority of breast fed infants cannot rely upon their mother to ensure an adequate daily vitamin D intake.

3. Regular sun exposure is practically not possible in most infants in the first months of life. Furthermore for those living in industrial cities the efficiency of sunlight skin synthesis is frequently inhibited due to ultraviolet absorption by pollution.

Thus it is clear that in our modern way of life most infants are spontaneously exposed to vitamin D deficiency unless dietary vitamin D supplementation is provided.

The consequence of vitamin D deficiency is reduced calcium (Ca) intestinal absorption and decreased extracellular Ca levels leading to defective mineralization and secondary hyperparathyroidism (Fig. 1). The defective mineralization of growing bone is responsible for the most distinctive, although non-specific, lesions of common rickets. On the rachitic epiphyseal plates, mitotic activity of the proliferative zone is maintained suggesting that vitamin D plays little role as a bone growth factor. By contrast there are major changes on the distal part of the plate which fails to differentiate into calcified bone. This results in an accumulation of cartilage cells and unmineralized osteoid tissue which is responsible for increased length and width of the epiphyseal plate. The growth in thickness of the bones is also affected with deposits of layers of uncalcified or poorly calcified osteoid by the osteoblasts. In

![Vitamin D deficiency diagram](image)

**FIG. 1.** Consequences of vitamin D deficiency. Whether vitamin D deficiency directly inhibits the mineralization of the forming bone, and/or acts through the depression of extracellular Ca is still a matter of debate. Note that the secondary hyperparathyroidism may play some role in the defective mineralization as a result of its inhibitory effect on phosphate (P) tubular reabsorption leading to depressed extracellular P. It also contributes to the reduction of the skeleton by increasing bone resorption and therefore causing demineralization of the existing bone.
addition in both cortical and trabecular bone, resorption (in relation to bone re-
modeling and secondary hyperparathyroidism) is followed by the deposition of os-
teoid, which fails to mineralize, the hallmark of the osteomalacic process. The gross 
consequence of this defective mineralization is reduced density and weakening of 
the bones which may deform under the stress of body weight and muscle traction.

CLINICAL AND RADIOLOGICAL BONE LESIONS

Although the mineralization defect is diffuse, clinical and radiological bone lesions 
predominate in the areas of rapid bone growth, namely the long bone epiphyses and 
the costochondral junctions. Thus the clinical manifestations of the disease are most 
striking at time of greatest growth velocity. This explains why common rickets is 
mostly observed before 18 months of age with a maximum frequency between age 
4 and 12 months. Indeed mean growth velocity is approximately 25 cm for the first 
year and decreases markedly thereafter. Boys are more frequently affected than girls 
in similar life conditions. The reason for this is unclear as growth velocity is identical 
in both sexes in prepubertal age. As a result of reduced vitamin D skin synthesis, 
children with darkly pigmented skin living in high latitude areas with limited sunshine 
periods are more at risk to develop rickets. There are large variations in the clinical 
and radiological spectrum of the disease, depending upon age and the duration and 
severity of the vitamin D deficiency. It is noteworthy that when clinical and radi-
ological signs become evident, vitamin D deficiency has already been of long duration.

Clinical Signs

Palpable and visible knobby enlargements of the extremities of the long bones and 
of costochondral junctions are the most constant clinical signs of florid rickets. They 
are often the only manifestations, particularly before the child is able to stand up 
and walk. On long bones these enlargements correspond to the expanded epiphyses 
and are mostly observed at the wrists and ankles. The enlarged costochondral junc-
tions spread on both sides of the thorax along the anterior axillary lines forming the 
“rachitic rosary.”

Skeletal deformations are usually the result of longstanding rickets. The most typ-
ical ones are seen in the lower limbs after weight bearing with tibial and femoral 
bowing. However in severe rickets they may also occur under muscle pull, in the 
lower limbs before weight bearing, and the forearms. Muscle traction on the softened 
rib cage is also responsible for chest deformation in severe cases leading to pectus 
carinatum, thoracic asymmetry, and widening of the thoracic base.

Skull examination will frequently show signs of poor mineralization such as un-
usual softening of the occipital area at thumb pressure in infants older than 3 months 
(so called “rachitic craniotabes”), enlarged sutures and fontanelles, delayed closing 
of fontanelles, and occipital or parietal flattening in the recumbent infant. Deformities 
of the spine and pelvis are very unusual today. They were described in severe long-
standing rickets in the past and were responsible for thoracic kyphosis and later dystocia.

