Osteogenesis Imperfecta Type VI: A Form of Brittle Bone Disease with a Mineralization Defect*

FRANCIS H. GLORIEUX, 1,2 LEANNE M. WARD, 1 FRANK RAUCH, 1,2 LJILJANA LALIC, 1 PETER J. ROUGHLEY, 1,2 and ROSE TRAVERS 1

ABSTRACT

Osteogenesis imperfecta (OI) is a heritable disease of bone in which the hallmark is bone fragility. Usually, the disorder is divided into four groups on clinical grounds. We previously described a group of patients initially classified with OI type IV who had a discrete phenotype including hyperplastic callus formation without evidence of mutations in type I collagen. We called that disease entity OI type V. In this study, we describe another group of 8 patients initially diagnosed with OI type IV who share unique, common characteristics. We propose to name this disorder “OI type VI.” Fractures were first documented between 4 and 18 months of age. Patients with OI type VI sustained more frequent fractures than patients with OI type IV. Sclerae were white or faintly blue and dentinogenesis imperfecta was uniformly absent. All patients had vertebral compression fractures. No patients showed radiological signs of rickets. Lumbar spine areal bone mineral density (aBMD) was low and similar to age-matched patients with OI type IV. Serum alkaline phosphatase levels were elevated compared with age-matched patients with type IV OI (409 ± 145 U/liter vs. 295 ± 95 U/liter; p < 0.03 by t-test). Other biochemical parameters of bone and mineral metabolism were within the reference range. Mutation screening of the coding regions and exon/intron boundaries of both collagen type I genes did not reveal any mutations, and type I collagen protein analyses were normal. Qualitative histology of iliac crest bone biopsy specimens showed an absence of the birefringent pattern of normal lamellar bone under polarized light, often with a “fish-scale” pattern. Quantitative histomorphometry revealed thin cortices, hyperosteoidosis, and a prolonged mineralization lag time in the presence of a decreased mineral apposition rate. We conclude that type VI OI is a moderate to severe form of brittle bone disease with accumulation of osteoid due to a mineralization defect, in the absence of a disturbance of mineral metabolism. The underlying genetic defect remains to be elucidated. (J Bone Miner Res 2002;17:30-38)

Key words: osteogenesis imperfecta, children, histomorphometry, osteomalacia

INTRODUCTION

Osteogenesis imperfecta (OI) is a heritable disorder of bone in which the hallmarks are bone fragility and low bone mass. Four different types are commonly distinguished based on clinical features and disease severity. Patients with OI type I have a mild phenotype with normal or near-normal height and typically blue sclerae, and OI type II is usually lethal in the perinatal period. OI type III, known as progressive deformating OI, is the most severe form in children surviving the neonatal period. These patients have a characteristic phenotype including extreme short stature, severe deformity of the spine, thoracic cage and

*Presented in part at the 22nd annual meeting of the American Society for Bone and Mineral Research, Toronto, Ontario, Canada, September 2000.
extremities, white or blue sclerae, and often triangular facies. Patients with a moderate to severe form of the disease who do not fit one of the foregoing descriptions are classified with OI type IV; as such, this group is extremely heterogeneous.

The underlying genetic defect in a proportion of OI patients is attributable to mutations in the genes encoding type I collagen; however, many with moderate (type IV) OI have no detectable mutation. Previously, we described a group of patients initially classified with OI type IV who presented a discrete phenotype including hyperplastic callus formation and calcification of the interosseous membrane. These patients also were unique histologically, with a coarsened, meshlike lamellar pattern of the bone matrix under polarized light. Mutations in type I collagen were absent. We called this disease entity OI type V.

In this study, we describe another group of patients initially diagnosed with OI type IV who share common clinical and unique histological characteristics. Notably, there is a mineralization defect. We propose to name this disorder “OI type VI.”

**MATERIALS AND METHODS**

**Patients and control groups**

The phenotype described in this report was found in 8 children (Table 1). These patients originally were classified among a group of patients with OI type IV according to the Sillence classification. The aim of this article was to describe the natural history of the disease up to 2.3 years and 14.3 years of age.

The control population for histomorphometric analyses consisted of 16 age-matched children (aged 2.0–13.3 years) with no bone disease from whom iliac bone biopsy specimens were obtained during various orthopedic procedures.

