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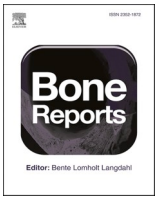

Lessons learned from the real-world diagnosis and management of hereditary hypophosphatemic rickets

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ABSTRACT

Hypophosphatemic rickets, which is often hereditary, is still under- or misdiagnosed in both children and adults, denying these individuals access to optimal management and genetic counseling. There have been recent calls to compile real-world data and share best practice on these rare conditions to guide clinical decision-making. Here we present eight clinical vignettes of patients with hypophosphatemic rickets encountered in our tertiary pediatric endocrinology practice. We describe the clinical features, genetics, and management of four cases of X-linked hypophosphatemia (*PHEX* mutations), one each of autosomal recessive hypophosphatemic rickets (*DMP1* mutation) and autosomal recessive vitamin D-dependent rickets type 1A (*CYP27B1* mutation), and two cases of distal renal tubular acidosis with *FOXI1* mutation-associated hypophosphatemic rickets. Our cases prompt consideration of the (i) frequent misdiagnosis of hypophosphatemic rickets in clinical practice and the importance of comprehensive genetic testing; (ii) variable expressivity of the causative mutations; and (iii) a lack of responsiveness and/or compliance to conventional therapy and the value of burosumab in modern management, provided access is equitable. These cases highlight common real-world themes and challenges to managing patients presenting with these diverse conditions, especially the burden of disease hidden by misdiagnosis. In sharing these cases, we hope to raise awareness of these conditions, promote best practice in genetic diagnosis and management, and further advocate for reimbursement equity for the best available therapies.

1. Introduction

Rickets is characterized by widening and delay of mineralization of the bone growth plates associated with osteomalacia, and it often causes leg bowing, short stature, and joint widening (Shore and Chesney, 2013). A complete understanding of the biology of vitamin D, calcium, and phosphate in bone health has almost completely eradicated nutritional rickets in many countries, especially high-income countries, although relaxation of effective public health education and surveillance may be driving an increase in incidence (Goldacre et al., 2014; Ahmed et al., 2011). Although nutritional rickets is still the predominant form in terms of absolute numbers, the burden of disease has proportionally shifted towards "phosphopenic" forms of rickets (*i.e.*, characterized by low serum levels of phosphorus rather than calcium deficiency) which, although sometimes caused by dietary phosphate deficiency or impaired phosphate absorption, are usually due to chronic renal phosphate wastage (Carpenter et al., 2017). These latter forms of hypophosphatemic rickets, which often form part of a hereditary multisystem disorder, are caused by specific genetic variants (usually in *PHEX*) that increase expression of fibroblast growth factor-23 (FGF23) (Lang et al., 2018; Clinkenbeard and White, 2017) or inactivate genes encoding sodium-dependent phosphate transporters in the proximal renal tubule (Segawa et al., 2015). Hypophosphatemia impairs apoptosis of terminally differentiated chondrocytes and growth plate mineralization (Sabbagh et al., 2005), resulting in skeletal deformities and growth plate abnormalities that present in infancy or early childhood including the characteristic deformities of genu varum or valgus, the "rachitic rosary" of the costochondral junctions, and wrist, knee, or ankle enlargement (Carpenter et al., 2017). X-linked hypophosphatemia (XLH, caused by *PHEX* mutations) is the archetypal and most common heritable cause of

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hypophosphatemic rickets, but it is still rare, with an incidence of 1 in 20,000 to 60,000 individuals (Endo et al., 2015; Beck-Nielsen et al., 2009; Rafaelsen et al., 2016). Given the profound and often lifelong impact of these disorders not only on the patient and their families but, when genetic, also future offspring, securing the correct diagnosis is essential to guide therapy and prompt genetic counseling where indicated.

Nevertheless, hypophosphatemic rickets is still underdiagnosed or misdiagnosed in both children and adults, leading to inappropriate treatment and denying these individuals access to appropriate therapies, optimal management, and counseling (Gonzalez-Lamuno, 2020; Al Juraibah et al., 2021). There have been several excellent recent reviews on the biology, diagnosis, and management of hypophosphatemic rickets (Gonzalez-Lamuno, 2020) and XLH (Al Juraibah et al., 2021) and the spectrum of genetic variants associated with the hereditary forms of the disease (Marik et al., 2022; Ackah and Imel, 2022). Instead of repeating these aspects of hypophosphatemic rickets, and inspired by encouragement from the recent XLH Matters meeting to compile real-world data and share best practice to guide treatment decisions for people living with XLH (Seefried et al., 2023), here we present eight clinical vignettes of patients with hypophosphatemic rickets encountered in our "real-world" tertiary pediatric endocrinology practice at Sheikh Shakhbout Medical City, Abu Dhabi, UAE, over the last seven years. In doing so, we highlight several important learning points about the current diagnosis and management of the condition, including diagnostic pitfalls, genetic considerations, clinical features, and real-life barriers to optimal care.

2. Case series

For all cases, whole exome sequencing (WES) was performed by a CAP-accredited diagnostics laboratory (Centogene, Rostock, Germany) with type and classification of mutations reported according to the ACMG guidelines (Durkie et al., 2023). Clinical data were retrieved from the case notes.