Dental development is frequently impaired in vitamin D deficiency with delayed eruption, enamel hypoplasia, and early numerous caries. This mostly concerns deciduous teeth but permanent teeth may also be affected in late or long-standing rickets.

**Radiological Signs**

When present the skeletal radiological signs reflect an already severe mineralization defect. Nevertheless they are very useful for early diagnosis of rickets, as minor radiological abnormalities occur before any clinical signs can be found at physical examination. In advanced rickets any part of the skeleton may show radiological abnormalities, many of them corresponding to the clinical signs. However in clinical practice only a limited number of x-ray pictures are necessary for the diagnosis of rickets. Films of the wrist in the supine position and a frontal x-ray of the knees are the most useful as they show the areas most sensitive to early rachitic changes.

Alterations of the epiphyseal regions of the long bones are most characteristic. There is widening of the radiolucent space between the end of the bone shafts (the metaphyseal lines) and the epiphyses which reflects the accumulation of uncalcified cartilage. The metaphyseal lines, normally seen as well defined dense lines, are distorted and take various aspects: irregular, stippled, fuzzy, frayed, or fringed. They are frequently hollowed with loss of their flat or convex configuration (so called “cupping”) and spread laterally forming “cortical spurs” (Fig. 2).

On an x-ray picture of the thorax the same alterations are observed at the costochondral junctions where “cupping” develops rapidly giving the so-called “champagne cork aspect” which corresponds to the palpable costal rosary (Fig. 3).

The other skeletal alterations appear more tardily. As a result of insufficient mineralization, the centers of ossification are pale and irregular and their appearance may be delayed. The shafts of the long bones usually show diminished density with thinning of the cortices. In severe rickets in the young infant, this may lead to a shadowy aspect of the shafts and an almost complete disappearance of the cortices (Fig. 4). Conversely in older children with long-standing rickets an apparently paradoxical thickening of the cortex may be observed. This results from the superimposition of layers of partially mineralized osteoid and is mainly seen on the long bones of the lower limbs. It is usually associated with bowing predominantly at the concave aspect of the bone shaft. At the same time, decreased density may also be observed in other parts of the skeleton, particularly ribs, scapula, pelvis, and skull. Only in severe long-standing rickets are small bones and vertebrae also involved.

Besides these signs reflecting defective mineralization, bone x-rays may show deformities, bowing of the tibia and femurs being the most common, but also shipped epiphyses and unrecognized fractures followed by callus formation, particularly in the ribs and fibula.
FIG. 2. X-ray of the lower limbs of a 6-month-old infant with common rickets. Serum calcium level was 1.56 mmol/l (62.4 mg/l). Note the enlarged spaces between the metaphyseal lines and the centers of ossification. Cupping is present at the lower ends of the tibias and fibulas. The metaphyseal lines at the knees level have lost their convex configuration; they are irregular, stippled, and slightly frayed; cortical spurs are visible laterally.

EXTRASKELETAL MANIFESTATIONS

Various clinical signs of hypocalcemia may reveal common rickets. Seizures are the most frequent manifestations in infants. Tetany, laryngospasm, or hypocalcemic myocardiopathy may also be observed.

Delayed motor development with hypotonia is frequently evident in infants, even
in the absence of hypocalcemia. However this is not a constant finding and florid rickets may be seen without any delayed motor development.

On the other hand, protuberant abdomen with umbilical hernia may result from hypotonia of the abdominal wall muscles. Similarly the weakness of the thoracic muscles, together with the softening of the rib cage, may cause defective ventilation with respiratory obstruction and infection. In the older child and adolescent, symptoms similar to those observed in adult osteomalacia such as bone pain, waddling gait, and fatigue may be present.