Clinical, biochemical, molecular, and histomorphometric results in patients with the type VI phenotype also were compared with those in 16 age-matched children with OI type IV (aged 2.2–13.5 years). The results of these patients had been included in earlier reports.

**Clinical follow-up**

All OI patients were seen at least once per year in our department. Clinical examination, biochemical measurements, and areal bone mineral density (aBMD) analyses were performed at each visit. The birth and fracture histories were obtained from the parents. For consistency, anthropometric measures and aBMD results are given at the time of biopsy. Results for height and weight were transformed to gestational or chronological age and sex-specific Z scores using standard growth curves. X-ray surveys of the entire skeleton were obtained at the time of first presentation. Thereafter, radiological imaging studies were performed when required for clinical management. None of the participants in this study had received pharmacologic treatment other than vitamin and calcium supplementation in the 6 months preceding the biopsy. Informed consent was obtained in each instance from the subject and/or a legal guardian, as appropriate. The study protocol was approved by the Ethics Committee of the Shriners Hospital.

**Biochemical measurements**

Serum calcium, inorganic phosphorus, creatinine, and alkaline phosphatase levels were measured using colorimetric methods (Monarch; Instrumentation Laboratory, Inc., Lexington, MA, USA). Serum parathyroid hormone levels were determined by radioimmunoassay. Osteocalcin was quantified with an immunoradiometric assay (N-tact Osteo SP; DiaSorin, Stillwater, MN, USA). 25-Hydroxyvitamin D and 1,25-dihydroxyvitamin D were measured with radioimmunoassays (Osteo SP; DiaSorin). Urine creatinine and calcium were measured colorimetrically and urinary cross-linked N-telopeptides (uNTx) of type I collagen were measured by enzyme-linked immunoabsorbent (cAMP) levels were quantified by a competitive protein-binding assay [Cyclic AMP (N H) Assay System; Amersham, Cleveland, OH, USA]. Patients were fasting at the time of blood and urine sampling.

**Radiological studies and aBMD**

aBMD and coronal area in the anteroposterior direction were determined at the lumbar spine (L1–L4) using a Hologic QDR 2000W or 4500A device (Hologic, Inc., Waltham, MA, USA; entrance radiation dose <5 mrem).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Geoethnic origin</th>
<th>Family history of OI</th>
<th>Family history of consanguinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>French-Canadian</td>
<td>Yes (brother, patient 2)</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>French-Canadian</td>
<td>Yes (brother, patient 1)</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>French-Canadian/Irish</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>Nicaraguan</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>French-Canadian/German</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>Inuit from N. Quebec</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>German/Polish</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>Ecuadorian</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

F, female; M, male.
Results for aBMD were transformed to age-specific Z scores using data provided by the densitometer manufacturer.

**Histology and histomorphometry**

Full-thickness transiliac bone biopsy specimens were obtained with a Bordier trephine (5- to 6-mm core diameter) under general anesthesia, from a site located 2 cm below and behind the anterior superior iliac spine. In both patients and controls, biopsy specimens were collected on the fourth day or fifth day after dual tetracycline labeling (Declomycin; Wyeth-Ayerst Canada, Inc., Montreal, Canada). The tetracycline dose was 15–20 mg/kg per day taken orally during two 2-day periods separated by a 10-day free interval. Biopsy specimens were processed and analyzed as previously described. (13)

**Molecular and cytogenetic analyses**

Mutation analyses were performed according to the following methods. First, total cellular RNA was extracted from skin fibroblasts and complementary DNA (cDNA) was obtained by reverse transcription. The coding regions of the type 1 collagen genes (COL1A1 and COL1A2) cDNAs were amplified by polymerase chain reactions (PCRs), using 10 primer pairs for each cDNA, which created overlapping sequences of 510–662 base pairs (bp) in length. The primers and PCR conditions were chosen from the published sequence of the COL1A1 and COL1A2 genes and are available from the authors on request. PCR products were screened for mutations by conformation-sensitive gel electrophoresis,(11) and those products containing heteroduplexes were then sequenced using the ThermoSequenase kit (Amersham).

In the second technique, genomic DNA from peripheral blood leukocytes was analyzed, as described by Korkko et al.(12) All exons of the COL1A1 and COL1A2 genes and their respective exon-intron boundaries, with the exception of the six exons encoding the N-propeptides, were amplified by PCR. This was followed by heteroduplex mutation screening and sequencing of positive PCR products, as described previously. If the analysis was negative using messenger RNA (mRNA) extracted from skin fibroblasts, it was repeated using genomic DNA extracted from peripheral blood leukocytes.

