Osteogenesis Imperfecta
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Abstract
Background: Osteogenesis imperfecta (OI) is a rare metabolic bone disorder characterized by increased bone fragility, low bone mass, recurrent fractures and numerous extra-osseus features. Many patients remain undiagnosed and unattended particularly in developed countries. Presently, medical management with bisphosphonates has changed the scenario.

Materials and Methods: Twenty consecutive patients of OI were enrolled over a period of four years. Their clinical features, radiology, and biochemical parameters and treatment outcome were analysed.

Results: Of the 20 patients, 16 (80%) were male and 4 (20%) were female. Mean age (SD) of the patients was 20.8 (13.8) years. All the patients had presented with fractures, the number of fractures per person varying from 1 to 20. Long bones were predominantly involved and thirteen (65%) had deformities of long bones. Ten (50%) had a positive family history of fractures after trivial trauma. Eleven (55%) patients had dentinogenesis imperfecta (DI) and ten (50%) had blue sclerae at presentation. Impaired hearing was present in 1 patient only. Calcium profile was normal. Nine patients received pamidronate. Fracture frequency and pain decreased remarkably in these patients.

Conclusion: Patients with OI presented late, predominantly with fracture of long bones, deformities and blue sclerae. Pamidronate therapy remarkably decreased fractures and pain in these patients. ©

INTRODUCTION
Osteogenesis imperfecta (OI) is a genetic disorder characterized by increased bone fragility and low bone mass. The patients have recurrent pathological fractures, which vary in number and severity depending on the type of OI. (Expanded Sillence’s classification).1 It is also associated with numerous extraosseus features like blue sclerae, dentinogenesis imperfecta (DI), hyperlaxity of skin and ligaments, hearing impairment and presence of wormian bones in the skull.

Most patients have mutation in one of the two genes encoding alpha chains of collagen type 1 (COL1A1 AND COL1A2). Type I collagen fibers are found in the bones, organ capsules, fascia, cornea, sclera, tendons, meninges, and dermis. Type I collagen, which constitutes approximately 30% of the human body by weight, is the defective protein in OI.

The traditional management of OI has been physiotherapy, orthosis, orthopedic surgery and rehabilitation. Presently medical management in the form of bisphosphonates are also in offer to the patients, though their overall efficacy is still in question. Other treatments include growth hormone, parathormone, bone marrow transplantation and gene based therapy.1

We report a clinical profile of 20 cases of Osteogenesis Imperfecta from a single centre in North India.

PATIENTS AND METHODS
Data from 20 consecutive patients of osteogenesis imperfecta who have attended the Endocrinology department of the Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh from January 2003 to June 2007 were analyzed. Osteogenesis Imperfecta was diagnosed and classified using the modified Sillence’s classification. Their demographic details, clinical features, biochemical and radiological abnormalities were noted and analyzed.

For each patient blood samples were collected for three consecutive days after an 8-hour fast to estimate serum calcium, inorganic phosphorus, serum alkaline phosphatase, albumin and creatinine. Reference ranges for serum calcium, inorganic phosphorus, serum albumin and creatinine were 9-11mg/dl, 3-5 mg/dl, 3-5 gram/dl respectively). Calcium values were corrected for respective serum albumin level. Parathormone (iPTH) was measured by immunochemiluminiscence assay (ICMA) (reference range: 10-69 pg/ml). Serum 25(OH)D was estimated by radioimmunoassay (RIA) (reference range 9-37 ng/ml) (Diasorin, Stillwater, Minnesota, U.S.A.).
In addition, skeletal survey (radiograph of hands, skull and lumbar spine including pelvis) and 99mTc MDP whole body bone scan was performed in all. All patients underwent a pure tone audiometry testing in the Rhinootolaryngology department of our institution. All patients were also evaluated by a single dental surgeon for dentigenious imperfecta.

Patients with more than one fracture in the last one year at the time of presentation were offered pamidronate therapy. Nine patients received pamidronate according to protocol (<2 years of age, 0.5 mg/kg/d for three days; 2 to 3 years, 0.75 mg/kg/d for 3 days and greater than 3 years, 1 mg/kg/d for three days). Calcium profile was repeated for three consecutive days after therapy. Side effects if any were noted. The same protocol was repeated after 3 months and continued till there was a fracture free period of 1 year.

In all patients who received treatment, clinical features were reviewed, and biochemistry and radiology were repeated after 3 months to look for healing of fractures.