Hematologic disorders may also be observed in common rickets. Besides moderate hypochromic anemia, usually resulting from iron deficiency, a rare and very peculiar syndrome known in the European literature as the Von-Jacksch-Luzet syndrome (14–16) may be seen. It is characterized by severe anemia and a profile of chronic myeloid leukemia with erythroblastosis, leukocytosis (up to 30,000 white blood cells per mm$^3$), myelocytosis, and possible myeloblastosis. Spleen and liver are enlarged with sometimes enormous splenomegaly resulting from extramedullary hematopoiesis. The bone marrow is hypoplastic but there is also evidence for an hemolytic component. The pathogenesis of the Von Jacksch-Luzet syndrome is unclear. It is rapidly cured by vitamin D therapy so that a direct involvement of the vitamin D deficiency is possible. This is to be put together with experimental data showing that severe vitamin D deficiency in the rat may induce a marked increase in bone
FIG. 4. Atrophic form of common rickets in a 7-month-old boy. Serum calcium was 1.48 mmol/l (59.2 mg/l). Note the almost complete disappearance of the lower femoral and upper tibial centers of ossification and the absence of upper femoral centers of ossification.

marrow mast cells and also the observation that, in vitro 1,25-dihydroxyvitamin D [1,25(OH)_{2}D] inhibits proliferation and stimulates the differentiation of myeloid leukemia cell lines (17). On the other hand the syndrome is a rare complication of common rickets in infants and one cannot exclude the causative role of other vitamins or trace mineral deficiencies.

BIOCHEMICAL MANIFESTATIONS

Because of its clinical consequences, hypocalcemia is the most important biochemical abnormality in vitamin D-deficient rickets. However it is not a constant
finding as it is observed in only approximately half of the patients at time of diagnosis. In many instances an intercurrent illness, such as gastroenteritis or respiratory tract infection, seems to precipitate the fall in serum Ca concentration leading to clinical signs of hypocalcemia. Usually hypocalcemia occurs in the presence of marked clinical and radiological signs of rickets indicating a severe mineralization defect. However, not unfrequently, normal or only slightly diminished serum Ca levels are associated in severe rickets.

On the other hand, in a few instances, hypocalcemia is the early manifestation of a clinically asymptomatic rickets with mild radiological signs (“early hypocalcemic type”). It is not clear why in these cases hypocalcemia, generally profound with clinical symptoms, occurs in the early phase of the disease, nor why this takes place mostly in young infants below 6 months of age. Fraser et al. (18) have hypothesized that this could be the first transient step (“stage 1”) in the evolution of vitamin D-deficient rickets as a consequence of a still inadequate parathyroid response. According to these authors it would precede by a few days a second step (“stage 2”) in which serum Ca returns to normal under the effect of secondary hyperparathyroidism, and finally a third step (“stage 3”) showing a definitive decrease in serum Ca levels, related to parathyroid hormone (PTH) refractoriness in the presence of persisting vitamin D deficiency and extensive bone demineralization. However in clinical practice this concept of three successive stages appears very theoretical. Indeed early hypocalcemic rickets (“stage 1”) is seen only in a small number of patients and there is evidence that some of them at least, present a picture of “partial hypoparathyroidism” as they remain hypocalcemic if not treated with vitamin D. In addition, contrary to what one would expect, there is no obvious clinical or radiological differences between “stage 2 and 3.” Thus normocalcemia may still be present with extensive bone demineralization, while profound hypocalcemia may be associated with moderate clinical and radiological signs of rickets.

In most cases serum phosphate (P) levels are low compared to normal age-matched values and are associated with diminished tubular P reabsorption and low urinary Ca excretion. In some cases, particularly in older infants and children with longstanding normocalcemic rickets, serum P levels may be very low (<0.8 mmol/l) so that the diagnosis of primary hypophosphatemia may be considered. This is of particular interest as it indicates that vitamin D deficiency does not usually induce renal refractoriness to PTH in infants and children. It is therefore a clinical observation at variance from experimental data suggesting that vitamin D deficiency leads to tubular resistance to PTH (19). By contrast in the rare “early hypocalcemic type,” serum P levels are usually normal or moderately elevated which can be interpreted as a sign of parathyroid insufficiency or defective renal responsiveness to PTH. Similarly elevated serum P levels have been reported in longstanding hypocalcemic rickets in adolescents suggesting that chronic hypocalcemia, rather than vitamin D deficiency per se, may possibly cause renal refractoriness to PTH. This is reminiscent of data in adult patients with hypocalcemic vitamin D-deficient osteomalacia showing a dissociation between the effects of PTH on adenosine 3′, 5′ monophosphate (cAMP) production, and phosphate reabsorption (20).
Increased serum alkaline phosphatase activity is a constant finding which appears to result from the multiplication and stimulation of osteoblasts in a Ca-deficient environment. Very high levels greater than 2000 IU/ml may be observed in florid rickets. By contrast levels are usually only moderately elevated in the “early hypocalcemic type,” in agreement with the mild lesions of rickets.

