Nutritional deficiency of vitamin D and calcium is the most common cause of rickets in children and responds satisfactorily to its treatment. Rickets secondary to hypophosphatemia, vitamin D dependence, renal tubular acidosis (RTA), liver disease, malabsorption and chronic renal failure does not respond to therapy with vitamin D, and is defined as refractory rickets(2). An accurate diagnosis of the underlying cause of refractory rickets allows initiation of specific therapy, often with satisfactory results.

There is paucity of published data on the etiology of refractory rickets in children. We report our experience on the etiology of this condition in patients attending this hospital during the last 13 years. While children with chronic renal failure comprise a significant proportion of subjects with refractory rickets, this diagnosis is readily established following estimation of blood levels of serum creatinine. Differentiation between other conditions is more difficult and was the subject of the study.

Subjects and Methods

Case records of children referred for evaluation of refractory rickets to the Renal Metabolic Clinic of the All India Institute of Medical Sciences during 1990 to 2002 were reviewed. Rickets was defined radiologically as presence of widened and irregular epiphyseal-metaphyseal junctions or evidence
of bone softening (bowing) in long bones(3) and elevated levels of serum alkaline phosphatase. Since patients with distal RTA and bony deformities often show normal blood levels of alkaline phosphatase, the presence of clinical and radiological features of rickets was considered sufficient for the diagnosis(4).

Subjects with rickets were treated with a total dose of 6,00,000 IU of vitamin D administered orally over a period of 10 days. An X-ray wrist was done, three weeks later, for healing of rickets, which was defined by the radiological presence of the line of healing. Patients not showing healing were retreated with same dose followed by an X-ray 3 weeks later. Patients who failed to show radiological healing despite two doses of vitamin D were diagnosed as refractory rickets(2). Patients with impaired renal functions [creatinine clearance < 50 mL/min/1.73 m², calculated by Schwartz formula(5)], deranged liver functions (blood bilirubin level >2 mg/dL and/or aspartate or alanine trans-aminase >5 times normal) or malabsorption (history of diarrhea, and abnormal D-xylose test and/or high 24 hr fecal fat) were excluded.

The case notes were reviewed for age at onset of symptoms and family history of similar disease. The height, weight, pattern of skeletal deformities, dentition and findings on systemic examination were noted. Eye examination for cataract, cystine crystals, KF ring and intraocular tension was performed in all patients. Blood levels of calcium, phosphate, alkaline phosphatase, urea, creatinine, albumin, pH, bicarbonate, electrolytes, bilirubin and transaminases were estimated. Urinalysis and measurement of calcium, phosphate, creatinine, sugar and albumin was done on timed and spot specimens; urine was also examined for abnormal aminoaciduria. Tubular maximum of phosphate factored by GFR (TmPO₄/GFR) was determined on timed urine collection using normograms(6). Hypercalciuria was diagnosed when the 24-hour urinary calcium excretion exceeded 4 mg/kg. Patients with metabolic acidosis (pH < 7.25 or base excess > –5 mEq/L) were further evaluated with urine pH. Fractional excretion of bicarbonate and urine to blood CO₂ difference were determined after bicarbonate loading in these subjects(7). Intact parathormone (PTH) levels were measured in subjects with normal blood levels of calcium, creatinine, pH and bicarbonate. Diagnostic criteria for etiology of refractory rickets are shown in Table I.

Data are represented as mean (95% confidence interval, CI) unless otherwise stated. Significance of difference in means was tested using one-way analysis of variance (ANOVA).

Results

Of 260 records reviewed, complete clinical and biochemical workup was available in 241. One hundred and ten patients with impaired renal functions (n = 110) were excluded from the study. The underlying diagnosis in remaining patients was hypophosphatemic rickets in 34 patients (25.9%), vitamin D dependent rickets (VDDR) in 26 (19.8%), distal RTA in 34 (25.9%), proximal RTA in 15 (11.5%), liver disease in 12 (9.2%) and malabsorption in 8 (6.1%). Pseudo-hypoparathyroidism was diagnosed in 2 siblings with hypocalcemia, hyperphosphatemia, normal blood levels of creatinine and elevated parathormone. Data of patients with hypophosphatemic rickets, vitamin D dependent rickets and RTA is presented.

