Hereditary Pseudo-Deficiency Rickets or Vitamin D-Dependency Type I

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Following the description in 1937 by Albright, Butler, and Bloomberg (1) of “rickets resistant to vitamin D,” a number of observations were published, particularly by Van Crefeld and Arons (2), Fraser and Salter (3), and by Royer (4) which indicated that there was a variant of resistant rickets which differed from classical hereditary hypophosphatemic vitamin D-resistant rickets by its clinical and biological symptoms, and response to therapy. It was thanks to the study of Prader, Illig, and Heierli (5) that “hereditary pseudo-deficiency rickets” was clearly identified as a new form of hereditary vitamin D-resistant rickets.

This rare condition was the first identified inborn error of vitamin D metabolism. Although direct evidence for a deficit in renal 25-hydroxyvitamin D 1α-hydroxylase has only been obtained in the animal model of this disease in a variety of piglets (6,7), there is convincing indirect evidence that “pseudo-deficiency rickets,” recently also called “vitamin D dependency,” is the consequence of a deficit in this essential renal enzyme in humans (8,9). Another inborn error of vitamin D metabolism has been recently isolated: “pseudo-deficiency rickets type II or vitamin D dependency type II.” This disorder is due to end-organ resistance to 1,25(OH)₂D₃ and is now usually called “hereditary resistance to 1,25(OH)₂D₃” (10) (see chapter by S. Marx).

The mode of inheritance of vitamin D-dependency type I (VDD) is autosomal recessive. The mutation causing the disease has been recently mapped to chromosome 12q14 by linkage analysis (11). This should allow for carrier detection in the families at risk.

Approximately 80 cases of VDD type I have been reported (2–5,8,9,12–27). However, this disorder is certainly more frequent than the scarcity of published cases would suggest. The fact that despite the severity of the symptoms at first presentation these patients are readily treated, also that the pathophysiology of this disease is now clearly understood probably explains why new observations are no longer published except to clarify particular pathophysiological issues (28) or if associated with unusual clinical features (29).

We have followed 12 patients with VDD type I, belonging to seven sibships over
the past 20 years. This chapter summarizes our experience and that of other investigators concerning this disorder of vitamin D metabolism.

**CLINICAL SYMPTOMS AND RADIOLOGICAL SIGNS**

The clinical symptoms of VDD type I are similar to those of common vitamin D-deficiency rickets. The onset in most cases occurs early during the second trimester of life. However, late onset during young adulthood has been reported in one family (21). In infants the symptoms include failure to thrive, tremulations and Bravais-jacksonian fits or generalized convulsions. The affected babies are apathetic and mostly lay supine because of severe muscle weakness and bone pain; this may explain the usual absence of gross skeletal deformities at this age. However, if diagnosis

![Fig. 1](image_url)  
**Fig. 1.** A: Severe ricketic metaphyseal abnormalities and massive osteopenia in a 5-month-old child with VDD type I before treatment. B: Normal aspect at age 7 years following therapy first with 25(OH)D$_3$ and then with 1α(OH)D$_3$.  

and treatment are delayed, very severe deformities of the long bones and the spine occur, together with generalized muscle weakness simulating myopathy.

Physical examination reveals a rachitic rosary, deformity of the thorax, softening of the skull (craniotabes), and enlargement of wrists and ankles. Deformities of the thorax may interfere with ventilation and predispose to pulmonary infection. The x-ray features include classic ricketic metaphyseal changes, extensive demineralization (Fig. 1A), Looser-Milkman's pseudofractures and incurvations of the shafts of long bones, especially in children more than 1–2 years of age.