Serum PTH levels are always clearly elevated in florid normocalcemic and hypocalcemic rickets while they remain normal or moderately elevated in “early hypocalcemic” rickets (21–25). The vitamin D deficiency is usually demonstrated by plasma 25(OH)D levels well below the normal range (below 11 nmol/l, i.e., 5 μg/l) (26–28). However, at times plasma 25(OH)D levels within the normal range may be found in the presence of otherwise typical common rickets, probably reflecting recent access to vitamin D sources. Similarly plasma 1,25(OH)₂D levels which are usually within normal or low normal range, indicating inappropriate vitamin D activation in the face of defective mineralization, hyperparathyroidism, hypophosphatemia, and hypocalcemia may be found elevated (27–29).

OTHER BIOCHEMICAL ABNORMALITIES

Secondary to hyperparathyroidism and/or hypocalcemia other biochemical abnormalities may be observed, many of them resulting from a functional tubular disorder (18,30). Their interest is mainly physiopathological but they may be misleading for the clinician as they may suggest primary tubular dysfunction. Hypocalcemia seems to induce generalized hyperaminoaciduria, possibly associated with mild glycosuria, without elevated plasma aminoacid, or glucose levels. Moderate hyperchloremic acidosis with defective bicarbonate tubular reabsorption and eventually hypokaliemia is a consequence of secondary hyperparathyroidism. Elevated urinary excretion of hydroxyproline and cyclic AMP (30,31) are the result of increased parathyroid activity on bone and kidney and, together with decreased tubular P reabsorption, are indirect evidence that PTH responsiveness is usually preserved in vitamin D deficiency in infants and children.

CLINICAL FORMS

Premature infants are very susceptible to rickets and, without prophylactic measures, frequently present with important lesions. The consequences are particularly severe on pulmonary function which is impaired due to rib cage weakening and deformities resulting in defective ventilation and infectious complications. This has been described in the past as “rachitic lungs” of the premature infant (32). Although vitamin D deficiency was probably not the only factor responsible for this form of rickets, as Ca or P deficiencies were likely to be frequently associated, the disease has completely disappeared with the systematic early administration of vitamin D to premature infants. The particular susceptibility of premature infants is now clearly
linked to low levels of plasma 25(OH)D at birth indicating low stores of vitamin D. This can be corrected by early vitamin D supplementation.

Neonatal rickets is well known from experimental data showing severe rachitic lesions at birth in animals born from severely vitamin D-deficient mothers. It is occasionally observed in term or preterm newborns from hypocalcemic vitamin D-deprived mothers, as consequence of insufficient sunlight exposure, or intestinal malabsorption (33,34).

Adolescents are particularly exposed to rickets when their living habits lead to poor sun exposure. This is especially the case among the immigrant population in Europe (5,8). Adolescents with darkly-pigmented skin living in industrialized cities appear more at risk. Bone pain and fatigue are the usual revealing symptoms but many cases remain clinically asymptomatic. As suggested by the elevation of plasma 1,25(OH)_2D levels during the pubertal growth spurt in non-vitamin D-deficient adolescents (29,35), it is possible that the need for vitamin D increases at that time explaining the particular susceptibility of adolescents to rickets. However, in our experience, Ca deficiency resulting from faulty nutritional habits is frequently an additional factor which suggests that low Ca nutritional intake may increase vitamin D needs.

PREVENTION OF VITAMIN D DEFICIENCY

Regular sun exposure is the most physiological and effective way to prevent vitamin D deficiency in infants as well as in children and adults (36). Indeed it has been shown that an average daily exposure of only the face and hands for 1 to 2 hours in infants without vitamin D supplementation, results in normal plasma 25(OH)D concentrations (37). Similar observations have been made in children older than 18 months receiving no vitamin D supplements but having a normal way of life with regular sun exposure during their spontaneous outdoor activities (7,38,39). However regular sun exposure is unpractical and often not possible in most young infants, especially those living in cold countries of high latitude and short daily sunlight periods of weak intensity from mid autumn to mid-spring. As a consequence the most reliable method to prevent vitamin D deficiency in infants is to provide them with oral vitamin D supplementation (see chapter by L. Paunier).