Clinical features (Table II)

The mean age at onset of skeletal
### TABLE I–Criteria for Etiology of Refractory Rickets.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D dependent rickets</td>
<td>Normal or low serum phosphate*, serum calcium &lt; 8.5 mg/dl and/or high intact blood PTH (&gt; 150 pg/ml)</td>
</tr>
<tr>
<td>Hypophosphatemic rickets</td>
<td>Low serum phosphate*, low TmPO₄/GFR, normal blood calcium and PTH levels</td>
</tr>
<tr>
<td>Distal RTA(7)</td>
<td>Metabolic acidosis (pH &lt; 7.25, base excess &gt; -5 mEq/L), urine pH &gt; 5.5 On bicarbonate loading (at blood bicarbonate &gt; 22 mEq/L): fractional excretion of bicarbonate &lt;10% urinary to blood PCO₂ difference &lt;10 mm Hg</td>
</tr>
<tr>
<td>Proximal RTA(7)</td>
<td>Metabolic acidosis (pH &lt; 7.25, base excess &gt; -5 mEq/L), urine pH &lt; 5.5 On bicarbonate loading (at blood bicarbonate &gt; 22 mEq/L): fractional excretion of bicarbonate &gt;15% urinary to blood PCO₂ difference &gt;10 mm Hg</td>
</tr>
<tr>
<td>Fanconi syndrome</td>
<td>Proximal RTA with glucosuria, aminoaciduria and low TmPO₄/GFR†</td>
</tr>
</tbody>
</table>

* Normal range for blood phosphate levels(7) 0-5 days of life: 4.8-8.2 mg/dL, 6 days-4 years: 4.6.8 mg/dL, 4-11 yr: 3.7-5.6 mg/dL, 12-15 yr: 2.9-3.4 mg/dL.

† TmPO₄/GFR(6) 0-1 month: 4-10.7 mg/dL, 1-3 months: 4-9.5 mg/dL, 3-6 months: 4-8.2 mg/dL, 6 months-5 yr: 2.9-4.6 mg/dL, 5-12 year: 2.8-4.4 mg/dL.

### TABLE II–Clinical Features in Chief Etiological Categories.

<table>
<thead>
<tr>
<th>Boys : Girls</th>
<th>Distal RTA n = 34</th>
<th>Proximal RTA n = 15</th>
<th>Vitamin D dependent rickets n = 26</th>
<th>Hypophosphatemic rickets n = 34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (yr)*</td>
<td>3 (2-4) [1 mo-10 yr]</td>
<td>2 (0.7-3.3) [1 mo-10 yr]</td>
<td>1.9 (1.1-2.7) [18 days-9 yr]</td>
<td>2.7 (2.1-3.3) [1-10 yr]</td>
</tr>
<tr>
<td>Onset &lt;1 yr</td>
<td>12</td>
<td>7</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Onset &gt;1 yr</td>
<td>22</td>
<td>8</td>
<td>13</td>
<td>31</td>
</tr>
</tbody>
</table>

#### Clinical features

- Polyuria: 34
- Fractures: 7
- Enamel hypoplasia: 3
- Seizures: –
- Families affected: 6

1. Tetany was seen in 6 subjects and alopecia in 2 with vitamin D dependent rickets.
2. Hypokalemic muscle weakness was seen in 3 patients with distal RTA.
3. Expressed as mean (95% confidence interval) [range].

deformities was similar in all etiological groups. Of 8 patients who presented before the age of 3 months, 5 had VDDR while 3 had proximal RTA. Most patients with hypophosphatemic rickets (31 out of 34, 91.2%) and distal RTA (22 out of 34, 64.7%)}
presented after the age of 1 year. Rickets was incidentally diagnosed during evaluation for seizures (7 with VDDR), polyuria and polydipsia (4 with distal RTA), hypotonia (2 with proximal RTA due to Lowe syndrome) and extrapyramidal involvement (1 with proximal RTA secondary to Wilson disease).

The pattern of skeletal deformities was similar in children with VDDR and RTA with involvement of both upper and lower limbs. A significant number of patients with hypophosphatemic rickets (19 out of 34) showed clinical involvement of lower limbs with sparing of the upper limbs and skull.

Proximal RTA was isolated in 2 (13.3%) and associated with Fanconi syndrome in 13 (86.7%). Fanconi syndrome was secondary to Lowe syndrome in 2 and Wilson disease in 1. Distal RTA was considered primary in all cases; none of the patients had deafness. Hypophosphatemic rickets was secondary to McCune Albright syndrome with fibrous dysplasia in one subject.

Laboratory profile (Table III)

Serum calcium levels were lower in patients with VDDR compared to other conditions. Low serum calcium levels (<8.5 mg/dL) were also present in 4 (26.7%) patients with proximal RTA and 3 (8.8%) with distal RTA. Low serum phosphate and reduced TmPO4/GFR were found in all patients with hypophosphatemic rickets, 5 (19.2%) with VDDR and 6 (17.6%) with distal RTA. Serum alkaline phosphatase levels were lower in children with distal RTA compared to other patients, with 22 (64.4%) having levels in the normal range (<840 IU/L). Radiological evidence of fractures was present in 7 (20.6%) patients with distal RTA, 3 (11.5%) with VDDR and 3 (8.8%) with hypophosphatemic rickets.