Because of the family histories of consanguinity and the theoretical possibility of a homozygous form of the disease in patients 1, 2 (brothers), and 8, the second technique was repeated with wild-type DNA added to the samples of patients 1, 2 (brothers), and 8, before heteroduplex screening.

Type I collagen protein analyses were carried out in patients 1, 2, and 6 using published techniques.(13,14) Fibroblasts were derived by outgrowth culture from skin biopsy specimens obtained from the patients and a healthy control. For protein labeling, fibroblasts were incubated for 4 h in fresh Dulbecco’s modified Eagle’s medium containing 50 μg/ml ascorbate and 50 μCi/ml 1,2,3,4,5-3H proline (100 Ci/mmoll; Amersham). The culture medium and cell layer were harvested and analyzed separately. The newly synthesized type I collagen was digested with pepsin at 4°C and analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis.

Karyotype analyses from lymphocytes of 6 patients with OI type VI (patients 3–8) were performed according to standard procedures by direct visualization of G-banded chromosomes.

**Statistical analyses**

Differences between OI type VI patients and controls or the OI type IV group were tested for significance using Student’s unpaired t-test or the Mann-Whitney U test, as appropriate. All tests were two-tailed. Throughout, a p < 0.05 was considered significant. These calculations were performed using the SPSS software, version 10.0 for Windows (SPSS, Inc., Chicago, IL, USA).

**RESULTS**

**Demographic data and clinical evaluation**

Demographic data and clinical findings in patients with OI type VI are summarized in Tables 1 and 2. The patients first presented at our institution between 1.3 and 13.5 years of age. None had offspring at the most recent follow-up (ages 2.9 to 20.8 years). Two of the patients were brothers; no other affected family members were identified. The two brothers (patients 1 and 2) and patient 8 were the offspring of consanguineous parents (Fig. 1); these three patients also showed the most severe phenotype. Birth length and weight were appropriate for gestational age, similar to OI type IV (Table 2). However, at the time the bone biopsy was taken, three of the OI type VI patients had heights that were >2 SD below the mean (Table 2). No difference in height and weight was found between OI types VI and IV. Patients with OI type VI sustained more frequent fractures than patients with OI type IV (Table 2). None of the patients with type VI had a history of fractures documented at birth compared with 9 patients in the type IV group. Fractures in patients with OI type VI were first documented between 4 and 18 months of age and led to long bone deformity in all but 1 patient (patient 7).

The phenotype was characterized further by uniform absence of dentinogenesis imperfecta. The sclerae were white or faintly blue and considered normal in all cases. Ligamentous laxity was present in one-half of the patients. There was
no tendency to easy bruising and the skin was normal. At the time the bone biopsy was done, 4 patients were wheelchair bound and 4 patients were ambulatory (2 of the 4 ambulatory patients needed assistance).

Biochemical studies

Biochemical parameters of bone and mineral metabolism were within the reference range and similar to age-matched patients with OI type IV, with the exception of alkaline phosphatase. Serum alkaline phosphatase levels were elevated in the patients with OI type VI compared with patients with OI type IV (Fig. 2).

Radiological studies and aBMD

The radiological findings are presented in Table 3 and in Fig. 3. Wormian bones were absent in all 8 patients, and vertebral compression fractures were uniformly present, to varying degrees (Fig. 3A). Scoliosis was evident in 5 of the 8 patients. Coxa vara was found uni- or bilaterally in 5 of 8 patients and protrusio acetabuli was present in one-half of them (Fig. 3B). Patients 1 and 2 were unusual in that the metaphysyes were bulbous (Fig. 3C). These 2 patients showed particularly severe osteopenia and limb deformity. No patients showed radiographic signs of rickets (Fig. 3D), but Looser zones were identified in the scapulae, ribs, and diaphyses of long bones.

The aBMD at the lumbar spine (L1–L4) was low in all patients, with values similar to OI type IV (Table 2). The size of the vertebrae was also similar to OI type IV.

Histology and histomorphometry

Qualitative evaluation of iliac crest biopsy samples (Fig. 4) showed loss of the normal orientation of the lamellae, often with a “fish-scale” pattern under polarized light. In OI
type IV, the lamellae were thinner than in controls, but, generally, their organization was normal. Inspection under fluorescent light revealed poor, diffuse uptake of the tetracycline labels in OI type VI, and dual labeling was preserved in OI type IV.

