A case study of X-linked hypophosphataemia: The effect of conventional therapy from childhood to adulthood in Saudi Arabia

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BACKGROUND

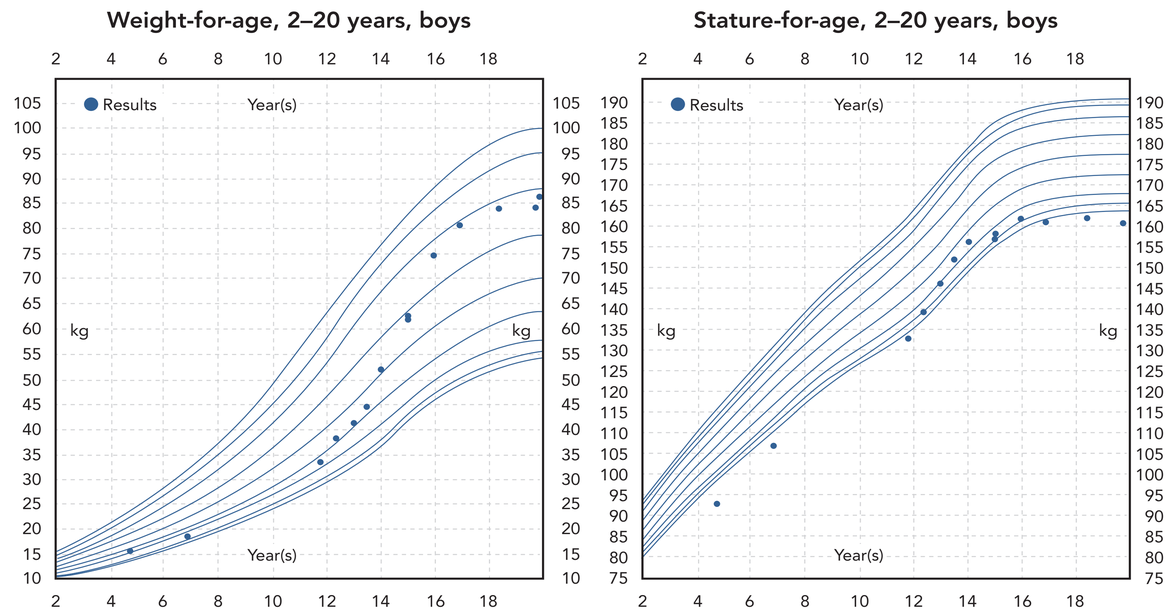
- X-linked hypophosphataemia (XLH) is the most common form of inherited hypophosphataemic rickets, caused by loss-of-function mutations in the gene encoding phosphate-regulating endopeptidase homologue X-linked (*PHEX*), resulting in excess circulating fibroblast growth factor 23 (FGF-23)[1,2]
- In children, therapy includes daily oral phosphate and active vitamin D analogue (alfacalcidol or calcitriol) supplementation, but is associated with gastrointestinal side effects, hyperparathyroidism, hypercalciuria and nephrocalcinosis[2,3]
- In adults who have undergone conventional therapy during childhood, but are still symptomatic, conventional treatment is usually maintained or re-initiated in order to reduce pain as a result of micro-fractures and/or osteomalacia; however, the side effects of conventional treatments persist[2]
- Here we report the case of an adult patient with XLH who has been treated with conventional treatment, and the subsequent long-term impact of the side effects of this therapy since his diagnosis

CASE PRESENTATION

Patient history

- The patient was diagnosed with XLH at aged 4 years, which was confirmed by whole exome analysis and revealed a heterozygous loss of functional variant of *PHEX* gene (exon14:c.1536T>G:p.Y512X)
- He had a history of leg bowing, which had previously resolved with treatment
- At age 20 years, he presented with pain during walking
- He had no hearing issues, dental issues or limb deformities and was being treated with oral phosphate supplementation (30–50 mg/kg three times a day [t.i.d.]) and alfacalcidol (1.5–3.0 µg daily [q.d.])
- The patient has a history of short stature and his current height is 160.5 cm (standard deviation –2.27; **Figure 1**)
- His current weight is 85 kg

Figure 1. Patient growth chart (males aged 2–20 years old)



Growth chart shows weight and height for males aged 2–20 years. Blue points indicate the patient's weight and height.