LABORATORY DATA

The biological abnormalities (Table 1) are essentially those of hypocalcemic vitamin D-deficiency rickets. Serum calcium concentration is low or very low, whereas serum phosphorus may be low, normal, or even high. Plasma iPTH concentration and alkaline phosphatase activities are increased. Citratenia is decreased and urinary cAMP excretion is elevated. Generalized hyperaminoaciduria and slight hyperchloremic acidosis are observed in the hypocalcemic and hypophosphatemic forms. However, in those patients whose active therapy has been interrupted for several years, a state of tubular unresponsiveness to PTH may develop as a possible consequence of long-standing severe hypocalcemia. In such patients hyperaminoaciduria is no longer observed and the serum phosphorus concentration is high with elevated

| TABLE 1. Biological symptoms, bone histology, and tooth abnormalities in patients with VDD type I |
| Biological symptoms |
| Serum         |
| Ca ↓         |
| P ↓ or N or ↑ |
| Alk Pase ↑    |
| Citrate ↓     |
| Hyperchloremic acidosis |
| Plasma        |
| iPTH ↑       |
| Urine         |
| Ca ↓         |
| Amino acids ↑ |
| cAMP ↑       |
| TRP ↓ or ↑   |
| Intestinal malabsorption of Ca and P |
| Bone histology |
| Mineralization defect |
| Hyperresorption with or without marrow fibrosis |
| Teeth         |
| Enamel hypoplasia |

↑, increase; ↓, decrease. TRP, tubular reabsorption of phosphate.
tubular reabsorption of phosphate in spite of overt secondary hyperparathyroidism as indicated by high plasma iPTH and histological signs of increased bone resorption (24).

Balance studies in patients with VDD type I show malabsorption of calcium and phosphorus with very low urinary excretion of calcium. Normalization of calcium and phosphorus intestinal absorption is obtained after administration of small doses of 1,25(OH)₂D₃ or 1α(OH)D₃. Withdrawal of therapy is rapidly followed by a relapse of the intestinal malabsorption processes (Fig. 2).

SERUM VITAMIN D METABOLITE CONCENTRATIONS

The first reports on the circulating concentrations of 1,25(OH)₂D showed uniformly low values in six patients with VDD type I (30). These observations have led to the assumption that VDD type I is characterized by low serum 1,25(OH)₂D concentrations as compared to normal age-matched controls. This statement should be viewed with some reservation. In eight patients with VDD type I we have observed less uniform results: four children had low circulating levels of 1,25(OH)₂D (equal to or less than 20 pg/ml), whereas four others were repeatedly found to have serum 1,25(OH)₂D concentrations in the normal range (Table 2). However, these normal
TABLE 2. Circulating concentrations of 25(OH)D and 1,25(OH)\textsubscript{2}D in 8 patients with VDD type I

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Serum concentration</th>
<th>Serum concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25(OH)D (ng/ml)</td>
<td>1,25(OH)\textsubscript{2}D (pg/ml)</td>
</tr>
<tr>
<td>1</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>22–91</td>
<td>19–21</td>
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<td>3</td>
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<td>4</td>
<td>106</td>
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<td>5</td>
<td>34</td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td>230 ± 32</td>
<td>68 ± 8</td>
</tr>
<tr>
<td>7</td>
<td>224 ± 35</td>
<td>40 ± 13</td>
</tr>
<tr>
<td>8</td>
<td>231 ± 38</td>
<td>79 ± 13</td>
</tr>
<tr>
<td>Normal range</td>
<td>8–30</td>
<td>20–110</td>
</tr>
</tbody>
</table>