2.1. Case 1

A six-year-old girl had previously attended several other hospitals for short stature and leg bowing, prompting guided bone growth control surgery (hemiepiphysiodesis). On presentation to a private facility in July 2018, clinical examination revealed bilateral genu valgum deformities (Fig. 1A), worse on the left, together with dolichocephaly and rachitic rosary. Her height z-score was −1.92. There was no past medical history of fractures, and she had normal teeth and hair growth. There was a positive history of consanguinity (parents were second cousins), and, while her mother had a history of leg bowing and was of short stature, she had not received any formal diagnosis.

Plain radiographs of the legs showed classical radiological changes of rickets with metaphyseal widening, cupping, and fraying (Fig. 1B). Her height velocity was 4.8 cm/year (normal 6.53 ± 0.86 cm/year (Kelly et al., 2014)). Biochemistry reported a serum phosphate of 0.85 mmol/L (normal age-based range 1.20–1.80 mmol/L), urinary phosphate of 78.8 mmol/L (normal age-based range 1.20–1.80 mmoL/L), serum creatinine of 20 μmol/L (normal age-based range 25–42 μmol/L), urinary creatinine of 8.79 mmol/L, and serum alkaline phosphatase 569 IU/L (normal age-based range 156–369 IU/L). The tubular resorption of phosphate corrected for glomerular filtration rate (TmP/GFR) was 0.66 mmol/L (normal age-based range 1.15–2.44 mmol/L (Al Juraibah et al., 2021)).

Given the features of hypophosphatemic rickets and the family history, the patient underwent WES, which detected a heterozygous likely-pathogenic variant in the *PHEX* gene (c. 1079 + 1_1079 + 3del) predicted to disrupt the highly conserved donor splice site of exon 9, securing a genetic diagnosis of XLH. She was started on conventional XLH treatment with phosphate salts (with which she was poorly compliant) and the active vitamin D analog alfacalcidol (1-hydroxycholecalciferol) (Al Juraibah et al., 2021), with follow-up kidney ultrasound six months after starting treatment showing no evidence of nephrocalcinosis.

Routine, regular follow-up appointments over the following year revealed a failure to normalize serum phosphate levels (0.64–0.88 mmol/L), variable urinary phosphate (23.17–46.05 mmol/L), and her serum alkaline phosphatase remained persistently high (594–735 IU/L). Although there was some radiographic evidence of healing rickets, distal femoral and proximal tibial metaphyseal Looser-Milkman lines and metaphyseal flaring persisted. In March 2020, the patient was referred to our tertiary center for further consideration of treatment with burosumab, a recombinant human IgG1 monoclonal antibody that targets

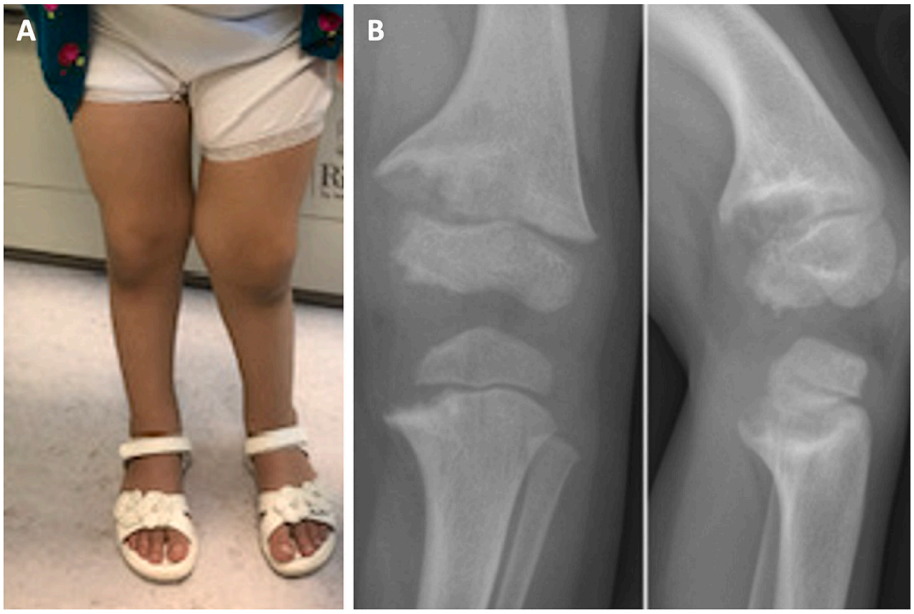

Fig. 1. (A) Bilateral genu valgum deformities in Case 1 (six-year-old girl, prior to treatment), worse on the left. (B) Antero-posterior and lateral radiographs of the left knee in Case 1 showing widening, cupping, and fraying of metaphyses. The metaphyses show a trabecular pattern and the severity of rachitic changes at the growth plate are asymmetric, with the medial side being more severely affected (wider and more frayed) than the lateral side.

and inhibits the raised FGF23 present in XLH patients (Al Juraibah et al., 2021; Gordon and Levine, 2019). After discontinuing oral phosphate and alfacalcidol and determining baseline biochemistry, in April 2020, she was started burosumab subcutaneous solution 30 mg (0.8 mg/kg) every two weeks together with oral ergocalciferol (vitamin D2) 50,000 units weekly. Although alkaline phosphatase and serum and urinary phosphate levels were initially labile over the following few months, after careful dose adjustment (to 1.0 mg/kg), serum and urinary phosphate levels were restored to within normal limits, and alkaline phosphatase levels decreased to plateau at approximately 350 IU/L, at the high end of normal (normal age-based range 156–369 IU/L; Fig. 2A–C). Consistent with the biochemistry, although genu valgum persisted, follow-up X-rays six months later confirmed healing rickets with no osseous lesions and normal mineralization, and she continued to grow at