TREATMENT OF COMMON RICKETS

Besides the necessity to specifically treat hypocalcemia, when present, usually with a 1–3 day Ca infusion, vitamin D is the only treatment of common rickets. There is no place for the use of vitamin D metabolites such as 25(OH)D or 1,25(OH)_2D. However there is no agreement on the modality of treatment and the amount of vitamin D to be given. Several therapeutic schemes are advocated in the literature: low oral daily doses for several weeks or months (2000 IU per day for 6 months, 5000 IU per day for 2 months), or one oral, single large dose (200,000 IU,
600,000 IU), that may be repeated one to two months later. Intramuscular treatment using a single large dose is probably of little interest as its effect has been shown to be markedly delayed.

It is clear, and not surprising, that small daily doses of vitamin D as low as 400 IU given for several months can cure rickets as efficiently as a single large dose (44). However the former appears to take a much longer time to completely heal the rickets and normalize the biological parameters. Thus plasma P and PTH levels normalize within a few days following the administration of a single large dose (24,45) while several weeks are necessary with a daily dose of 400 IU (44). Similarly the rise in plasma 1,25(OH)\(_2\)D levels which follows the administration of vitamin D appears to be slower with a delayed maximum increase with low daily doses as compared with a single large dose. As there is good evidence that the functional activity of the 1-\(\alpha\)-hydroxylase enzyme is in part substrate dependent, these observations suggest that the quicker the vitamin D pool and particularly the 25(OH)D concentration is restored, the faster the optimal production of 1,25(OH)\(_2\)D is obtained. Thus a single large dose might be more advisable.

Apart from these differences in the delay of healing there are important practical and economical aspects that have to be considered when discussing a choice between low daily doses and a single large dose. Indeed vitamin D-deficient rickets is frequently the result of lack of compliance to a daily preventive therapy, poor socio-economical status, and/or special nutritional habits. Hence, to be reliable a daily treatment must be regularly supervised and requires a prolonged hospitalization in hypocalcemic rickets. On the contrary once the single large dose is given under supervision, one may be sure that the cure of rickets is on its way.

Finally, the risk of vitamin D intoxication is frequently advocated as an argument against the treatment with a single large dose. However there are no convincing data showing that this treatment is harmful when given to vitamin D-deficient children.

Whatever the method used it is important to make sure that the child is also receiving an adequate daily amount of dietary Ca. A daily intake of 800 mg in infants and children, and 1 g in adolescents, is the required minimum during the first month of treatment. This can easily be provided through milk and dairy products but, when this does not seem possible, Ca supplementation must be provided. The only clinical sign really useful to evaluate the effectiveness of the treatment is the rapid motor improvement. The biological and radiological changes are certainly more precise parameters. While plasma Ca, P, and PTH levels normalize within days or weeks, plasma concentrations of 1,25(OH)\(_2\)D and phosphatase alkaline activity may remain elevated for months until definite healing of rickets is achieved. The first radiological sign of healing rickets is the appearance, 2–4 weeks after initiating vitamin D therapy, of linear dense deposits at the cartilage bone demarcation in the long bone. Later on, radiological aspect of the bones, together with the clinical skeletal signs, progressively return to normal. Dense metaphyseal zones of calcification corresponding to the calcified rachitic cartilage persist as "radiological scars" for 2 to 3 years. Bowing of the long bones may take 4 to 5 years to disappear and orthopedic treatment is seldom necessary.
REFERENCES


**DISCUSSION**

**Dr. Marx:** How do you see the relationship between serum levels of 25(OH)D and 1,25(OH)2D during development and the diagnosis of vitamin D deficiency?