serum 1,25(OH)\textsubscript{2}D concentrations do not justify discarding the diagnosis of a deficiency in the synthesis of this metabolite in patients suspected of having VDD type I. It is, in effect, clearly inappropriate to have normal serum 1,25(OH)\textsubscript{2}D levels in a state characterized by active rickets, hypocalcemia, and secondary hyperparathyroidism, and in the presence of enough substrate, i.e., 25(OH)D. This view is supported by findings in nutritional rickets (31). After administrations of a single oral dose of 25(OH)D\textsubscript{3} (10 μg/kg body weight) or small daily doses of vitamin D (2000 IU), we have observed supra-normal concentrations of serum 1,25(OH)\textsubscript{2}D in all vitamin D-deficient children, reaching several hundreds of picograms per milliliter in most patients. These high levels persisted for several weeks as long as all biochemical parameters had not returned to normal. These results confirm that normal serum 1,25(OH)\textsubscript{2}D concentrations associated with normal or high serum levels of 25(OH)D are inappropriate in any child with hypocalcemia, elevated plasma iPTH, and rickets. They also show that high circulating 1,25(OH)\textsubscript{2}D\textsubscript{3} levels in patients with rickets or osteomalacia do not necessarily imply a state of resistance to 1,25(OH)\textsubscript{2}D\textsubscript{3}. Patients with VDD type I have normal circulating concentrations of 25(OH)D after exposure to sunlight or after oral intake of small doses of vitamin D and the concentrations increase if higher doses are given. This indicates that there is no associated deficit in vitamin D-25-hydroxylase in this disorder. Similarly, we found no abnormality in the circulating concentrations of 24,25(OH)\textsubscript{2}D in children with VDD type I. A similar finding was also reported by Aarskog et al.(29). These authors also demonstrated normal or elevated circulating levels of 25,26(OH)\textsubscript{2}D in a child with VDD type I.

TREATMENT AND OUTCOME

Late diagnosis and inappropriate treatment may be the cause of death during infancy, by hypocalcemia or severe pulmonary infections, as was the case in two of
the families we studied. Intermittent therapy and interruption of treatment for long periods of time may, in older children, lead to dwarfism and marked skeletal deformities requiring orthopedic surgery (25). However, provided patients with VDD type I are diagnosed and treated in early childhood, and receive appropriate individual treatment throughout life their outcome is excellent: normalization of all parameters, catch-up growth leading to a normal statural height (Fig. 3), and healing of skeletal lesions (Fig. 1B) are achieved and maintained.

The treatment of choice in patients with VDD type I is replacement therapy with 1,25(OH)2D3. However, since there is no pharmaceutical preparation of 1,25(OH)2D3 in solution, and since, for obvious reasons, capsules cannot be administered to infants and young children, the treatment of choice for this age group is 1α(OH)D3 in solution. But, neither drug is available as yet in many countries. This is not a major handicap because VDD type I can be well treated using pharmacological doses of the parent vitamin D (D2 or D3), dihydrotachysterol, or 25(OH)D3. Table 3 summarizes the daily requirements in our experience for the various vitamin D preparations, during the active phase of the disease, and for maintenance therapy once skeletal healing has been achieved.

In patients with severe hypocalcemia, parenteral administration of calcium in association with oral vitamin D therapy is usually necessary for a few days. Oral calcium supplements (0.5 to 1 g elemental calcium per day) must be given thereafter until complete healing of skeletal lesions.

Whatever the vitamin D preparation used, regular and repeated medical and biological surveys of the patients are mandatory. These should include, in addition to the monitoring of serum and urinary parameters: serum calcium, plasma iPTH, urinary calcium excretion (Ca mg/24 h or Ca/creatinine ratio on a fasting morning sample), regular measurements of blood pressure, and survey of the lenses since early cataract has been reported in late diagnosed patients (22). The occurrence of hypercalciciuria should be considered as a signal of vitamin D overdosage and lead to reduction of the daily dosage.

Women with VDD type I can undergo an uneventful pregnancy and give birth to normal children, as we observed with two of our patients (unpublished data). They usually need oral calcium supplements (1 g elemental calcium per day) after the sixth month of pregnancy in addition to vitamin D therapy.

In conclusion, VDD type I is a metabolic disorder which usually shows very severe

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Active rickets</th>
<th>Maintenance</th>
</tr>
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<tbody>
<tr>
<td>Vitamin D (mg/d)</td>
<td>1–7</td>
<td>0.5–1</td>
</tr>
<tr>
<td>25(OH)D3 (mg/d)</td>
<td>0.25–2.5</td>
<td>0.07–0.5</td>
</tr>
<tr>
<td>1α(OH)D3 (µg/d)</td>
<td>2–8</td>
<td>1.5–3</td>
</tr>
<tr>
<td>1,25(OH)2D3 (µg/d)</td>
<td>1–4</td>
<td>0.75–1.5</td>
</tr>
</tbody>
</table>
Fig. 3. Statural growth in a child with VDD type I. 25(OH)D₃ Therapy induced catch-up growth. Shifting to 1,25(OH)₂D₃ treatment provoked a further increase in height velocity. At 18 years of age the statural height is normal.
symptoms at first presentation. But, the treatment of this condition is now well established and the results obtained are rewarding both for the patients and their physicians.