Results of quantitative histomorphometry are given in Table 4. Cortical width and trabecular thickness were diminished in OI type VI, similar to OI type IV. However, trabecular number was similar to healthy controls. Total cancellous bone volume was normal in OI type VI, but the mineralized bone volume tended to be low. This discrepancy was caused by the fact that a considerable proportion of the cancellous bone volume consisted of osteoid. Both osteoid thickness and surface were significantly increased in OI type VI compared with healthy controls, resulting in a grossly elevated osteoid volume. Although the osteoid surface extent was similar in the two OI types, osteoid seams were thicker in OI type VI than OI type IV. The mineralization lag time was significantly prolonged in OI type VI and the mineral apposition rate and the adjusted apposition rate were decreased. Osteoid-based formation parameters (osteoblast surface, mineralizing surface, and adjusted apposition rate) were lower in OI type VI than in OI type IV. The bone resorption parameters were not significantly different from controls and OI type IV.

Molecular and cytogenetic studies

In no patients with type VI OI did screening of the COL1A1 and COL1A2 genes using cDNA and genomic
DNA detects mutations that would create premature stop codons, frameshifts, or in-frame insertions or deletions; replace glycine or create cysteine residues; or alter splice donor, acceptor, or branch-point sites. Using the same techniques, such mutations were found in 6/9 patients with OI type IV (three in COL1A1 and three in COL1A2). Type I collagen protein analyses showed normal electrophoretic migration of the α1(I) and α2(I) chains (patients 1, 2, and 6), indicating no overt changes in chain length or retardation in triple helical formation influencing hydroxylation or glycosylation of the α-chains.

Cytogenetic analyses in patients 3–8 showed no evidence of a chromosomal abnormality on direct observation of G-banded chromosomes to a resolution of 500–550 bands.

DISCUSSION

In this study we describe a disease entity, which we propose to call OI type VI. Similar to OI type V, OI type VI can be discriminated clearly from other forms of OI on clinical, histological, and molecular grounds.

Clinical aspects

OI type VI is a moderate to severe form of the disease. The patients sustained frequent fractures and in this series, fractures occurred more often than in patients with OI type IV. Frequent fractures led to long bone deformity in all but 1 patient and contributed to severe ambulatory restriction in one-half of them. Sclerae and teeth do not appear to be affected and wormian bones are absent. Initially, our patients were diagnosed with OI type IV according to the traditional classification of Sillence. However, the striking histological features were the initial clue that these patients showed a novel phenotype. The OI VI phenotype is rare, as the 8 patients described in this report have been identified from 128 patients with OI from whom bone biopsy specimens were available. Therefore, the incidence of OI type VI is estimated to be about 6% in our patient population.
Histological and histomorphometry

The most obvious histological abnormality in OI type VI was the abundance of osteoid. Both osteoid thickness and osteoid surface extent were twice as high as in controls. This finding clearly points to a defect in mineralization. Poor mineralization could already be suspected from the blurred aspect of many tetracycline labels and was proven by quantitative histomorphometry. Increased osteoid thickness and a prolonged mineralization lag time are the defining elements of osteomalacia.\(^{15}\) As seen in severe mineralization defects, adjusted apposition rate—a marker of osteoid deposition—was very low.\(^{15}\)

The finding of an increased osteoid surface extent is not specific for OI type VI, but also is found in OI types I, III, and IV.\(^{16}\) However, in these OI types, osteoid surface extent is elevated because of high remodeling activity,\(^ {16}\) whereas osteoid thickness is normal because mineralization is not impaired. In contrast, there is no indication that remodeling activity is increased in OI type VI. The defect in mineralization causes an increase in both osteoid surface and thickness. Thus, the histological characteristics of OI type VI clearly are different from those of the other OI types.

Biochemical and radiological aspects

Biochemical parameters of bone and mineral metabolism were unremarkable. The exception was a moderate increase in alkaline phosphatase levels, which is consistent with a mineralization defect.

The disturbance in mineralization also was apparent radiologically, because Looser zones were identified in the scapulae, long bones, and ribs. However, patients with OI type VI showed no radiological signs of growth plate involvement. In other forms of impaired mineralization such as vitamin D deficiency or hypophosphatemia, the abnormality affects both bone tissue and growth plate cartilage, which clinically presents as rickets.\(^ {16}\) Thus, the disturbance in mineralization is restricted here to the bone matrix, while mineralization appears to proceed normally at the growth plate.