**Table 1 : Demography, clinical presentation and response to pamidronate**

<table>
<thead>
<tr>
<th>Serial number</th>
<th>Patient number</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Total number of fractures</th>
<th>Predominant site of fracture</th>
<th>Number of fractures / year before treatment</th>
<th>Number of fractures / year after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>12</td>
<td>M</td>
<td>6</td>
<td>Left femur</td>
<td>0.6</td>
<td>Not yet f/u</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>2.5</td>
<td>M</td>
<td>8</td>
<td>Long bones</td>
<td>3.2</td>
<td>0.5(f/u 2y)</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>5.5</td>
<td>F</td>
<td>4</td>
<td>Long bones</td>
<td>0.7</td>
<td>0 (f/u 1.5y)</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>9</td>
<td>M</td>
<td>4</td>
<td>Long bones</td>
<td>4.5</td>
<td>0 (f/u 2.5y)</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>32</td>
<td>M</td>
<td>1</td>
<td>Left Femur</td>
<td>0.125</td>
<td>0 (f/u 2y)</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>6</td>
<td>M</td>
<td>1</td>
<td>Right humerus</td>
<td>0.167</td>
<td>0 (f/u 2y)</td>
</tr>
<tr>
<td>7</td>
<td>11</td>
<td>10</td>
<td>M</td>
<td>6</td>
<td>Long bones</td>
<td>0.6</td>
<td>0 (f/u 1y)</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>21</td>
<td>M</td>
<td>20</td>
<td>Vertebral, Long bones</td>
<td>1</td>
<td>0 (f/u 1y)</td>
</tr>
<tr>
<td>9</td>
<td>16</td>
<td>22</td>
<td>F</td>
<td>7</td>
<td>Long bones</td>
<td>0.39</td>
<td>0 (f/u 2y)</td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>13.33</td>
<td>6.33</td>
<td></td>
<td></td>
<td></td>
<td>1.25</td>
<td>0.125</td>
</tr>
</tbody>
</table>

Pamidronate lines were observed in few patients.4 The mean values (SD) for calcium (corrected for serum albumin), phosphate, 25(OH) Vitamin D, and parathormone were 9.10 (0.32) mg/dl, 4.21(0.07) mg/dl, 24.2(17) ng/dl and 58.53(50) pg/ml respectively. All the patients had normal calcium and phosphate values. One patient had severe Vitamin D deficiency (5 ng/ml) as per the Lips’ classification.3 His corresponding PTH value was 116 pg/ml.

Nine (45%) patients received pamidronate according to the protocol mentioned. The mean number of fractures / year (SE) decreased from 1.25 (0.51) to 0.125 (0.125). (p =0.05). Side effects were noted in two patients. One developed fever for two days and the other had hypocalcemia on the second day after receiving pamidronate (corrected calcium 8.2 mg/dl), however he did not develop clinical features of the same.

All patients reported considerable relief in pain. Of the bones were predominantly involved, particularly of the lower limb. Out of the 133 fractures recorded, femoral fractures constituted the majority, followed by the tibiae. One patient had 20 fractures by the time of presentation; all of them involved either of the two femorii. One patient had fractures of the lumbar vertebrae, besides fractures of the femur (20 fractures in all). The time taken for the fractures to heal was normal in all cases. Ten (50%) patients had a positive family history of fractures following trivial trauma. Four of our patients belonged to the same family. Thirteen (65%) patients had deformities (Fig.1), 4 (20%) had multiple (more than or equal to 2) deformities.

Dentigenious imperfecta (DI) (Fig. 2) was noted in 11 (55%) of the patients. Two of the four patients who were less than nine years of age had DI in their temporary teeth. Ten (50%) had blue sclerae (Fig. 3) at presentation. Joint hyperextensibility was noted in 4 (20%) patients. Pure tone audiometry revealed impaired hearing (sensorineural) in one (5%) patient only. No patient had abnormal bruisability and abnormal scarring.

Radiology confirmed the sites of present fractures in all. Extensive callus formation at the site of previous fractures was noted in 3 (15%) patients. Wormian bones in the skull were noted in 3 (15%) patients. One patient had rhizomelia. Pamidronate lines were observed in few patients.4

**RESULTS**

All patients hailed from the neighbouring north Indian states of Punjab, Haryana, Himachal Pradesh, Jammu and Kashmir, Uttar Pradesh or Rajasthan. Of the 20 patients, 16 (80%) were male and 4 (20%) were female. Mean age (SD) was 20.8 (13.8) years.

