CASE REPORT

Hepatic osteodystrophy with hypophosphataemia and elevated fibroblast growth factor-23

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Case Report

A 14-year-old boy with a history of end stage liver disease (ESLD) from autoimmune hepatitis associated with sclerosing cholangitis (AISC) presented with acute onset atraumatic severe lower back pain. His AISC had been difficult to control, and he had been on azathioprine and chronic low dose prednisolone (5 mg) daily at presentation. There was no weakness, sensory changes, bowel or bladder dysfunction, or constitutional upset. On examination, he was jaundiced with clinical evidence of portal hypertension, and was prepubertal with testicular size of 3 cm³ bilaterally. There was mild genu varum and prominence of costochondral junction, but no wrist flaring. His weight and height were significantly below the third percentile for age.

An urgent thoraco-lumbar spinal x-ray showed severe vertebral osteopenia with compression fractures at multiple vertebral levels (Fig. 1). Biochemical evaluation showed 25-hydroxy-vitamin-D3 deficiency but normal levels of serum calcium, phosphate and alkaline phosphatase (ALP) levels (Table 1). The patient’s liver function tests showed cholestasis, transaminitis, hypoalbuminemia and mild coagulopathy, reflective of the underlying ESLD state. A bone mineral density (BMD) scan showed significantly decreased BMD with Z-scores (adjusted for age) –4.9 SD (lumbar vertebrae), –5.5 SD (hip) and –6.6 SD (total body), respectively, though these scores may be lower than the true BMD Z-scores due to the lack of height adjustment. As the patient had been on chronic glucocorticoid therapy for the past 8 years for AISC control, the low BMD and fractures were thought to be contributed by chronic steroid use on a background of vitamin D deficiency. The patient was initiated on high dose cholecalciferol with calcium carbonate supplementation and counselled on bisphosphonate therapy.

After 2 months, he was found to have new-onset hypophosphataemia with normal adjusted calcium and normal serum parathyroid hormone (PTH) levels. Urine phosphate studies done showed a tubular maximum reabsorption of phosphate (TmP) to glomerular filtration rate (GFR) ratio of 0.81 (normal 1.29–1.94), indicating significant renal phosphate wasting. Creatinine was normal at 22 μmol/L, with corresponding eGFR of 217 mL/min/1.73 m². Further evaluation was not suggestive of renal Fanconi syndrome.

Key points

1 Hepatic osteodystrophy (HOD) is a heterogeneous condition with multifactorial aetiology. In this case, chronic glucocorticoid exposure, delayed puberty and possibly fibroblast growth factor-23 (FGF23)-induced hypophosphataemia were contributing factors to the HOD.

2 FGF23-mediated HOD appears to be fully reversible with liver transplantation.

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Fig. 1 Plain radiographs (anteroposterior and lateral) of the thoracolumbar spine, showing general osteopenia, loss of height of the thoracic (T10-T12) and lumbar vertebrae (L1-L3), with significant anterior wedging of T12 and L1 consistent with compression fractures. There is also kyphosis of the thoracolumbar spine.
Table 1  Serum biochemistry of the patient at presentation and subsequent follow-up, until eventual liver transplantation