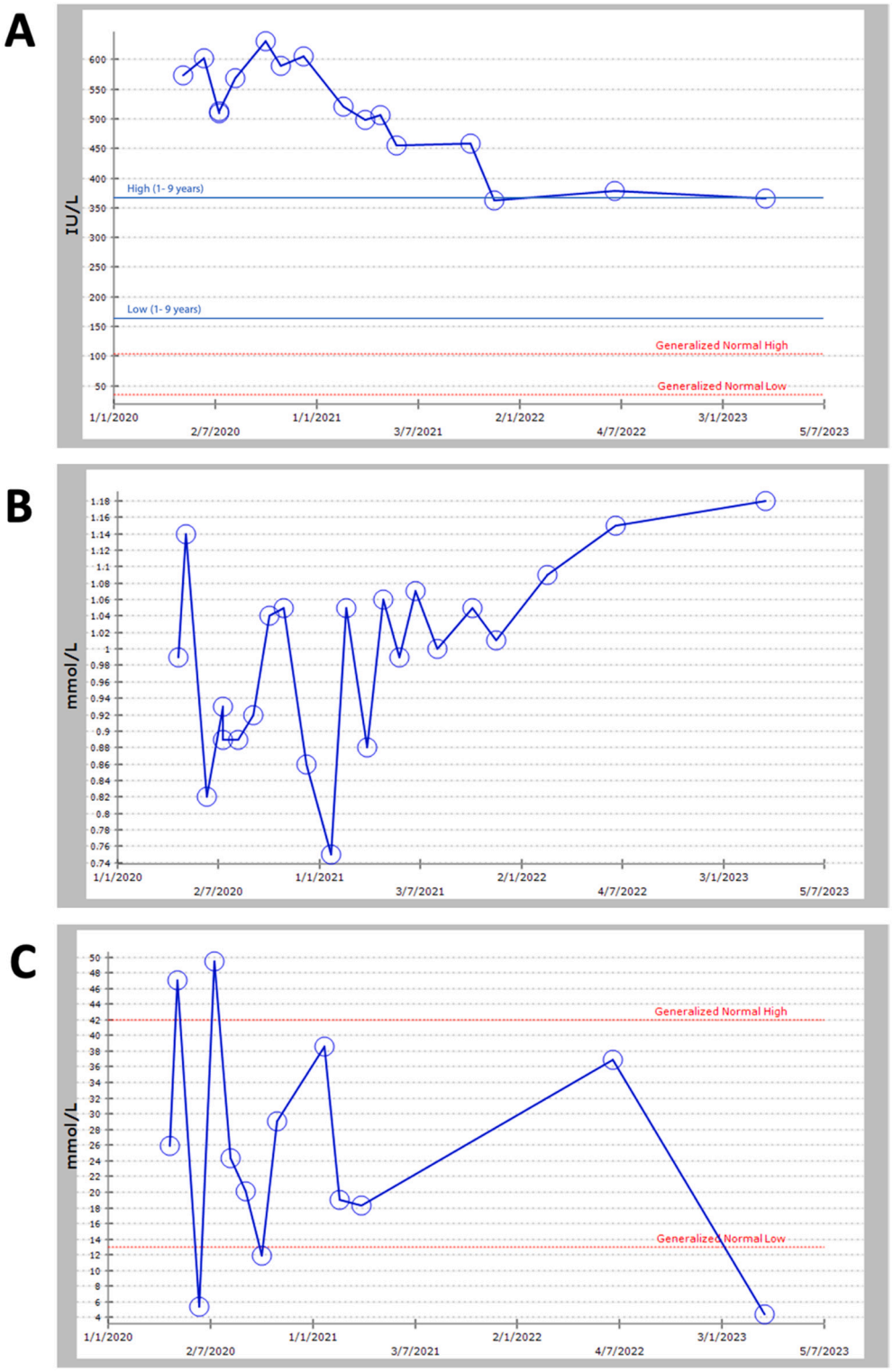

Fig. 2. Trajectory of serum alkaline phosphatase (blue lines: normal age-based range) (A), serum phosphate (normal 1.2–1.8 mmol/L) (B), and urinary phosphate (C) levels after starting burosumab in Case 1.

an accelerated rate, with a height z-score of −1.25 in December 2022.

Importantly, the girl was very satisfied with the treatment; although she had to have injections, she preferred this to taking tablets, especially the phosphate tablets.

2.2. Case 2

A two-year-old girl born normally at term with no initial health problems presented with a 10-month history of bowed legs, which had recently worsened and become more prominent. There was no history of skin, dental, or hair abnormalities. She had been seen by many endocrinologists privately, who diagnosed hypophosphatemic rickets, for which she was initially treated with calcium and active vitamin D and later with phosphate supplementation. There was a family history of minor leg bowing in her father, who had not received any formal diagnosis. There was no family history of consanguinity.