Short stature in children was defined as height below the 3rd percentile of the CDC (Centre for Disease Control and Prevention) growth charts.2 Short stature in adults was defined as 10 cm below the target height calculated from the mid-parental height. Nine (45%) patients had short stature by definition.

All (100%) patients presented with fractures, the number of fractures varying from 1 to 20. Mean (SD) number of fractures by the time of presentation was 6.8 (4.51). Long
9 patients who had received pamidronate, 8 have followed up for more than one year. Only one of them had a fracture (fracture shaft of humerus) after the therapy. In one patient, who had no eruption of permanent teeth, the same appeared after pamidronate therapy. The same patient also had corrective surgery for deformities of the lower limbs and had not sustained any fractures after treatment.

**DISCUSSION**

The present study has twenty patients of a rare metabolic bone disease from a single centre in North India. Many of the patients were diagnosed in early adulthood. Nine of them received pamidronate and responded favorably.

The mean age of our patients was 20.8 (13.8 years). This is higher than the mean ages noted in most of the studies. The reasons for this could probably be due to low index of suspicion of the disease in early childhood for the milder types of OI (types I, IV, V, VI and VII). Another reason could be referral bias as our department caters predominantly to adult endocrinology. No sex predilection has been noted in previous studies. We had only 4 females in our series. This could be due to the low number of patients and also probably due to social stigmata attached to deformities in our country.

Patients with OI most commonly present with pathological fractures. However, these fractures heal readily, with exuberant callus formation in some variants of OI. The number of fractures varies according to the severity of disease. Most patients with OI seen clinically are of type III, where the number of fractures may vary from one to multiple. On the contrary, mild forms (type 1) may present with no fractures. In severe cases, fractures may be present in utero, and prenatal screening sonography performed during second trimester may show bowing of long bones, fractures, limb shortening, and decreased skull echogenicity. In a compilation of case reviews by Albright JA, the maximum number of fractures noted was 61 in a 12 year old person. In our study, number of fractures varied between 1 to 20.

Dentiginous imperfecta (DI) may or may not be present in all types of OI. DI was noted in 11 (55%) of our patients. Hearing abnormalities are common especially in type I and most patients have some degree of hearing loss by the age of 40. In our study however deafness was found only in one patient. This could probably be due to the low number of patients and also lower mean age of the patients at presentation. Blue sclerae occur in OI due to defective collagen in sclerae. It was seen in 10 (50%) patients.

Calcium profile is within the normal limits in OI, unless complicated by fractures or other diseases like concurrent vitamin D deficiency. The same trend was observed in our study.

There are several specific radiological features reported in OI. They include wormian bones, beaded ribs, broad bones, numerous fractures with deformities of the long bones, platyspondylia, cystic metaphyses, popcorn appearance of the growth cartilage, rib fractures, vertebral fractures, and extensive callus formation. Wormian bones were found in three of our patients, deformities in 13, and extensive callus formation in 3.

The main stays of treatment of OI remain physiotherapy, orthosis, orthopedic surgery and rehabilitation. Presently medical management in the form of bisphosphonates is also in offer to the patients, though their overall efficacy is still in question. The other treatments being investigated are parathyroid hormone, bone marrow transplantation and growth hormone.

Bisphosphonates represent a class of drugs that are potent inhibitors of bone resorption and are widely used to treat children and adults with osteogenesis imperfecta. Bisphosphonates tried clinically in the treatment of OI are pamidronate, zoledronate, neridronate and olpadronate. They have shown to reduce both bone pains and fractures. This has been attributed to decrease in the bone resorption and increase in the cortical width, however there is no effect on collagen. In the present study, bone pain decreased and the number of fractures per year in every patient also significantly reduced after pamidronate therapy. Acute side effects include nausea, vomiting, diarrhea, flushing, pyrexia and hypocalcemia, as was seen.
in one of our patients who had fever and hypocalcemia.

In conclusion, patients with OI were diagnosed late, predominantly with fracture of long bones, deformities and blue sclerae. Pamidronate therapy remarkably decreased fractures in these patients. We need to have a high index of suspicion to diagnose these patients. Timely intervention can prevent deformity and crippling.

**REFERENCES**