**Dr. David:** It is paradoxical to find that plasma levels of 1,25(OH)2D are often within normal range and sometimes elevated in infants with clinically and radiologically typical deficient rickets. One can argue that values within the normal range are unadapted in face of secondary hyperparathyroidism, hypophosphatemia, and, when present, hypocalcemia. Indeed this suggests that there is a limitation of the synthesis of 1,25(OH)2D which is probably related to the deficiency of the substrate 25(OH)D. As far as calcium absorption is concerned, I would
suggest that a level of 1,25(OH)₂D within the low normal range might be inadequate for an appropriate calcium absorption. In other words, it is possible that in those infants, although normal, 1,25(OH)₂D levels are below the individual threshold of efficiency. On the other hand one has to consider that the situation is not similar to a well planned experimental design of vitamin D deficiency, and it is likely that for some infants, normal or elevated plasma 1,25(OH)₂D are reflecting recent sources of vitamin D either from sun exposure or from the diet.

Dr. Marx: Does this mean that this form of rickets is basically a state of deficiency of 1,25(OH)₂D and that when we test a patient with established disease, we do not necessarily obtain an accurate index of the average serum 1,25(OH)₂D levels that prevailed during evolution of the disease?

Dr. David: Yes. Children with vitamin D-deficient rickets when studied in a hospital, are in a situation quite different from what happens in experimental animal studies, where as expected, 1,25(OH)₂D plasma levels are low and even undetectable. The actual vitamin D status of our young patients may be quite variable depending upon possible access to vitamin D sources during the few days preceding admission, particularly through recent sun exposure.

Dr. Markestad: We have studied consecutive cases of vitamin D-deficiency rickets in Norway and Libya. At the time of diagnosis one-third to one-half of the patients had elevated, while some had normal and some low 1,25(OH)₂D levels (1). 1,25(OH)₂D in the normal range is probably pathologically low in rickets since these patients have secondary hyperparathyroidism.

Dr. Mautalen: I am also surprised that, even if it is a minority of cases, 25-hydroxy D levels are sometimes normal. Shouldn’t low 25(OH)D be the hallmark of nutritional rickets?

Dr. David: This also probably indicates that these infants had recent access to a source of vitamin D. From what we learned from Dr. Holick, this may be simple exposure of hands and face to the sun during the first warm days of spring. Furthermore one must remember that although treatment of rickets with vitamin D results in increases of 25(OH)D and 1,25(OH)₂D levels within a few hours, clinical and radiological improvements are not apparent before days or even weeks.

Dr. Heinrich: Is there a connection between vitamin D deficiency or early rickets, and the classical transient hypoparathyroidism, as described by Prader in the children who are fifteen days old and have hypocalcemia. We know that this problem appears mainly at the end of the winter, so there must be some relation to vitamin D deficiency in the pregnant mother.

Dr. David: There is indeed good evidence that a relationship exists between the frequency of late neonatal hypocalcemia with the picture of partial, or transient, hypoparathyroidism and vitamin D deficiency. Thus, the frequency of late neonatal hypocalcemia is known to be much higher in countries where vitamin D deficiency is frequent. Similarly, as you mentioned, in the absence of systematic prevention of vitamin D deficiency in infants, there are seasonal variations in the frequency of late neonatal hypocalcemia which is more frequent in late winter and spring than the rest of the year. In keeping with this, the study by Brooke et al. in England is of interest: they showed that in a population at high risk for vitamin D deficiency, the frequency of late neonatal hypocalcemia drops when the mothers are receiving vitamin D supplements during pregnancy (2). In our own series of late neonatal hypocalcemia we found, almost always, low levels of plasma 25(OH)D in addition to low serum levels of PTH. In my opinion, this indicates that some infants are born with a limitation of parathyroid function. If they don’t have to face vitamin D deficiency (or another calcium depressing event like a phosphate load for example), partial hypoparathyroidism will remain unnoticed. On the other hand, in case of vitamin D deficiency they will be unable to maintain calcium
COMMON VITAMIN D-DEFICIENCY RICKETS

homeostasis and late neonatal hypocalcemia or, later on, early hypocalcemic rickets will result.

Dr. Heinrich: Are you aware of studies comparing sun exposure to vitamin D supplementation as treatment for vitamin D deficiency?