On examination, she had a severe genu varum deformity (Fig. 3), rachitic rosary, wide wrists, but normal range of joint motion and strength without any tenderness. Her height z-score was −1.93. Knee and wrist X-rays confirmed rickets, with bilateral widening and fraying of the metaphysis of the distal femur with leg bowing and sclerosis, cupping, and fraying of the metaphysis of the distal radius and ulna. Biochemistry revealed a serum phosphate of 0.93 mmol/L (normal age-based range 1.25–2.10 mmol/L), urinary phosphate of 32.9 mmol/L (normal age-based range 1.20–1.80 mmoL/L), serum creatinine of 22 μmol/L (normal age-based range 25–42 μmol/L), urinary creatinine of 3.47 mmol/L, and serum alkaline phosphatase 475 IU/L (normal age-based range 156–369 IU/L). The TmP/GFR was 0.72 mmol/L (normal age-based range 1.15–2.44 mmol/L).

The patient underwent WES, which detected a heterozygous likely-pathogenic variant in *PHEX* (c.1601C > T; p.Pro534Leu), securing a genetic diagnosis of XLH. She was started on conventional XLH treatment with phosphate salts and alfacalcidol. However, she did not tolerate the phosphate tablets, prompting refusal and consequent parental anxiety, although she tolerated the alfacalcidol well. At most recent follow-up a year after starting conventional therapy, her leg deformity had continued to progress, and her serum phosphate remained abnormally low and alkaline phosphate abnormally high. Her parents remained concerned about the progressive leg deformity, but orthopedic consultation advised continuation of medical treatment and future consideration of surgical options after her fifth birthday. Although the child was a candidate for burosumab, the parents could not afford it and it was not reimbursed through public funding.

2.3. Case 3

An 18-month-old boy was referred to our clinic due to low serum phosphate levels discovered during routine testing for a febrile illness. He was born full term at 38 weeks by caesarean section due to maternal bone deformities. There was a family history of maternal severe short stature from birth with bilateral leg deformities requiring several corrective surgeries, and she has been diagnosed with osteogenesis imperfecta (see Case 4). There was no family history of consanguinity.

On examination, the boy showed features of mild developmental delay, still sitting and able to stand by himself but not walking for more than a few steps. He had mild wrist widening with frontal bossing of an abnormally-shaped head. He had no significant leg bowing. His height z-score was −1.58. Knee X-ray revealed features of rickets evidenced by diffuse osteopenia and metaphyseal irregularity, especially in the distal femur, with cupping, fraying, and radiological evidence of anterior bowing of the distal femur. A chest X-ray also showed generalized osteopenia. Even at 18 months, he had developed recurrent dental abscesses requiring systemic antibiotics. Biochemistry revealed a serum phosphate of 0.60 mmol/L (normal age-based range 1.25–2.10 mmol/L), urinary phosphate of 18.10 mmol/L (normal age-based range 1.20–1.80 mmoL/L), serum creatinine of 11 μmol/L (normal age-based range 25–42 μmol/L), and urinary creatinine of 2.69 mmol/L. The TmP/GFR was 0.50 mmol/L (normal age-based range 1.15–2.44 mmol/L).

The patient underwent WES, which detected a heterozygous likely-pathogenic variant in *PHEX* (c.436 + 2 T > C), securing a genetic diagnosis of XLH. No other pathogenic variants, such as in osteogenesis imperfecta genes were detected. He was started on burosumab at a dose of 0.8 mg/kg every two weeks, which resulted in a modest increase in his serum phosphate, but his alkaline phosphate remained high. On increasing the dose to 1.0 mg/kg, his serum phosphate and alkaline phosphatase normalized.

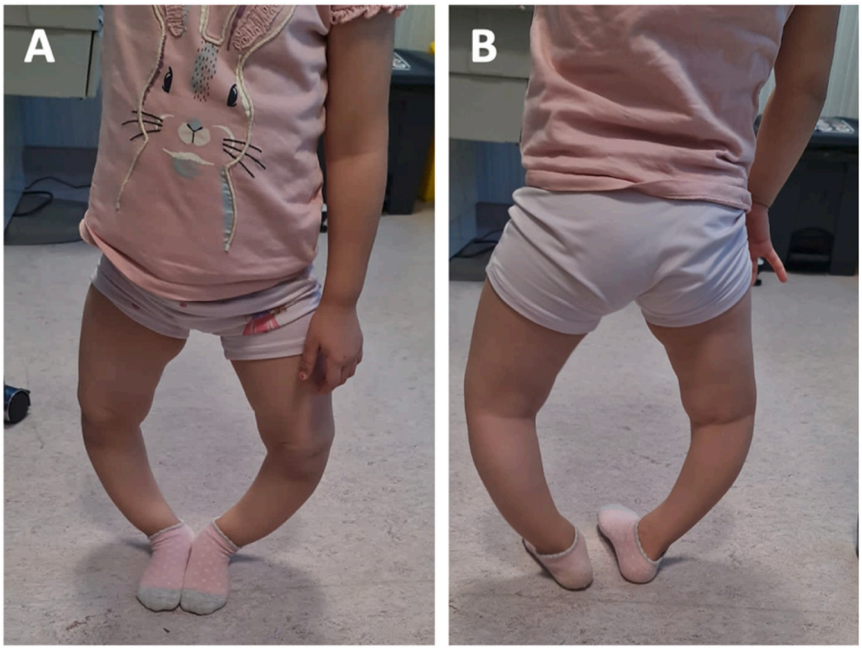

Fig. 3. Severe bilateral genu valgum deformities in Case 3. (A) Front, (B) back.