Genetic aspects

The pattern of inheritance cannot be ascertained at the present time because none of our patients has affected parents or has offspring. A variety of geoethnic groups are represented in OI type VI, and the disease affects both sexes similarly. Interestingly, the 3 boys (2 brothers) with the most severe phenotype are the products of consanguineous parents. This may suggest that they have a homozygous form of OI type VI. For the two brothers, parental mosaicism with autosomal dominance also is a possible mode of transmission.

The striking histological differences as well as the absence of abnormalities in COL1A1 and COL1A2 suggest

### Table 4. Histomorphometric Data in OI Type VI, Compared with Healthy Controls and OI Type IV

<table>
<thead>
<tr>
<th></th>
<th>Type VI</th>
<th>Controls</th>
<th>Type IV</th>
<th>p (C)</th>
<th>p (IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>6.9 ± 4.1</td>
<td>7.4 ± 4.0</td>
<td>6.9 ± 3.4</td>
<td>0.77</td>
<td>0.60</td>
</tr>
<tr>
<td>n (m/f)</td>
<td>8 (6/2)</td>
<td>16 (9/7)</td>
<td>16 (8/8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Structural parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical Width (μm)</td>
<td>0.48 ± 0.17</td>
<td>0.89 ± 0.38</td>
<td>0.46 ± 0.19</td>
<td>0.01</td>
<td>0.83</td>
</tr>
<tr>
<td>Bone Volume/Tissue Volume (%)</td>
<td>19.3 ± 9.0</td>
<td>21.0 ± 4.1</td>
<td>9.6 ± 3.7</td>
<td>0.67</td>
<td>0.04</td>
</tr>
<tr>
<td>Mineralized Bone Volume/Tissue Volume (%)</td>
<td>15.7 ± 7.0</td>
<td>20.4 ± 4.1</td>
<td>9.2 ± 3.6</td>
<td>0.07</td>
<td>0.01</td>
</tr>
<tr>
<td>Trabecular Thickness (μm)</td>
<td>86 ± 11</td>
<td>122 ± 21</td>
<td>103 ± 27</td>
<td>0.0007</td>
<td>0.15</td>
</tr>
<tr>
<td>Trabecular Number (t/mm)</td>
<td>2.34 ± 1.27</td>
<td>1.73 ± 0.23</td>
<td>0.93 ± 0.30</td>
<td>0.30</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Formation parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoid Thickness (μm)</td>
<td>12.9 ± 4.5</td>
<td>5.7 ± 1.2</td>
<td>5.1 ± 1.1</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Osteoid Surface/Bone Surface (%)</td>
<td>60 ± 23</td>
<td>30 ± 11</td>
<td>50 ± 11</td>
<td>0.02</td>
<td>0.34</td>
</tr>
<tr>
<td>Osteoid Volume/Bone Volume (%)</td>
<td>20.3 ± 10.4</td>
<td>2.9 ± 12</td>
<td>5.1 ± 2.2</td>
<td>0.002</td>
<td>0.004</td>
</tr>
<tr>
<td>Mineralizing Surface/Bone Surface (%)</td>
<td>16 ± 9</td>
<td>13 ± 5</td>
<td>25 ± 9</td>
<td>0.38</td>
<td>0.12</td>
</tr>
<tr>
<td>Osteoblast Surface/Bone Surface (%)</td>
<td>12.2 ± 12.3</td>
<td>7.8 ± 4.3</td>
<td>23 ± 12</td>
<td>0.42</td>
<td>0.07</td>
</tr>
<tr>
<td>Mineralizing Surface/Osteoid Surface (%)</td>
<td>24 ± 13</td>
<td>46 ± 21</td>
<td>50 ± 18</td>
<td>0.09</td>
<td>0.03</td>
</tr>
<tr>
<td>Osteoblast Surface/Osteoid Surface (%)</td>
<td>21 ± 17</td>
<td>27 ± 15</td>
<td>46 ± 20</td>
<td>0.45</td>
<td>0.01</td>
</tr>
<tr>
<td>Mineral Apposition Rate (μm/d)</td>
<td>0.61 ± 0.10</td>
<td>0.92 ± 0.10</td>
<td>0.72 ± 0.17</td>
<td>&lt;0.0001</td>
<td>0.17</td>
</tr>
<tr>
<td>Mineralization Lag Time (d)</td>
<td>100 (42–102)</td>
<td>13 (9–29)</td>
<td>14 (8–34)</td>
<td>0.007</td>
<td>0.007</td>
</tr>
<tr>
<td>Adjusted Apposition Rate (μm/d)</td>
<td>0.14 ± 0.09</td>
<td>0.42 ± 0.18</td>
<td>0.35 ± 0.11</td>
<td>0.02</td>
<td>0.04</td>
</tr>
<tr>
<td>Bone Formation Rate/Bone Surface (μm²/μm²/y)</td>
<td>35 ± 23</td>
<td>44 ± 18</td>
<td>64 ± 25</td>
<td>0.49</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Resorption parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erosion Surface/Bone Surface (%)</td>
<td>19 ± 8</td>
<td>16 ± 5</td>
<td>23 ± 9</td>
<td>0.36</td>
<td>0.33</td>
</tr>
<tr>
<td>Osteoclast Surface/Bone Surface (%)</td>
<td>2.7 ± 3.2</td>
<td>1.0 ± 0.5</td>
<td>1.4 ± 0.9</td>
<td>0.25</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Values are means and SDs or medians and ranges; p values calculated by unpaired t-test or Mann-Whitney test as appropriate; p(C): significance of difference between OI type VI patients and controls; p(IV): significance of difference between OI type VI patients and OI type IV patients.
that OI type VI also is distinct from the other OI types at the molecular level. Further, the type I collagen protein analyses were normal in 3 patients and another 2 patients (patients 5 and 8) have been analyzed similarly elsewhere without evidence of a type I collagenopathy (P. Byers and M. Pepin, unpublished data, 1990, 1994).