| Serum biochemistry | 14 months before presentation | Presentation with vertebral fractures | 2 months post-presentation | 4 months post-presentation | 5 months post-presentation | 8 months post-presentation (prior to LT) | 10 months post-presentation (2 months post-LT) | 12 months post-presentation (4 months post-LT) |
|--------------------|-------------------------------|--------------------------------------|---------------------------|---------------------------|---------------------------|-----------------------------------------|-------------------------------------------|-----------------------------------------------|
| Total calcium (mmol/L) | 2.27                          | 2.29                                 | 1.88                      | 1.95                      | 1.99                      | 1.94                                    | 2.13                                      | 2.04                                          |
| NR: 2.15–2.55 |                                |                                      |                           |                           |                           |                                         |                                          |                                               |
| Adjusted calcium (mmol/L)† | 2.45                          | 2.48                                 | 2.27                      | 2.30                      | 2.28                      | 2.27                                    | 2.48                                      | 2.33                                          |
| Phosphate (mmol/L) | 1.07                          | 1.31                                 | 0.83                      | 0.89                      | 0.93                      | 0.92                                    | 1.30                                      | 1.27                                          |
| NR: 1.05–2.10 |                                |                                      |                           |                           |                           |                                         |                                          |                                               |
| 25-hydroxy-vitamin D3 (pg/mL) | 44.7                          | 12.9                                 | 14.9                      | 15.0                      | 9.3                       | 50.8                                    | 59.8                                      | 58.4                                          |
| NR: 30–100 (sufficient) |                                |                                      |                           |                           |                           |                                         |                                          |                                               |
| 1,25-dihydroxy vitamin D3 (pg/mL) | ‐                            | ‐                                    | ‐                         | ‐                         | ‐                         | ‐                                       | ‐                                         | ‐                                             |
| Alkaline phosphatase, ALP (IU/L) | 383                          | 344                                 | 359                      | 351                      | 371                      | 304                                    | 648                                      | 846 (likely from biliary pathology)          |
| NR: 24–86 |                                |                                      |                           |                           |                           |                                         |                                          |                                               |
| Parathyroid hormone (pmol/L) | ‐                            | ‐                                    | 2.3                      | 3.3                      | 2.7                       | ‐                                       | 4.7                                      | ‐                                             |
| NR: 1.3–9.3 |                                |                                      |                           |                           |                           |                                         |                                          |                                               |
| Serum FGF23 (RU/mL) | ‐                            | ‐                                    | ‐                         | ‐                         | 840                      | 620                                    | 195                                      | 143 (while on phosphate 4 mmol/kg/day)       |
| NR: <230 |                                |                                      |                           |                           |                           |                                         |                                          |                                               |
| Urine phosphate (mmol/L) | 8.3                           | 9.4                                  |                           |                           |                           | 12.5                                    |                                          |                                               |
| TmP/GFR ratio | 0.81                          | 0.71                                 |                           |                           |                           | 0.78                                    |                                          |                                               |
| New treatment changes initiated in response to clinical and biochemical status above | Continue cholecalciferol 100 000 units daily | Phosphate 0.8 mmol/kg/day Cholecalciferol 200 units daily | Phosphate 2.5 mmol/kg/day Calcitriol 0.25 mcg 4×/per day Cholecalciferol 4000 units daily | Phosphate 3.2 mmol/kg/day Calcitriol 0.25 mcg 4×/per day IM Vitamin D3 100 000 units for 2 days Cholecalciferol 4000 units twice daily Calcium carbonate 1.25 g twice daily Started on IV zoledronic acid 0.02 mg/kg 6 monthly | Phosphate 4.5 mmol/kg/day Calcitriol 0.25 mcg 4×/per day Ergocalciferol 50 000 units weekly × 8 weeks Calcium carbonate 2.5 g thrice daily IV zoledronic acid 0.02 mg/kg 6 monthly | Gradual wean of phosphate over 2 months Calcitriol 0.25 mcg daily Cholecalciferol 2000 units daily Calcium carbonate 625 mg 3×/per day IV zoledronic acid 0.02 mg/kg 6 monthly | Phosphate supplementation discontinued Ergocalciferol 50 000 units weekly × 8 weeks Calcium carbonate 2.5 g thrice daily IV zoledronic acid 0.02 mg/kg 6 monthly | Phosphate supplementation discontinued Ergocalciferol 50 000 units weekly × 8 weeks Calcium carbonate 2.5 g thrice daily IV zoledronic acid 0.02 mg/kg 6 monthly | Phosphate supplementation discontinued Ergocalciferol 50 000 units weekly × 8 weeks Calcium carbonate 2.5 g thrice daily IV zoledronic acid 0.02 mg/kg 6 monthly | Phosphate supplementation discontinued Ergocalciferol 50 000 units weekly × 8 weeks Calcium carbonate 2.5 g thrice daily IV zoledronic acid 0.02 mg/kg 6 monthly |

NR, normal range, LT, liver transplantation. †Phosphate supplementation was given as Phosphate Sandoz tablets. For daily doses between 2 and 3 mmol/kg/day, the dose was divided into four doses per day. Doses beyond 3 mmol/kg/day were split into five doses throughout the day. †Adjusted for serum albumin.
The patient was commenced on high doses of phosphate supplementation on top of ongoing vitamin D supplementation. Despite increasing doses of phosphate and calcitriol supplementation, there was ongoing hypophosphataemia and hyperphosphaturia. This was concerning for excessive circulating fibroblast growth factor-23 (FGF23) levels. Serum FGF23, measured using the immunometric enzyme assay (Mayo Clinic Laboratories) had returned significantly elevated at 840 (normal < 230) RU/mL. This was despite the hypophosphataemia and hyperphosphaturia, which in a homeostatic state would lead to suppression of FGF23. The patient was evaluated for possible tumour-induced osteomalacia as a cause for the high FGF23 levels. He underwent a Ga68-DOTANOC PET-CT, which did not show any abnormal uptake. Considering the overall clinical picture, the team postulated that this high FGF23 may have been related to the cholestatic liver disease, where there is overexpression of FGF23 from the diseased liver, a phenomenon which has previously been reported in children.1

The patient was maintained on high doses of calcium, phosphate, vitamin D supplementations and received a trial of cyclical intravenous zolendronic acid. Despite compliance to supra-physiological doses of phosphate replacement, phosphate levels remained suboptimal. The patient eventually underwent a successful living-related liver transplant. Two months post-transplant, serum FGF23 levels returned to normal range while on phosphate supplementation, which was subsequently weaned off gradually. His bone health had marginally improved with cyclical zolendronic acid post-transplantation, where repeat BMD 15 months post-transplantation showed gradual improvement of age-adjusted Z-scores: –4.3 SD (lumbar spine), –4.7 SD (hip) and –5.2 SD (total body), respectively, despite his prepubertal state and use of higher doses of glucocorticoids, which were used as part of his immunosuppressive regimen.