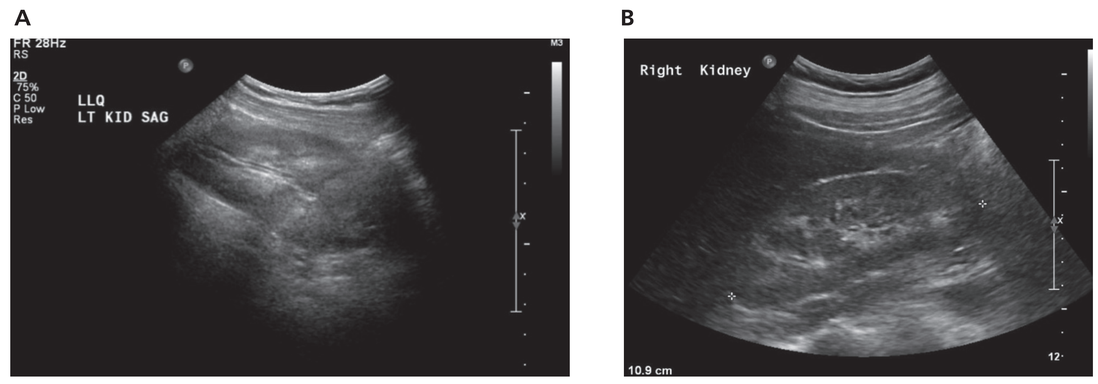
Conventional treatment and monitoring

- During puberty, the patient was treated with oral phosphate supplementation (30–50 mg/kg t.i.d.) and alfacalcidol (1.5–3.0 µg q.d.)
- Whilst on conventional treatment, growth, leg deformities, dental health and serum levels of alkaline phosphatase (ALP), parathyroid hormone (PTH), calcium and creatinine were monitored every 6 months, as were urine levels of calcium and creatinine
- A renal ultrasound was performed every 12 months. A parathyroid ultrasound scan was performed when the patient was aged 19 years

Outcomes of conventional treatment

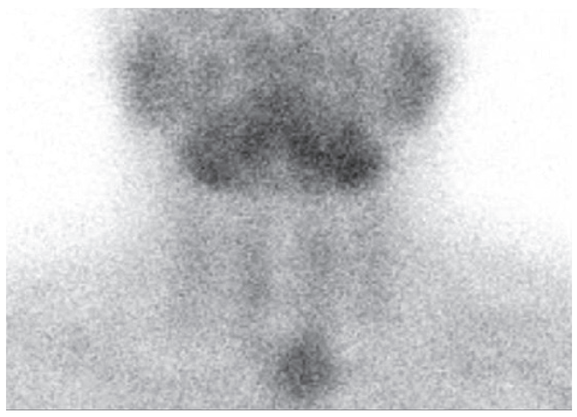
- A renal ultrasound at age 9 years revealed increased echogenicity in the pyramids of both kidneys, indicating nephrocalcinosis (**Figure 2a**)
- The most recent ultrasound at age 19 years showed that the right kidney (measuring 10.9 cm) had mild-to-moderately increased echogenicity, which had improved since the previous scan at age 9 years; however, there was increased medullary echogenicity, suggesting medullary nephrocalcinosis (**Figure 2b**)
- At age 20 years, the patient developed a large parathyroid adenoma and was referred to a surgeon (**Figure 3**). Following surgery, his PTH levels improved

Figure 2. Renal ultrasound at age A. 9 years and B. age 20 years



Patient's renal ultrasound scans at A. Age 9 years and B. Age 20 years.

Figure 3. Parathyroid ultrasound at age 20 years



Standard parathyroid scan with SPECT using technetium 99m sestamibi.

- Both nephrocalcinosis and the parathyroid adenoma were thought to be related to long-term conventional therapy with oral phosphate and alfacalcidol, so these therapies were discontinued when the patient was aged 19 years
- Following treatment discontinuation, most recent serum levels were as follows: high ALP, 566 U/L; high PTH, 550 ng/L; low phosphate, 0.75 mmol/L and low urine calcium/creatinine ratio of 0.07

DISCUSSION

- In this adult case of XLH, long-term treatment with oral phosphate and vitamin D supplementation therapy since childhood has resulted in significant side effects, highlighting that coordination of care is required for the optimal treatment of XLH and involves various specialists in paediatric and adult fields
- Burosumab is a novel monoclonal FGF-23 antibody indicated for the treatment of XLH in adult and paediatric patients that targets the underlying pathophysiology of XLH, i.e. FGF-23 excess, and has fewer side effects versus conventional treatment[4]
- In paediatric patients, the starting dose regimen is 0.8 mg/kg of body weight rounded to the nearest 10 mg, administered every 2 weeks. The minimum starting dose is 10 mg up to a maximum dose of 90 mg[4]
- In adults, the recommended dose regimen is 1 mg/kg of body weight, rounded to the nearest 10 mg up to a maximum dose of 90 mg, administered every 4 weeks[4]
- Significantly greater clinical improvements have been demonstrated in rickets severity, growth, and biochemistries among adults and children with XLH treated with burosumab compared with those continuing conventional therapy[4]

CONCLUSIONS

- While attention is focused on treating skeletal abnormalities and growth failure in children, adults should be nonetheless regularly monitored for the prevention and limitation of symptoms as well as side effects of conventional treatment, which impact their quality of life

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DISCLOSURES

The presenting author declares that she has no conflicts of interests.

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