Metabolic acidosis was more severe in distal RTA {mean blood pH - 7.21 (95% CI 7.19 - 7.23) [range 7.04 - 7.3]} than proximal RTA {mean blood pH 7.26 (95% CI 7.23-7.29) [range 7.1-7.34]} (P = 0.03). The mean blood bicarbonate levels were 13.9 (95% CI 13 - 14.8) [range 9.5 - 19 mEq/L] and 15.8 (95% CI 14.6 - 17) [range 12 - 19 mEq/L] respectively (P = 0.002). Mean fractional excretion of bicarbonate in subjects with distal RTA was 5.5% (95% CI 5.1 - 5.9%) [range 4 - 8%] compared to 23% in proximal RTA (95% CI 20.6 - 25.4) [range 15.5-33%] (P = 0.001). Ultrasound abdomen showed features of medullary nephrocalcinosis in 11 (32.4%) patients with distal RTA and one (2.9%) with hypophosphatemic rickets. Hypercalciuria was seen in 24 (70.6%) patients with distal RTA, 8 (53.3%) with proximal RTA and 4 (11.8%) with hypophosphatemic rickets.

Discussion

The chief causes of refractory rickets in the present study included chronic renal failure, hypophosphatemic rickets, distal and proximal RTA, vitamin D dependent rickets, and liver disease. These findings show that etiology of refractory rickets can be determined with proper application and interpretation of available laboratory findings. Specific therapy is possible in most instances making establishment of diagnosis a desirable goal.

Hypophosphatemic rickets was an important cause of refractory rickets in the present study. Presentation after infancy with predominant involvement of lower limbs and absence of hypocalcemia is characteristic, as was also observed in our patients(9). Treatment of these patients comprises of administration of phosphate supplements and vitamin D analogs. Clinicians should, however, be aware of the subgroup of patients with hypercalciuria, as seen in 4 subjects in this report(10). Therapy of the latter is
restricted to phosphate supplements; treatment with vitamin D analogs is avoided in view of the risk of nephrocalcinosis.

Bone disease in distal RTA has classically been described as mild osteopenia, while frank rickets is not common(3). The presence of severe bony deformities, including pathological fractures, in patients in the present study, is therefore significant. Despite presence of frank radiological changes of rickets, almost two-third patients showed normal blood levels of alkaline phosphatase. Blood levels of alkaline phosphatase are index of bone formation. Since persistent metabolic acidosis, in patients with distal RTA, results in reduced rate of bone formation, blood levels of the enzyme may be normal.

The etiology of rickets in distal RTA is not clear. The rachitic deformities resolve following alkali supplementation and treatment with vitamin D is not necessary(11). While chronic metabolic acidosis is speculated to adversely affect vitamin D metabolism, blood levels of vitamin D metabolites are reported to be normal(12). Caldas, et al., in a study on 28 patients with distal RTA proposed that the vitamin D status might determine the severity and extent of bony deformities(13). Low dietary intake of calcium and phosphorus is common in school-going children in our country(14), and if associated with reduced vitamin D stores may contribute to rickets and an increased the risk of fractures in these patients.

VDDR characterized by impaired synthesis (type I) or resistance to the action of 1, 25 dihydroxyvitamin D3 (type II)(15), was also an important cause of refractory rickets in our subjects. While estimation of blood levels of vitamin D metabolites was not possible in

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**TABLE III — Biochemical Investigations in Refractory Rickets.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Distal RTA (n = 34)</th>
<th>Proximal RTA (n = 15)</th>
<th>Vitamin D dependent rickets (n = 26)</th>
<th>Hypophosphatemic rickets (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium mg/dL*</td>
<td>9.4 (9.1 + 9.7)</td>
<td>9.5 (9-10)</td>
<td>6.9 (6.4-7.4)</td>
<td>9.6 (9.4-9.8)</td>
</tr>
<tr>
<td></td>
<td>[7.9-11.8]</td>
<td>[8.1-10.7]</td>
<td>[4.2-8.5]</td>
<td>[8.6-11.3]</td>
</tr>
<tr>
<td>Phosphate mg/dl #</td>
<td>3.2 (3-3.4)</td>
<td>2.7 (2.3-3.1)</td>
<td>3.5 (3.2-3.8)</td>
<td>2.5 (2.3-2.7)</td>
</tr>
<tr>
<td></td>
<td>[1.9-4.4]</td>
<td>[1.6-4.3]</td>
<td>[1.5-4.8]</td>
<td>[1.4-3.4]</td>
</tr>
<tr>
<td>Alkaline phosphatase IU/L @</td>
<td>866 (611-1121)</td>
<td>1196 (944-1448)</td>
<td>1749 (1356-1842)</td>
<td>1209 (955-1463)</td>
</tr>
<tr>
<td></td>
<td>[199-4212]</td>
<td>[342-2222]</td>
<td>[655-4530]</td>
<td>[207-4645]</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>6</td>
<td>10</td>
<td>5</td>
<td>34</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>3</td>
<td>4</td>
<td>26</td>
<td>–</td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>24</td>
<td>8</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
<td>11</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Aminoaciduria</td>
<td>4</td>
<td>12</td>
<td>2</td>
<td>–</td>
</tr>
</tbody>
</table>