Dr. David: Sun exposure is certainly as effective as vitamin D supplementation to cure rickets as it is to prevent it, but I don't know of any study comparing the effect of sun exposure versus vitamin D supplementation on the evolution of the biological parameters of rachitic infants. One should remember that the first demonstration that vitamin D-deficient rickets can be cured by sun exposure has been an historical event in the story of vitamin D when Hess and Unger cured rachitic children by exposing them to the sun on the roof of a hospital in New York (3). Not so long ago, and for the same reason, many European rachitic children were sent to nursing homes by the seaside. Of course this is not done any more, mainly for obvious psychological and economical reasons. Vitamin D therapy is indeed convenient, cheap, and rapidly effective; it is thus understandable that it is preferred to treatment by sun exposure.

Dr. Marx: Would you expand on your recommendation in favor of brief high doses as opposed to lower doses given repeatedly for initial treatment of vitamin D deficiency. I believe there is no study where the two protocols have been compared directly.

Dr. David: On a theoretical point of view, low daily doses given for several weeks are as effective as a unique high dose, although, it seems that a unique high dose might normalize more rapidly the biological parameters. As far as toxicity is concerned I don't really think that, when given in a situation of vitamin D deficiency, there is a risk of overtreatment with a unique dose, not higher than 200,000 IU. To prove this, one needs a well designed study. On the practical and economical standpoints, a unique high dose appears preferable. From my experience in France, most of the infants with vitamin D-deficient rickets are from low income families and, often, we cannot rely on the parents to give a long daily treatment. On the contrary, once the high dose is given, whether it is during a hospitalization, or at the outpatients clinics, we are confident that the treatment will be effective.

Dr. Coates: We have experience with nutritional rickets in the first year of life in São Paulo, because in spite of existing sunlight during many months of the year, mothers leave their babies indoors: Vitamin D intoxication is still not so rare because of wrong indications. We treat our well documented (by serum calcium, phosphorus, alkaline phosphatase and x-ray) cases with 600,000 IU vitamin D₃, p.o. We give the first dose of 100,000 IU fasting and then 100,000 IU every hour until we reach 600,000 IU. This schedule of administration, recommended by Dr. Harrison years ago, ensures better absorption. 10–14 days later, we measure serum phosphate. Usually it is back to normal and no more vitamin D is necessary. However, if it is still low, often when there is a concurrent pulmonary infection, or diarrhea, we administer a second oral dose of 600,000 IU. Rarely, is a third dose necessary. With this regime, we never saw vitamin D intoxication.

Dr. David: I still think that a unique dose as large as 600,000 IU is not absolutely necessary, particularly in infants below 6 months of age, even if it runs a very small risk of overtreatment. Until a scientific study will clearly show the effects of a dose of 600,000 IU in the rachitic infants, I would advise using the lower dose of 200,000 IU which is certainly as effective and runs a lesser risk of intoxication.

Dr. Glorieux: In newborns affected with vitamin D pseudo-deficiency, or dependency (VDD1), where there is an inherited defect in 1,25(OH)₂D synthesis, the progressive depletion of the maternal vitamin D pool and the inability to make 1,25(OH)₂D induce the clinical picture of rickets to develop exactly in the same framework and timetable as in pure D
deficiency. It is, thus, clear that when you have pure 1,25(OH)$_2$D deficiency, you develop the full picture of rickets. In nutritional vitamin D deficiency with the active renal enzymatic machinery, there can be variable synthesis of 1,25(OH)$_2$D depending on the availability of calcium, phosphate, and 25(OH)D. Thus levels measured are merely snapshots on the background of a long-standing evolution.

**Dr. Marx:** There is another potentially important difference between VDD1 and nutritional deficiency of vitamin D. Only in nutritional deficiency is there also deficiency of all vitamin D metabolites, in addition to the deficiency of 1,25(OH)$_2$D. We do not know the precise mixture of metabolites that normally sit upon and activate the receptor for 1,25(OH)$_2$D; in this regard, the term 1,25(OH)$_2$D receptor may give the wrong impression. Some prefer to call it the vitamin D receptor. A “normal” 1,25(OH)$_2$D level in the face of low levels of other metabolites could, in fact, be insufficient for a normal degree of activation of “1,25(OH)$_2$D receptors.”

**Dr. David:** Let me say however that vitamin D-deficiency rickets can be cured by small daily doses of 1,25(OH)$_2$D, which give support to the concept of a pure 1,25(OH)$_2$D deficiency disease with little consequences of the deficiency of the other vitamin D metabolites.

**REFERENCES**

