STUDIES ON THE PATHOGENESIS OF HYPOPHOSPHATEMIC VITAMIN D REFRACTORY RICKETS OF THE SIMPLE TYPE OR PHOSPHATDIABETES

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Of all types of vitamin D refractory rickets the commonest is hypophosphatemic vitamin D refractory rickets of the simple type or "Phosphatdiabetes". Investigations on the pathogenesis of this disease by many workers were recently reviewed in detail (Fanconi, 1956; Swoboda, 1956; Winter et al., 1958). Of many hypotheses regarding the cause of the disease the following two are most widely credited. One is the hypothesis suggested by Albright et al. (1937; 1940) and Fraser et al. (1959) that the disease is caused by the secondary parathyroid hyperfunction resulting from the lowering of serum calcium through the deficient absorption of calcium from the gastrointestinal tract. The other is the hypothesis proposed by Dent (1952; 1956) and Fanconi (1952; 1954; 1955) that the disease is caused by the basic defect in the renal tubular mechanism for the reabsorption of phosphate from the glomerular filtrate. Which of the two hypothesis is true has not been decided yet.

The purpose of this paper is to make clear the pathogenesis of this disease by using parathyroid function test and the balance study of phosphorus and calcium.

MATERIALS AND METHODS

Eight children with vitamin D refractory rickets between ages of 10 months and 14 years, 5 males and 3 females, were selected.

(1) Blood and urine were subjected to general chemical analysis. Phosphate clearance tests were performed.

(2) Parathyroid function tests of 3 kinds were made concerning 6 cases out of the above 8.
   (a) Howard (1953) test
   (b) Ellsworth and Howard (1934) test (Lubell, 1957)
   (c) Fraser (1959) test

Saline solution containing calcium as a salt was continuously injected into the vein for the duration from 10 to 13 hrs., and its quantity was gradually increased so that the value of calcium in serum might be kept either increasing at a moderate rate or within normal limits. And when the phosphate excretion in urine markedly decreased, 50 u./m² body surface of parathormone was injected into the vein and changes in urinary phosphate excretion were examined.

(3) Balance study of calcium and phosphorus was made in 6 cases by determining the amount of the two substances in the diet, urine and feces.

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RESULTS

(1) In Table 1 are shown the results obtained by general chemical analysis and phosphate clearance tests. Serum inorganic phosphorus concentration was low and alkaline phosphatase activity increased in all cases. The serum calcium was low in 4 out of 8 cases. Phosphate clearance was elevated in all of the 4 cases tested.

Table 1. Blood and urine chemical analysis and phosphate clearance in 8 patients

<table>
<thead>
<tr>
<th>Name</th>
<th>Sex</th>
<th>Age</th>
<th>Ca mg/dl</th>
<th>P mg/dl</th>
<th>Alk. Phosphatase</th>
<th>Co2 vol. %</th>
<th>Citric acid mg/dl</th>
<th>Glucose Protein Concentration test</th>
<th>P/Ca</th>
<th>P clearance ml/min.</th>
<th>Amino acid mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.S.</td>
<td>♂</td>
<td>1:8</td>
<td>8.3</td>
<td>3.9</td>
<td>24.5</td>
<td>45.2</td>
<td>(−)</td>
<td>(−) −1</td>
<td>17.5</td>
<td>17.63</td>
<td>122.9</td>
</tr>
<tr>
<td>T.S.</td>
<td>♂</td>
<td>0:10</td>
<td>8.8</td>
<td>3.5</td>
<td>20.9</td>
<td>43.9</td>
<td>0.94</td>
<td>(−) −1</td>
<td>7.9</td>
<td>33.8</td>
<td></td>
</tr>
<tr>
<td>T.O.</td>
<td>♂</td>
<td>1:11</td>
<td>5.1</td>
<td>4.2</td>
<td>19.7</td>
<td>52.7</td>
<td>1.12</td>
<td>(−) −1</td>
<td>37.7</td>
<td>33.13</td>
<td>54.8</td>
</tr>
<tr>
<td>M.K.</td>
<td>♂</td>
<td>1:10</td>
<td>7.8</td>
<td>2.1</td>
<td>23.1</td>
<td>45.7</td>
<td>1.59</td>
<td>(−) −1</td>
<td>26.3</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>K.M.</td>
<td>♂</td>
<td>2:1</td>
<td>9.0</td>
<td>2.3</td>
<td>17.3</td>
<td>41.9</td>
<td>1.00</td>
<td>(−) −1</td>
<td>33.6</td>
<td>46.37</td>
<td>37.5</td>
</tr>
<tr>
<td>T.I.</td>
<td>♂</td>
<td>14:0</td>
<td>10.0</td>
<td>3.6</td>
<td>32.0</td>
<td>—</td>
<td>2.48</td>
<td>(−) −1</td>
<td>4.0</td>
<td>27.61</td>
<td>98.7</td>
</tr>
<tr>
<td>H.U.</td>
<td>♂</td>
<td>2:5</td>
<td>10.2</td>
<td>2.6</td>
<td>17.0</td>
<td>45.4</td>
<td>1.34</td>
<td>(−) −1</td>
<td>20.1</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Y.Y.</td>
<td>♂</td>
<td>6:0</td>
<td>9.1</td>
<td>3.6</td>
<td>20.6</td>
<td>47.0</td>
<td>—</td>
<td>(−) −1</td>
<td>25.2</td>
<td>−</td>
<td></td>
</tr>
</tbody>
</table>

N=normal * S.J.R.U. normal range=2~10

(2) (a) Howard Test The results are shown in Figure 1. According to Howard's standard of judgment 1 case out of 5 was normal, 2 cases were in hyperparathyroid state and 2 other defied the judgment in deciding whether they were in hyperparathyroidism or hypoparathyroidism.