REFERENCES

HEREDITARY PSEUDO-DEFICIENCY RICKETS


**DISCUSSION**

*Dr. Glorieux:* Having acted as Dr. Balsan's mouthpiece,¹ I wish now to comment about our own studies on the same disease. In Quebec, we have the largest known group of such patients with at least 50 cases, half of them under our direct care. This high incidence is largely due to the inbreeding that prevailed in the early times of the colony in Quebec. With the cooperation of large affected families, we have assigned the VDD I gene to chromosome 12 and indicated that the most likely target for the mutation was the specific P450 component of the renal 25(OH)D-1α-hydroxylase system (1). From our experience of fifteen years with VDD I patients, I wish to underline some clinical facts. First, in the untreated state, circulating levels of 1,25(OH)₂D have always been very low (under 10 pg/ml). It is only in those patients, referred to us, partially treated with various amounts of vitamin D, that we observed higher (sometimes low normal) values of 1,25(OH)₂D concomitant to increased concentrations of 25(OH)D and 24,25(OH)₂D. Whether this represents imperfect response of a modified renal enzyme, or the presence of extra renal sites of 1α-hydroxylase activity remains to be established. Second, in our patients, now young adults, the maintenance dose of 1,25(OH)₂D₃ is remarkably stable at 0.25-1 μg/d. In three instances, during pregnancy, we had to increase the daily dosage up to 2-2.5 μg/d. Three normal babies were delivered. Interestingly the decidual cells collected from the placenta of two of the affected mothers exhibited complete absence of 1α-OHase activity normally present. The specific importance of this local production of 1,25(OH)₂D is presently unknown. One last point, concerns the comparative values of 1,25(OH)₂D₃ and 1α(OH)D₃ for long term treatment of VDD I. In our experience, 1,25(OH)₂D₃ is not only more potent on a weight basis than its monohydroxylated analogue, but, in some instances, it is the only efficacious treatment agent. Indeed, some of our patients did respond poorly, or not at all, to 1α(OH)D₃. We are still investigating this unexpected discrepancy.

*Dr. Delvin:* Concerning the detectable levels of serum 1,25(OH)₂D found in untreated VDD I patients, one can hypothesize that they represent either extra renal synthesis of the hormone

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¹ Dr. Balsan could not attend the meeting.
or that there is in the assay a contamination of the fraction containing 1,25(OH)₂D. As suggested by Dr. Holick, the possibility of other metabolites comigrating with 1,25(OH)₂D despite careful high performance liquid chromatography cannot be excluded. Another argument supporting this hypothesis is coming from data obtained in VDD 1 mutant piglets where Harmeyer et al. have found no renal 1α-hydroxylase activity, yet serum 1,25(OH)₂D₃ was detectable (2). In view of those possible artifacts, we have therefore to be careful in interpreting the results.

Dr. Marx: I believe this disease is similar to defects in biosynthesis of other steroid hormones. Those defects, such as adrenogenital syndrome resulting from defects in cortisol synthesis, are often partial defects in which endogenous regulation maintains normal or near-normal serum levels of the hormonal product of the defective enzyme. For this reason, I am not sure there is any real discrepancy between the serum 1,25(OH)₂D levels in your families and those in Dr. Balsan’s. The two of you may be looking at a slightly different spectrum of enzyme defects (less severe in Dr. Balsan’s series) that produce the same outcome at the clinical level.

Dr. Glorieux: To answer that question, one will have to wait a detailed understanding of the molecular basis of the mutation and of its possible heterogeneity.

