Hypophosphataemic rickets/osteomalacia: A descriptive analysis

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Background & objectives: Hypophosphataemic rickets/osteomalacia (HRO) is an uncommon metabolic bone disorder which affects all ages and either sex. It is characterized by low concentration of serum phosphate levels leading to impairment of mineralization of bone matrix with variable aetiology. We present clinical profile and treatment outcome of 17 patients of HRO.

Methods: Seventeen consecutive patients (8 were < 18 yr of age, with median age of presentation being 27.5 yr) of HRO who came to the department of Endocrinology in a tertiary care hospital in north India from January 2000 to December 2006 were included in the present study. Their aetiology, clinical features, biochemical parameters, radiographic features, treatment and outcome were analyzed.

Results: HRO was commoner in females (70.5%) with positive family history observed in 6 (35.3%) patients. Common presenting features were short stature (58.8%), backache (58.8%), bony deformities (58.8%), joint pain (52.9%), fractures (29.4%) and dental abnormalities (23.5%). Radiological abnormalities noted were generalized bony deformities (58.8%), fractures (29.4%), and pseudo fractures (17.6%). Mesenchymal tumours were localized in the pelvis in one patient and in the right jaw in another. The patients were treated with calcium (elemental calcium 1 g/d) and oral phosphate supplements (dose 30 – 50mg/kg/day in divided doses) along with active vitamin D supplements (dose 1- 3 µg/day) and followed up for a mean of 2 yr. Two patients also received growth hormone (GH) therapy in the dose of 2U/day for 6 and 18 months respectively. Symptomatic well being was reported by all the patients and improvement was noted in the levels of phosphate (P<0.005) and alkaline phosphatase (P<0.05) after treatment.

Interpretation & Conclusions: A diagnosis of HRO should be considered in all patients presenting with short stature, deformities or musculoskeletal pains along with low serum phosphate with normal iPTH and 25 – hydroxy vitamin D.

Key words HRO - hypophosphataemia - tumour induced osteomalacia

Hypophosphataemic rickets/osteomalacia (HRO) is a rare disorder of phosphate metabolism characterized by low serum phosphate levels leading to impaired mineralization of bone matrix. Young patients present with disproportionate short stature and classical features of rickets whereas adults present with bone pains, proximal myopathy and enthesopathy. Biochemical abnormalities include hypophosphataemia, normal or low serum calcium, normal or high normal alkaline phosphatase, low or inappropriately normal serum 1, 25 dihydroxy vitamin D, normal serum intact parathormone (iPTH) concentration and low maximum tubular reabsorptive capacity for phosphorusglomerular filtration rate (TmP/GFR).
Prototype disorders are X linked hypophosphataemic rickets/osteomalacia (XLH), autosomal dominant hypophosphataemic rickets/osteomalacia (ADHR) and tumour induced hypophosphataemic rickets/osteomalacia (TIO). These and other disorders leading to HRO such as fibrous dysplasia (FD) are associated with increased secretion of phosphaturic substances called ‘phosphatonins’ which cause proximal tubular leak of phosphate resulting in hypophosphataemia. Identified phosphatonins include fibroblast growth factor – 23 (FGF -23), secreted frizzled protein 4 and matrix extracellular phosphoglycoprotein (MEPE) as well as non collagenous matrix proteins called SIBLINGS. Mainstay of therapy includes oral phosphate with active vitamin D and surgical excision of offending focus in cases of TIO. Recombinant growth hormone (GH) therapy has been used in isolated case series and has been reported to be beneficial.

Literature regarding this entity is scarce, mainly in the form of case reports and only a few case series, and to our knowledge no data exist from India. We here describe clinical features, biochemical abnormalities, radiographic features and the outcome of treatment in 17 patients of HRO from a tertiary care hospital from north India.

Material & Methods

Seventeen consecutive patients of HRO who presented to the department of Endocrinology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, from January 2000 to December 2006 were included in this retrospective analysis. Written informed consent was obtained from all the patients. A diagnosis of HRO was made on the basis of clinical and radiological findings of rickets/osteomalacia in a patient with low level of serum phosphate, normal or low normal level of serum total calcium and normal levels of vitamin D and intact parathyroid hormone (iPTH) (or mildly elevated) with normal or high normal serum alkaline phosphatase and low TmP/GFR (calculated as per standard nomogram) values.

Short stature in children was defined as height below the 3rd percentile of the mean height of the age and sex matched child as per the World health Organization (WHO) growth charts, whereas in adults it was defined as 10 cm below the target height calculated from the mid-parental height. Clinical examination was performed to look for any deformities and dental examination was done by a dental surgeon.