2.4. Case 4

A 39-year-old lady and mother of Case 3 attended clinic to investigate her son's unexplained hypophosphatemia. While evaluating the child, and appreciating the hereditary etiology of some forms of hypophosphatemic rickets, she was noted to have short stature (131 cm) and questioning revealed an extensive orthopedic surgery to correct limb deformities. She had been diagnosed with osteogenesis imperfecta (treated by zoledronic acid infusion) and had undergone multiple surgeries of bilateral femoral and tibial corrective osteotomies with insertion of steel rods. There was no family history of note, and there was no history of consanguinity.

On examination, she had artificial teeth due to loss of dentition, right forefoot metatarsalgia, left lower limb shortening, left tibial bowing, and bilateral pes planus. Her height z-score was −1.25. Her serum phosphate was 0.56 mmol/L (normal 0.81 to 1.45 mmol/L), and her alkaline phosphatase was 125 IU/L (normal 44–147 IU/L). X-rays showed healing fractures of the metatarsals, internal fixation of the tibia with an intramedullary nail and screws from previous surgery, and osteoarthritic changes in the right hip. Exome sequencing detected a heterozygous likely-pathogenic variant in *PHEX* (c.436 + 2 T > C), securing a genetic diagnosis of XLH.

After diagnosis, the patient was referred to adult endocrinology for further evaluation and management with burosumab.

2.5. Case 5

A 17-year-old girl managed at our center for many years had a long history of leg bowing from 14 months of age, which was diagnosed as rickets, for which she was treated with vitamin D supplements. However, by five years of age, her leg bowing and other bone deformities had progressed, developing crus varum, genu varum, and femur varum. She was diagnosed with hypophosphatemic rickets and was started on phosphate and cholecalciferol, with calcitriol added after ruling out hypercalciuric hypophosphatemic rickets. She later underwent osteotomies of both distal femurs with frame tibia and epiphysiodeses of the distal right femur. There was no family history of endocrine or bone disease, but her parents were consanguineous, and her younger sister died at five years with an undiagnosed genetic muscular disease. The rest of her physical examination was normal.

Biochemical tests revealed hypophosphatemia (0.71 mmol/L, normal 0.80–1.5), normal alkaline phosphatase (105 IU/L, normal 48–130 IU/L), increased parathyroid hormone (10.3 pmol/L, normal 1.6–6.9 pmol/L), and normal 25-hydroxyvitamin D (54.5 nmol/L, normal 30–100 nmol/L) and calcium (2.4 mmol/L, normal 2.2–2.6 mmol/L). Moreover, her TmP/GFR was low at 2.18 mg/dL (age-based normal reference range 2.60–3.80 mg/dL). Her circulating FGF23 was 127 RU/mL (normal ⟨230).

Genetic testing showed a homozygous pathogenic variant in *DMP1* (c.1122 T > G, p.(Tyr374*)) confirming a genetic diagnosis of autosomal recessive hypophosphatemic rickets. She continues to take conventional treatment with phosphate and active vitamin D. She has also been considered for a trial with burosumab which, although not approved for patients with *DMP1* mutations, some patients are reported to benefit from it (Bai et al., 2022).

2.6. Case 6

A 13-month-old boy, born preterm at 33 weeks, had a complicated neonatal course with a low birth weight (1470 g) and respiratory distress syndrome. He was referred to the Pediatric Endocrinology service following a PICU admission due to respiratory illness, who detected low serum phosphate levels and high serum parathyroid hormone levels. His parents were consanguineous, and two maternal uncles had previously been diagnosed with hereditary rickets, for which they were taking alfacalcidol.

Physical examination revealed faltering growth with weight and height below the second percentile for gestation-corrected age and sex, delayed motor milestones, and wide wrists. Skeletal radiographs of the hands showed cupping, fraying, and splaying of ulnar and radius distal metaphysis (Fig. 4). Biochemistry revealed low serum phosphorous (0.58 mmol/mL, normal range 1–1.95 mmol/L), high serum alkaline phosphatase (2611 IU/L, normal age-based range 156–369 IU/L), and low 1,25 dihydroxyvitamin D (<19 pmol/L, normal range 58–207 pmol/L). Calcium, hydroxyvitamin D, serum creatinine, and urea nitrogen were normal. FGF23 levels were normal, but her tubular reabsorption of phosphate was low (0.63 mmol/L, normal range 1.13–1.88).

WES was performed, which revealed a homozygous pathogenic variant in the *CYP27B1* gene (c.429del, p.(Leu144Serfs*15)) consistent with a genetic diagnosis of autosomal recessive vitamin D-dependent rickets type 1 A, for which he was treated with alfacalcidol.