Dr. Marx: I am very puzzled by the poor response to 1α(OH)D₃ in some VDD 1 patients. These patients have normal 25-hydroxylation of vitamin D, and there is good evidence that 1α-OHD₃ is 25-hydroxylated by exactly the same enzyme (3,4). In doing comparisons of two patient groups for this evaluation, it is important that they be matched with regard to daily calcium requirement and with regard to body stores of vitamin D metabolites. Measurement of blood levels of 1α-(OH)D₃ would also be a very informative aspect of such a study.

Dr. Glorieux: Unfortunately, because of the lack of the suitable labeled compound, we have not been able, yet, to set up that assay. Those patients we studied were under excellent metabolic control, with no active bone disease. In each patient the two tests with 0.5 µg of 1,25(OH)₂D₃ and 1 µg of 1α(OH)D₃ were done at 48 hour intervals. Thus the metabolic status of the patients was similar. I have no explanation for the observed discrepancy.

Dr. Paunier: Prior to the availability of the active metabolites of vitamin D, these patients were treated with 20–50,000 IU of vitamin D₂. I was surprised to note that the three patients from Dr. Balsan, who had normal levels of 1,25(OH)₂D had very high 25(OH)D levels, suggesting that they had received previously large doses of vitamin D. Do you think that some of these patients may have a partial block of the 1α-hydroxylase enzyme which could explain these findings?

Dr. Glorieux: I think you are right. The enzyme is not absent, but its activity is affected by the mutation. We have shown that by greatly increasing the pool of circulating 25-hydroxy D with vitamin D₂ treatment, levels of 1,25(OH)₂D also increase, with respective amounts of the two metabolites being positively correlated (5). However, in our patients, as opposed to Dr. Balsan’s observation, levels of 1,25(OH)₂D never reach the normal range.

Dr. Pettifor: What is the earliest age you have diagnosed vitamin D-dependency rickets. In other words, when do they become clinically hypocalcemic?

Dr. Glorieux: Clinical onset occurs around four or six months of age, with progressive generalized hypotony, followed by hypocalcemia, bone pain, and rachitic changes. By measuring 1α-25 levels, we can make the diagnosis in the first week of life. We have done that, in families at risk.

Dr. Coates: I am following 12 cases of VDD 1 rickets; some of them we thought had nutritional rickets. We treated them with high doses of calciferol but they didn’t get better and continued to be hypotonic. They were started on calciferol D₂, 50,000 units daily and
within a few days to 2 weeks the hypotonia disappeared, and all other clinical, biochemical, and radiological parameters were improved. We have been following now these children for several years with 30,000 to 50,000 units of D\(_2\) daily. The majority made a "catch-up growth," and they are doing all right clinically and biochemically. Two patients were intoxicated during the years of treatment; we had to lower the dose temporarily or stop it. Some of them apparently reverted; now they have been for approximately two years without treatment and continue to be normal.

Dr. Glorieux: That corresponds to our experience with the parent vitamin before we converted to the active metabolite. I have, however, seen no case where we could withdraw treatment at a later age.

Dr. David: You showed us that although most of your patients were hypophosphatemic, some were hyperphosphatemic and you related the hyperphosphatemia to the chronic hypocalcemia. Could you comment on that and indicate to us how in your opinion chronic hypocalcemia may lead to hypophosphatemia?

Dr. Balsan: Our three patients with serum phosphorus levels in the high normal or hyperphosphatemic range were three siblings who had remained out of medical control and therapy for several years. Their hypocalcemia was very severe (serum calcium between 1.2 and 1.3 mmol/liter) and presumably long-standing. We could show (6) that they had no phosphaturic response to a parathyroid extract test while hypocalcemic but that their response was normalized after correction of their hypocalcemia with 1α(OH)\(_2\)D\(_3\) therapy. This observation suggests some degree of refractoriness to PTH during hypocalcemia. In addition, in 1965, Eisenberg did show that variations in serum calcium could modulate \textit{per se} and in the absence of PTH the tubular reabsorption of phosphate (7).

REFERENCES