Discussion

Hepatic osteodystrophy (HOD) is a prevalent complication affecting 60% of patients with CLD, particularly those with cholestasis.2 The mechanism of HOD was previously attributed to defective 25-hydroxylation, intestinal malabsorption and altered enterohepatic circulation of vitamin D. Over time, the complex pathogenesis of HOD has been increasingly uncovered, including the inhibitory effects of osteoblast proliferation by hyperbilirubinemia, decreased insulin-like growth factor-1 leading to reduced osteoblast stimulation, and cytokine–bone interactions disrupting osteoclastogenesis through the RANK-ligand-osteoprotegerin pathway.3 Our patient had additional risk factors that worsened his HOD, including delayed puberty and prolonged glucocorticoid exposure, which had led to vertebral fractures. In addition, in the year leading up to his liver transplantation, he developed hypophosphataemia and hyperphosphaturia which we believe may be explained by excessive FGF23 levels from the liver, particularly given the rapid resolution post-liver transplantation.

FGF23 is a key regulator of phosphate homeostasis. It acts at the proximal tubules to drive phosphate excretion and also directly inhibits 1-alpha-hydroxylase, thereby reducing production of 1,25-dihydroxyvitamin-D3.4 Excessive FGF23 production may result from hereditary or acquired causes. The complete resolution post-liver transplantation and absence of a positive family history made an inherited cause less likely in our patient, though sporadic mutations are not uncommon in certain inherited forms of hypophosphataemic rickets. Acquired FGF23-induced hypophosphataemia is most commonly associated with TIO, a paraneoplastic phenomenon caused by benign mesenchymal tumours.5 These tumours may occur in any bone and other tissues, often making localisation challenging. Functional radioisotope-guided imaging has improved this process, and was used in our patient to exclude TIO.

Evaluation of serum FGF23 levels should ideally be done prior to initiation of phosphate replacement therapy, which in itself can drive FGF23. That said, in our case, the spontaneous normalisation of serum FGF23 post-liver transplantation while still on high dose phosphate supplementation is supportive of our hypothesis of hepatic overexpression of FGF23 as a driver of the hypophosphataemia. High circulating FGF23 levels have previously been described in a case series of two infants with biliary atresia. There has been no reports of this in AISC or other childhood CLDs, but the same phenomenon has been described in adult patients with non-alcoholic fatty liver disease.6 In all these cases, ectopic overexpression of FGF23 from hepatocytes was demonstrated. Similar to our case, the infants in the biliary atresia case series also required high doses of phosphate and calcitriol replacement, with normalisation of phosphate levels post-transplantation.1 In an adult cohort with ESLD, elevated FGF23 levels were found in 63% of patients. Most significantly, this study found a strong correlation between FGF23 levels and mortality.7 The pathogenesis behind hepatic FGF23 overexpression in CLD remains poorly understood. Interestingly, a study showed an independent association between elevated hepatic-produced FGF23 with higher serum inflammatory cytokines (IL-6 and TNF-alpha) in patients with chronic kidney disease.8 We hypothesise that high FGF23 levels in CLD may reflect a pro-inflammatory state induced by the liver dysfunction, leading to upregulation of pro-inflammatory cytokines and FGF23 expression in hepatocytes.

The management of FGF23-induced hypophosphataemia would include high dose oral phosphate supplementation given over multiple doses per day, and active vitamin D analogues, though this may not entirely correct the deficiencies, as we have demonstrated. At present, the monoclonal antibody targeting FGF23, Burosumab, has been licensed for X-linked hypophosphataemic rickets, where it is effective in reducing rickets severity and improving phosphate levels.9 Though this may be a potential candidate for therapy, there has been no published reports of Burosumab use in FGF23-induced HOD. In such cases, eventual liver transplantation is likely to lead to reversal of the FGF23-induced hypophosphataemia.

Our case highlights that HOD is a heterogeneous condition with multiple contributing aetiologies. Additionally, excess circulating FGF23 should be considered in patients with a hypophosphataemia-hyperphosphaturia type of HOD. Though rare, it is important to recognise this entity, particularly since management would differ from that of standard HOD, where in this case, high dose phosphate and calcitriol was required on top of the usual therapy for hepatic rickets and vertebral fractures. We believe that severe HOD from any cause should be an indication for early liver transplantation independent of the state of liver disease, particularly in patients not responding to medical therapy.
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