2.7. Cases 7 and 8

Two patients in the same family presented with early-onset sensorineural deafness and distal renal tubular acidosis (dRTA), as described in our previous study (Enerback et al., 2018). The male proband (Case 7, eight years at diagnosis) was the eldest of three children, and he had one affected sister (Case 8, six years at diagnosis). Both patients had hypophosphatemic rickets, with height z-score of −2.9 and − 1.9, respectively. In addition to rickets, the sensorineural hearing loss required cochlear implants, and they had hypokalemic, hyperchloremic metabolic acidosis with inappropriately high urine pH, and bilateral nephrocalcinosis, consistent with dRTA. The dRTA was associated with hypercalciuria and nephrocalcinosis noted at presentation but responded to treatment with both alkali and potassium supplements with subsequent catch-up in growth of the children. Whole exome sequencing revealed novel homozygous missense mutations in *FOXI1* (c.436C > T, p.Leu146Phe) located within evolutionary highly conserved residues of the FOXI1 protein (Enerback et al., 2018). The patients responded to treatment with alkali and potassium supplements with subsequent catch-up in growth.

3. Discussion

In presenting this series of eight cases of patients presenting with hypophosphatemic rickets (see summary Table 1), we showcase many of the classical features seen across the spectrum of disease: (i) the morphological features of rickets (genu varum or valgus, the "rachitic rosary" of the costochondral junctions, and wrist, knee, or ankle enlargement); (ii) the heterogeneous set of mutations in different genes responsible for the X-linked and autosomal forms of the disease, especially mutations in *PHEX*; (iii) the heterogenous clinical manifestations and multi-system involvement; and (iv) the need for comprehensive, multidisciplinary clinical evaluation including thorough history taking, especially of the family history, physical examination, laboratory investigations, genetic analysis, and imaging to establish the underlying cause, monitor severity and treatment efficacy, and to guide the correct type of treatment. These aspects of hypophosphatemic rickets (Gonzalez-Lamuno, 2020), especially for XLH (Al Juraibah et al., 2021), and the underlying genetics (Marik et al., 2022; Ackah and Imel, 2022), are described in detail in several excellent recent reviews and clinical guidelines (Al Juraibah et al., 2021; Laurent et al., 2021; Haffner et al., 2019), and will not be repeated here.

Instead, we will use these vignettes to highlight other, real-world learning points to help all members of the multidisciplinary team in clinical practice. Our cases prompt consideration of the following learning points (Table 1): (i) frequent misdiagnosis in clinical practice and the importance of modern genetic testing; (ii) variable expressivity of the causative mutations masking clues to the diagnosis; and (iii) a lack of responsiveness and/or compliance to "conventional" treatments and the value of burosumab in modern management, provided access is

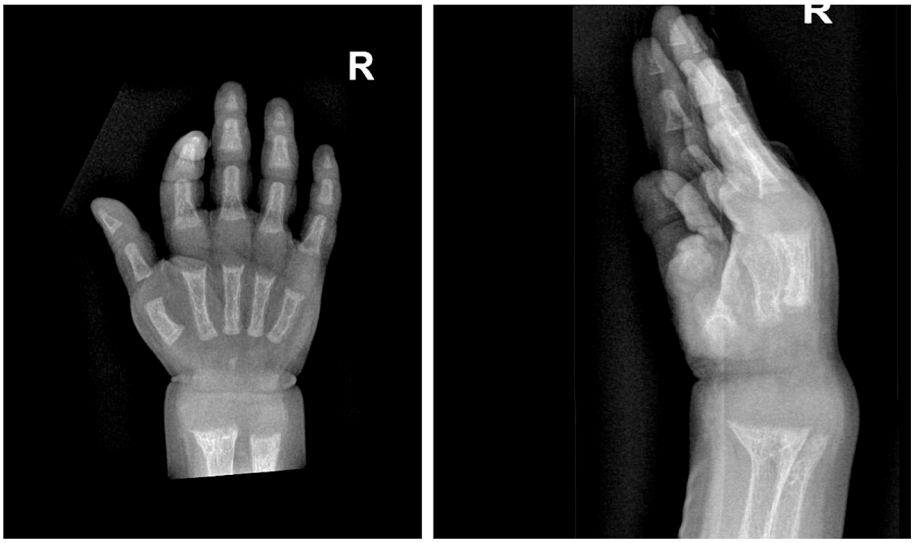

Fig. 4. Case 6: antero-posterior (left) and lateral radiographs (right) of the right hand showing marked cupping, fraying, and splaying of ulnar and radius distal metaphysis.

Table 1
Clinical and genetic characteristics of the case series, along with learning points.