Values represent mean (95% CI) [range].

* Significantly lower value for vitamin D dependent rickets (VDDR) compared to other categories (P <0.001)

# Significantly lower values in hypophosphatemic rickets and proximal RTA compared to VDDR and distal RTA (P <0.001).

@ Significantly lower values compared to VDDR in distal RTA (P = 0.003) and hypophosphatemic rickets (P = 0.04).
our patients, the presence of hypocalcemia and elevated blood levels of PTH were sufficient to differentiate VDDR from other causes, including hypophosphatemic rickets. Response to treatment with potent vitamin D analogs (alpha-hydroxyvitamin D or 1, 25 dihydroxyvitamin D) is useful for differentiating between VDDR types I and II(16).

Hypocalcemia characteristically seen in all patients with VDDR was also found in 26.7% and 8.8% patients with proximal and distal RTA respectively. Impaired metabolism of vitamin D and hypercalciuria may variably contribute to hypocalcemia in subjects with RTA. Similarly, while hypophosphatemia and low TmPO4/GFR is characteristic of phosphate losing states (hypophosphatemic rickets and proximal RTA), this was also present in 17.6% and 19.2% of our patients with distal RTA and VDDR respectively. These biochemical abnormalities are attributed to a phosphaturic effect of secondary hyperparathyroidism in the latter conditions, rather than primary phosphate wasting.

Our findings emphasize that hypophosphatemia and increased urinary excretion of phosphate is not diagnostic of hypophosphatemic rickets. Detailed clinical assessment and appropriate investigations (blood pH, bicarbonate, calcium and PTH) are necessary for establishing the correct diagnosis.

A limitation of this report concerns our not having screened all subjects for biochemical evidence of fluorosis. Fluorosis is endemic in this part of the country, attributed chiefly to high fluoride levels in ground water(17). Skeletal fluorosis may affect school going children, resulting in bony deformities and radiological changes that mimic rickets; osteosclerosis is uncommon. Based on the early age of onset of symptoms in this study, the possibility of skeletal fluorosis however seems remote. While most patients with skeletal fluorosis present in late childhood or adolescence(18), the mean age patients in the present study was 2.5 yr [90.1% below 5 years].

Our study emphasizes the need for a standard protocol at every referral center for evaluating patients with refractory rickets. The protocol followed in this hospital is shown in Fig 1. Initial investigations include estimation of blood levels of calcium, phosphate, alkaline phosphatase, creatinine, pH, bicarbonate and total CO₂. The presence of metabolic acidosis on 2 or more occasions suggests the diagnosis of RTA, which should be characterized further. Blood levels of calcium and PTH levels are useful in differentiating between VDDR and hypophosphatemic rickets.

**Key Messages**

- Hypophosphatemic rickets, vitamin D dependent rickets (VDDR) and renal tubular acidosis (RTA) are important causes of non-azotemic refractory rickets.
- Distal RTA in children may often present with severe bony deformities and pathological fractures without significant elevation of blood levels of alkaline phosphatase.
- Hypophosphatemia and increased urinary excretion of phosphate, characteristic of hypophosphatemic rickets and proximal RTA, may also be seen in patients with VDDR and distal RTA.
Refractory rickets

Serum calcium, phosphate, alkaline phosphatase,
urea, creatinine, venous blood gas

Normal or low blood phosphate

High blood phosphate

Metabolic acidosis
Renal tubular acidosis
(Characterize further, Table I)

Hypocalcemia, elevated PTH
Vitamin D dependent rickets

Normal calcium and PTH levels
Hypophosphatemic rickets

High blood urea, creatinine
Chronic renal failure

Normal blood urea, creatinine
Pseudohypoparathyroidism

Fig. 1. Evaluation of refractory rickets.
* Related to age specific norms (see Table I)

Contributors: MM, PH and AB were involved in management of patients. AB, AnB and AdB planned the study. AnB and AdB collected data. AnB performed literature review and drafted the manuscript. AB critically reviewed the manuscript and will act as its guarantor.

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Competing interest: None.

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