For each patient blood samples were collected for three consecutive days after an 8 h overnight fast to estimate serum total calcium, inorganic phosphorus, serum alkaline phosphatase, albumin and creatinine. Reference ranges for serum total calcium, inorganic phosphorus, alkaline phosphatase, albumin and TmP/GFR were 8.5 -10.2 mg/dl, 2.8 - 4.5 mg/dl, 3-13 King Armstrong Units/l, 3.5-5 g/dl and 2.5 -4 mg/dl respectively. Calcium values were corrected for respective serum albumin level. Patients were divided into two age groups : <18 and >18 yr to account for age related variation in values of serum inorganic phosphorus and alkaline phosphatase. Intact parathormone (iPTH) was measured by immunochemiluminiscence assay (ICMA) (reference range: 10-69 pg/ml). Serum 25 – hydroxy vitamin D was estimated by radioimmunoassay (RIA) (reference range 9-37 ng/ml) (both supplied by Diasorin, Stillwater, Minnesota, USA). In addition, skeletal survey (radiograph of limbs, hands, skull and lumbar spine including pelvis) was performed. CT/ MRI of the pelvis and the jaw region were performed to look for any mesenchymal tumour causing TIO in 9 adult patients.

All the patients were treated with oral calcium (elemental calcium 1 g/day) and phosphate supplements (prepared by mixing sodium dihydrogen phosphate and disodium hydrogen phosphate in the ratio of 1:3 in a dose of 30 – 50mg/kg/day given in 4-5 divided doses) along with 1, 25 hydroxy vitamin D (dose 0.25 – 1 µg/day). Mean (± SD) follow up was 2 ± 0.56 yr. Two patients received GH therapy in the dose of 2U/day for 6 and 18 months respectively. One of these had severe hypophosphataemia (serum phosphate level of 1.1 mg/dl) at presentation with severe musculoskeletal symptoms while other patient had concomitant short stature.

Statistical analysis: The Statistical Program for the Social Sciences (Release 10.01, PC Windows; SPSS Inc., Chicago IL) was used for the data analysis. Values were expressed as mean ± SD, until otherwise specified. Baseline and post-treatment data were compared using paired t test. P<0.05 was regarded statistically significant and was calculated two – tailed.

Results

Median age of these patients at presentation was 27.5 (range 5.5 - 58) yr, with female to male ratio being 2.4:1. Nine patients were <18 yr. Aetiologically, 6 patients had familial HRO demonstrating autosomal dominant/X-linked dominant inheritance pattern,
2 patients had TIO and only one of them underwent surgery, whereas one had fibrous dysplasia. Remaining eight patients were classified as having sporadic HRO as no identifiable cause or inheritance was demonstrated in them.

Most common clinical features at presentation were short stature, backache and bony deformities each in 10 (58.82%) patients, crippling deformities in five (29.4%); followed by joint pain in 9 (52.94%), fractures in 5 (29.4%) and dental abnormalities (tooth loss, dental abscess) in 4 (23.5%) (Fig. 1).

Baseline serum concentrations of total calcium, phosphate, alkaline phosphatase, 25, hydroxy vitamin D, iPTH were 9.7±0.7 mg/dl, 2.4±0.6 mg/dl, 23.4±12.2 KAU/l, 30.6 ± 15.9 ng/ml, 69.68±36 pg/ml respectively and TmP/GFR was 2.17±0.5 mg/dl. On subgroup analysis as per the age group (<and >18 yr) the serum phosphate (mg/dl) and alkaline phosphatase (KAU/l) 29.3±14.5 were 2.6±0.4 and 2.3±0.8; and 17.5 ± 6.9, respectively.

Radiologically bony deformities were seen in 10 (58.82%) patients which included genu varum in 9, genu valgum in 2, wind swept deformity in 1, bilateral coxa vara in 1, protrusio acetabulae in 1, fractures in 5, pseudofractures in 3, and lytic bone lesions with osteosclerotic margin over acetabular roof in 1 patient (Fig. 2). Mesenchymal tumours were localized in the pelvis by MRI in one and in the right jaw by CT in another patient, whereas one had polyostotic fibrous dysplasia involving the ends of long bones and pelvis in addition to other features of HRO and no features of any other endocrinopathy.