Case number	Age at diagnosis and sex	Diagnosis	Gene	Nucleotide and amino acid substitution	Clinical features	Learning points
1	6 years, female	XLH	*PHEX*	c. 1079 + 1_1079 + 3del	Long-term misdiagnosis, skeletal deformities without other systemic manifestations, improvement on starting burosumab	1. Misdiagnosis 2. Lack of response to conventional treatment 3. Improvement on burosumab 4. Variable expressivity in the same kindred 5. Adherence to therapy
2	2 years, female	XLH	*PHEX*	c.1601C > T (p. Pro534Leu)	Misdiagnosis, inequitable access to novel medications, progression to severe skeletal deformities	1. Misdiagnosis 2. Lack of response to conventional treatment 3. Equitable access to medications 4. Variable expressivity in the same kindred 5. Adherence to therapy
3	18 months, male	XLH	*PHEX*	c.436 + 2 T > C	Son of affected mother, abnormal head shape, and hypophosphatemia Dx in febrile illness, dental abscess	1. Lack of response to conventional treatment
4	39 years, female	XLH	*PHEX*	c.436 + 2 T > C	Bone deformities, carious teeth, severe short stature, misdiagnosis with osteogenesis imperfecta	1. Adult misdiagnosis 2. Dental involvement
5	17 years, female	Autosomal recessive hypophosphatemic rickets	*DMP1*	c.1122 T > G, p. (Tyr374*)	Long-term use of conventional treatment, persistence deformities, but late definitive diagnosis	1. Benefits of genetic testing
6	13 months, male	Autosomal recessive vitamin D-dependent rickets type 1A	*CYP27B1*	c.429del, p. (Leu144Serfs*15)	Hypophosphatemia, severe rickets, with respiratory compromise	1. Importance of family history 2. Importance of genetic diagnosis to avoid use of inappropriate medications for the wrong diagnosis
7	8 years, male	*FOXI1* mutation-associated hypophosphatemic rickets; distal renal tubular acidosis	*FOXI1*	c.436C > T, p. Leu146Phe	Hearing defects and kidney impairment can be primary features in hypophosphatemic rickets, not purely bone defects	1. Importance of genetic diagnosis to explain multi-system involvement
8	6 years, female	*FOXI1* mutation-associated hypophosphatemic rickets; distal renal tubular acidosis	*FOXI1*	c.436C > T, p. Leu146Phe	Hearing defects and kidney impairment can be primary features in hypophosphatemic ricket and not purely bone defects	1. Importance of genetic diagnosis to explain multiple systemic involvement

equitable.

3.1. Misdiagnosis and genetic testing

Three of our XLH patients (Case 1, Case 2, and Case 4) had been misdiagnosed or improperly diagnosed, and, consequently, the

definitive treatment had been delayed in the affected children. Worse still, the affected adult patient (Case 4) had been wrongly diagnosed as osteogenesis imperfecta, treated with zoledronic acid, and had been denied definitive conventional treatment that could have slowed or halted the development of bony deformities for which she had undergone repeated surgery. Therefore, the impact of misdiagnosis can be profound and lifelong. There are little data on the prevalence of misdiagnosis of hypophosphatemic rickets; in one self-administered questionnaire to 234 subjects belonging to one of three large XLH kindreds, 57 of whom were affected, only 22.6 % of affected individuals had been formally told by a physician that they had rickets or osteomalacia and only one patient was taking phosphate and vitamin D (Econs et al., 1994). In an Italian cohort of XLH patients, about 40 % were diagnosed after five years of age (Emma et al., 2019). The reasons for misdiagnosis are unclear, but probably include the rare nature of the disease; the fact that by virtue of rickets being a disorder of calcium and phosphate homeostasis, serum phosphate is low in all cases of rickets, so genetic causes are missed (Carpenter et al., 2017; Al Juraibah et al., 2021; Alenazi et al., 2017); multisystem involvement; and because in 20 % of cases there is no family history because the mutation has arisen *de novo* (Whyte et al., 1996). Furthermore, as seen in our series, even when there is a family history of bony deformities, the variable expressivity of the condition might mean that historical clues are missed or that the disease is not severe enough to attract medical attention (see below).

Genetic testing may not always be available and, when available, may not be sufficiently advanced or broad to detect every causative mutation. Marik et al. recently reported the spectrum of mutations responsible for hypophosphatemic rickets in a relatively large cohort of 66 patients and detected six pathogenic and 28 likely pathogenic variants in 16 different genes in 63 patients using WES (Marik et al., 2022), highlighting how targeted approaches (for instance sequencing candidate genes only) may fail to detect the causative mutation. Indeed, in our Case 5, focusing on *PHEX* and *FGF23* alone would have failed to detect the *DMP1* mutation responsible for autosomal recessive hypophosphatemic rickets, and, after lifelong treatment, we were finally able to detect the causative gene thanks to the broad genetic coverage of WES. Helpfully, Malik et al. also suggested a targeted panel of 16 genes to detect the pathogenic/likely pathogenic variations responsible for the majority of cases of hypophosphatemic rickets, which would help make the assay more affordable than WES and broaden its uptake (Marik et al., 2022). Securing the correct genetic diagnosis is mandatory, as it guides specific therapies, as exemplified by Case 6: establishing the diagnosis of autosomal recessive vitamin D-dependent rickets type 1A caused by a *CYP27B1* mutation requires treatment with specialized vitamin D replacement regimens (calcitriol for vitamin D-dependent rickets type 1A (Levine, 2020)) and, given it is not associated with raised FGF23, would not benefit from targeted biologic therapy such as burosumab.

In summary, avoiding misdiagnosis of hypophosphatemic rickets requires: (i) ongoing educational activities to increase knowledge about hypophosphatemic rickets and its clinical manifestations among healthcare providers, based on international and regional consensus guidelines (Al Juraibah et al., 2021; Laurent et al., 2021; Haffner et al., 2019); (ii) a low threshold for genetic testing in cases of early-onset rickets; and (iii) widespread access to comprehensive genetic testing for at least all known causative mutations.