(b) Ellsworth and Howard Test The results obtained by this method are shown in Figure 2. The responses of all the 6 cases tested were poor in comparison with those of normal children. Three out of 6 cases scarcely showed any response, while 3 others responded slightly.

(c) Fraser Test The results obtained by this method are shown in Figure 3. Three out of 5 (i.e. M.S., T.S., M.K.) showed a remarkable decrease in the amount of phosphate excretion in urine from 3 to 5 hrs. after the 1st injection of calcium salt into the vein, and they showed a marked increase in urinary phosphate excretion by injection of parathormone 7 to 8 hrs. after the 1st injection of calcium salt. One case (i.e. T.O.) showed a gradual increase in the quantity of phosphate excretion in urine after starting the injection of calcium salt and showed a slight decrease in urinary phosphate excretion 8 hrs. after the 1st injection of parathormone into the vein. Another case (i.e. K.M.) did not show any decrease even 10 hrs. after starting the injection of calcium salt, when the patient showed a slight increase in urinary phosphate excretion by the parathormone injection.

(3) The balance study of calcium and phosphorus: Three cases out of the 5 tested (i.e. M.S., T.S., T.O.) showed fecal calcium excretion above normal,
Fig. 1. Serum and urine phosphate response to the intravenous infusion of calcium salt according to Howard test in 5 patients and 2 normal children.
Fig. 2. Hourly excretion of phosphate before, and 3 to 5 hrs. after, the injection of parathormone according to Ellsworth and Howard test in 6 patients and 2 normal children.
DISCUSSION

The onset of rickets in these 8 children presumably ranged from 10 months to 2 years after birth. While hypophosphatemia and hyperphosphatasia were demonstrated in all, plasma NPN and CO₂ content gave normal values, analysis of urine revealed no glycosuria or aminoaciduria, and Sulkowitch test was negative. All of these cases failed to respond to normal amounts of vitamin D. For these reasons all of these cases were diagnosed as refractory rickets of the simple type. Phosphate clearance value, which was high, in all cases tested, is most likely responsible for hypophosphatemia. In 4 cases out of the 8 (i.e. M.S., T.S., T.O.,
hypocalcemia was present. In 3 of the 4 cases with hypocalcemia in which
calcium balance study was carried out, a high rate of fecal calcium excretion
was demonstrated. In view of the divergent results obtained, the quantity of
calcium salt injected into the vein in Howard test seems to be too small to assess
the parathyroid function accurately.

Ellsworth and Howard test revealed subnormal responses in all cases tested.
This seems to be due either to parathyroid hyperfunction or to the basic defect
in the renal tubular mechanism for the reabsorption of phosphate.

Fraser method revealed marked decreases in urinary phosphate excretion in
proportion to increases in the quantity of intravenously injected calcium salt in
3 cases (i.e. M.S., T.S., M.K.). Existence of a basic defect in the renal tubular
mechanism for the reabsorption of phosphate was therefore unlikely in these cases.
Normalization of responsiveness to parathyroid hormone due to the temporary
suppression of parathyroid function by calcium infusion would probably account
for the increase of urinary phosphate excretion in response to intravenous injec-
tion of parathormone. Hypocalcemia and deficient absorption of calcium from
the gastrointestinal tract moreover have already been known in these cases. It
would therefore be safe to assume that the deficient absorption of calcium from
the gastrointestinal tract resulted in the lowering of serum calcium which in turn
caused secondary parathyroid hyperfunction followed by the deficient reab-
sorption of phosphate by the renal tubular mechanism, hypophosphatemia and
finally rickets.

In another case (i.e. T.O.) the urinary phosphate excretion increased as the
quantity of calcium injected into the vein increased, showing a slight decrease 8
hrs. after the 1st intravenous injection of calcium and a marked hyperphosphaturic
response was obtained through parathormone. In this case the parathyroid gland
might possibly be in a state of too advanced hyperfunction to be inhibited by
intravenous calcium infusion, particularly in view of the fact that this case (i.e.
T.O.) was suffering from a high degree of hypocalcemia and a marked deficiency
in the absorption of calcium from the gastrointestinal tract.

The last case (i.e. K.M.) did not show any decrease in phosphaturia until 10
hrs. after starting the injection of calcium salt, when the patient showed a slight
increase in urinary phosphate excretion following the parathormone injection. This
case showed a normal serum calcium level, normal calcium absorption from the
gastrointestinal tract and a high phosphate clearance. A basic defect in the renal
tubular mechanism for the reabsorption of phosphate from the glomerular filtrate
might therefore explain the metabolic abnormality in this case.

From these results it is suggested that at least 2 groups may be distinguished
among cases of hypophosphatemic vitamin D refractory rickets of the simple type
or Phosphatdiabetes. In 1 group, the deficiency in the absorption of calcium
from the gastrointestinal tract is responsible, and the defect in the renal tubular
mechanism for the reabsorption of phosphate in the other. These 2 types may
show almost identical clinical picture but should be differentiated,
SUMMARY

The investigation into the pathogenesis of 8 cases with hypophosphatemic vitamin D refractory rickets of the simple type or Phosphatdiabetes shows that this disease is divided at least 2 types which are produced and developed respectively through the distinct pathogenesis, namely the pathogenesis of causing secondary parathyroid hyperfunction owing to the lowering of serum calcium through the deficient absorption of calcium from the gastrointestinal tract and the pathogenesis of causing the defect in the renal tubular mechanism for the reabsorption of phosphate.

REFERENCES

Dent, C. E. and H. Harris (1956). Ibid. 38 (B), 204.