Comparison with fibrogenesis imperfecta ossium

The histological findings in OI type VI resemble those in adults with fibrogenesis imperfecta ossium (FIO). FIO is a disorder of unknown etiology characterized by bone pain, fractures, osteopenia, and high serum levels of alkaline phosphatase but without evidence of a defect in calcium or phosphate metabolism. This is a rare, debilitating disease that occurs sporadically in adults, with the exception of one report of a father and 12-year-old daughter. Like patients with OI type VI, patients with FIO show osteomalacia and loss of the normal birefringent pattern of lamellar bone. The histological similarities between OI type VI and FIO are striking and suggest the possibility of a common etiology or pathogenesis. However, reports suggest that patients with FIO may be distinguished by normal bone size and shape, exuberant calluslike protuberances on the iliac wings, greater trochanters and scapulae, and dense vertebral end plates similar to a “rugger jersey” spine.

Nomenclature

The phenotype described in this article represents the first example of a congenital form of osteomalacia in the absence of rickets or a disturbance in mineral metabolism. However, this disorder remains most suitably classified as a form of OI, because bone fragility and osteopenia are the most prominent features of the disease. Furthermore, patients with OI type VI show only subtle distinguishing clinical features compared with patients with OI type IV, and they were not defined as a unique subgroup until bone biopsy results were available. Evidence is mounting in support of OI as a clinically and genetically heterogeneous disorder and further mutations in type I collagen are not always found. As such, OI remains a clinical diagnosis at this time. The emergence of novel forms of OI, such as OI types V and VI, underlines that the absence of abnormalities in COL1A1/COL1A2 and type I collagen does not preclude a diagnosis of OI. The histological delineation of new OI forms provides further support for the role of genetic abnormalities other than COL1A1/COL1A2 mutations in the pathogenesis of the disease. Therefore, until more is known about the underlying molecular mechanisms, we propose continuation of the numeric classification for novel OI forms.

ACKNOWLEDGMENTS

We thank Guy Charette for technical assistance with biopsy sample processing; Alessandra Duncan for the karyotype analyses; Mark Lepik and Guylaine Bédard for the figures and photography; Josée Dépôt, Anna Lis, and Mireille Dussault for the biochemical analyses; and Radomir Lalic for the heteroduplex analyses. This study was supported by the Shriners of North America.

REFERENCES


Address reprint requests to:
Francis H. Glorieux
Genetics Unit
Shriners Hospital for Children
1529 Cedar Avenue
Montréal, Québec, Canada H3G 1A6

Received in original form December 27, 2000; in revised form June 29, 2001; accepted August 2, 2001.