Post treatment, symptomatic improvement was reported by all the patients and was noted relatively earlier in GH treated patients (3 months) as compared to those who did not receive GH therapy (6-12 months). However, in one patient spontaneous improvement was noted 1 yr after stopping the GH therapy. Biochemically, significant changes were seen in the serum concentrations of phosphate (3.5 ± 0.8 mg/ dl; \( P<0.005 \)) and alkaline phosphatase (20.2 ± 10.6 KAU/l; \( P <0.05 \)) whereas those of total calcium (9. 7 ± 0.8 mg/dl) did not vary significantly, after therapy. No treatment related adverse events like development of hyperparathyroidism, nephrocalcinosis and episodes of hypercalcaemia were observed. Resection of pelvic mesenchymal tumour was done in one patient with TIO and showed features of hemangiopericytoma (Figs 3, 4). The patient showed a good response post-operatively with marked improvement in symptoms, normalization of serum phosphate levels and TmP/GFR. Other patient with TIO, however, refused surgery.
Discussion

This study showed that HRO had a variable age of presentation and multifactorial aetiology including sporadic (47.1%), familial (35.3%), TIO related (11.8%) and secondary to fibrous dysplasia (5.8%). Conventional treatment led to symptomatic improvement in all the patients along with biochemical improvement and addition of GH therapy led to an earlier response.

Most of the information in the literature comes from isolated case reports and occasional case series\textsuperscript{4,10} (Table). Patients in our series were significantly older than described by others (median age 27.5 yr vs 6 & 7 yr\textsuperscript{4,10} with a greater lag time at diagnosis from the onset of the symptoms (17.5 vs 4.5 yr)\textsuperscript{4}. This can be attributed to the lack of awareness to the approach of this entity among the internists and frequent neglect of health related matters by the ailing individuals. Other than that, most of these patients are treated with cholecalciferol and calcium supplementation for variable period of time without much clinical response.

In our series the disease was seen to affect mostly the females which was similar as reported by others\textsuperscript{4,10} Most common presenting feature in our series were short stature, backache, joint pain and bony deformities similar to earlier reports\textsuperscript{2-4}. A positive family history suggestive of X-linked hypophosphataemic rickets/osteomalacia (XLH), autosomal dominant hypophosphataemic rickets/osteomalacia (ADHR) was noted in one third of our patients as also variably described in the literature\textsuperscript{4,5}. Dental abnormalities\textsuperscript{17} and McCune Albright syndrome\textsuperscript{18} have also been described by others.

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<th>Parameters</th>
<th>Present study</th>
<th>Vaisbich et al\textsuperscript{4}</th>
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<td>ALP, alkaline phosphatase; iPTH, intact parathyroid hormone; Tmp/ GFR, tubular reabsorptive capacity for phosphorus/glomerular filtration rate; TIO, tumour induced hypophosphatemic rickets/osteomalacia</td>
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Fig 3. Microphotograph showing vascular channels with plump endothelial cells and oval to spindle shaped cells in the stroma (H & E, X540).

Fig 4. Microphotograph showing lesion rich in reticulin with rich capillary network (Reticulin stain, X280).

Table. Comparison of various series of HRO
Intact PTH and 25(OH) D levels are usually normal in untreated patients, however with treatment iPTH increases. More than half of patients in our series had increased iPTH levels. This was possibly related to oral phosphate supplementation prior to presentation in our institute. Other reason for increased iPTH in these patients may be related to evolution of tertiary HPT during follow up. Elevated FGF-23 in the presence of hypophosphataemia is a marker for TIO; however, we could not do the same in our patients.

Phosphatonin secretory tumour are often small, occult and benign in nature and hence difficult to localize. The reported lag time between symptoms and localization of these tumours varies from 5 months to 16 yr. In our study, the tumour was localized by MRI (pelvis) in one and by CT scan (faciomaxillary) in another patient. It took more than 4 yr to localize the mesenchymal tumour responsible for tumour induced osteomalacia in one patient, whereas in an earlier study the mesenchymal tumour in the left scapula was localized relatively earlier by using whole body F-18 FDG PET/CT scan. However, due to retrospective nature of this analysis, lack of availability of PET or octreotide scan at our institute and significant cost outside, these test were not carried out in our patients. This is one of the limitations of our study and may be a possible cause of relative low prevalence of TIO in our study.

Conventional treatment is the combined use of biologically active vitamin D (1, 25 dihydroxy vitamin D₃) (1-3 µg/day) along with high doses of inorganic oral phosphate salts (30-50 mg/kg) in divided doses. Improvement in the serum phosphate concentration results in healing of rickets; however, it may not always translate into increase in linear growth. Inspite of optimal phosphate and calcitriol supplementation, normalization of serum phosphate is difficult to achieve and this was also observed in our study. Early institution of therapy also leads to better height outcome, hence probably diagnosis at a late age also contributed to poor height gain in our patients. Recombinant GH therapy has shown to increase serum phosphate levels, growth velocity and improvement in final height, but a recent Cochrane database review did not find it to be so useful.

In conclusion, HRO has varying age of presentation with vivid presenting manifestations. It should be differentiated from rickets/osteomalacia of other aetiologies as their treatment differs. TIO should be diligently looked for in every patient with HRO, particularly in adults, since its treatment is more rewarding. Family members of HRO patients should undergo routine screening due to its inherited varieties.

Conflict of Interest: None

References


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