3.2. Variable expressivity of causative mutations

As noted above, the variable expressivity of the underlying gene defects in hypophosphatemic rickets may contribute to misdiagnosis by masking the disease or family history of the disease. Two of our children with XLH had parents with short stature and/or bony deformities that, while noted in childhood, had not been sufficiently severe to prompt further medical attention, in contrast to the affected offspring who had severe and progressive disease. Recognizing the family history may have prompted earlier diagnosis. While the difference in phenotype between related XLH family members may be due to *de novo* mutations in the affected offspring (Terracciano et al., 2023; Acar et al., 2018), which are relatively common for *PHEX* and usually result in a delayed diagnosis with more severe disease (Acar et al., 2018), the lack of a genotype-phenotype correlation for XLH is well established. The clinical severity of XLH is largely unrelated to genotype or sex and disease manifestations are variable, even within the same kindred (Zheng et al., 2020). Therefore, while it is essential to take a thorough family history, it is also important to be aware that a negative history does not preclude a diagnosis of hereditary hypophosphatemic rickets and to be especially sensitive to more subtle phenotypes in family members that might raise the index of suspicion.

3.3. Lack of responsiveness and/or adherence to "conventional" treatments and equitable access to burosumab

Our vignettes highlight that the management of hypophosphatemic rickets is far from straightforward and that outcomes can be poor. The goal of treatment is to accelerate growth by improving rickets and the consequent skeletal deformities and associated symptoms such as bone pain, recognizing that not treating these in childhood leads to a greater cumulative disease and quality of life burden in later life (Skrinar et al., 2019; Quinlan et al., 2012; Makitie et al., 2003). All of our pediatric cases of XLH and our adolescent patient with autosomal recessive hypophosphatemic rickets caused by a *DMP1* mutation had progressive disease on conventional management with phosphate salts and active vitamin D analogs. This is consistent with the published literature reporting that conventional therapy often has only a limited effect on disease progression in XLH, often not achieving metabolic not radiographic recovery (Skrinar et al., 2019; Makitie et al., 2003; Alikasifoglu et al., 2021; Yanes et al., 2022). This appears to not only be due to poor adherence (present in 30 %), since compliant patients were still short (Alikasifoglu et al., 2021). Furthermore, XLH patients treated conventionally still experience poor health-related quality of life (Skrinar et al., 2019; Yanes et al., 2022).

There are several reasons that might explain a lack of efficacy of conventional therapy. First, there is wide variability in clinical practice on the doses of phosphate salts and active analogs (calcitriol or alfacalcidol) of vitamin D administered as conventional therapy, and, although there have been several attempts to standardize regimens through the publication of consensus guidelines and recommendations, these differ (Al Juraibah et al., 2021; Laurent et al., 2021; Haffner et al., 2019). Indeed, an opinion survey of Italian experts highlighted significant variability in treatment protocols across centers (Makitie et al., 2003). Second, the conventional approach only addresses the correction of phosphate and active vitamin D and not the upregulated FGF23 that drives disease progression. Third, adherence to conventional therapy is notoriously poor, especially to oral phosphate, which must be taken several times a day, taste unpleasant, and frequently causes gastrointestinal side effects (Skrinar et al., 2019). Indeed, at least three of our patients were not compliant with their conventional therapy, with Case 1 even preferring the regular injections of burosumab to taking oral phosphate and Case 2 refusing to take phosphate altogether. Taken together, there is a dire need to progress from conventional therapy regimens to improve outcomes for these patients.

Fortunately, there has been progress in therapy, at least for children and adults with XLH. Burosumab, a monoclonal antibody targeting FGF23, has been shown to correct biochemistry, function, pain, and radiological features of rickets in both children and adults with XLH, with an acceptable safety profile (mainly nausea and headache) (Imel et al., 2019; Schindeler et al., 2020; Insogna et al., 2018; Whyte et al., 2019; Carpenter et al., 2018). Indeed, in the UAE, burosumab is indicated for the treatment of XLH in adult and pediatric patients six months of age and older and for the treatment of FGF23-related hypophosphatemia in tumor-induced osteomalacia associated with phosphaturic mesenchymal tumors. Furthermore, there is emerging evidence

that burosumab is effective in other forms of hypophosphatemic rickets that result in increased FGF23 levels, such as autosomal recessive hypophosphatemic rickets (Case 5) (Bai et al., 2022). Although only one of our patients eventually received burosumab (Case 1), she enjoyed clinical improvements in rickets severity, growth, and biochemistries and, furthermore, was very satisfied with the treatment. While burosumab was approved for the treatment of adults and children with XLH aged 6 months and older in the UAE, treatment remains out of reach for some patients where the medicine is not reimbursed by public or institutional funding, as out-of-pocket funding is not an option for many, such as in Case 2.

Given that burosumab appears to outperform conventional therapy for the treatment of hypophosphatemic rickets caused by mutations that increase circulating FGF23, equitable access to burosumab for every patient and a reduction in reimbursement inequality must become a policy priority. Although health economic analyses are lacking, given the lifelong and chronic health burden of undertreated hypophosphatemic rickets, it seems likely that equitable access to targeted therapy would be both medically and fiscally advantageous.

4. Conclusions

Although rare, hypophosphatemic rickets incurs a disproportionate personal and societal burden due to misdiagnosis and mismanagement, multidisciplinary care, lifelong sequalae, the need for sophisticated genetic diagnosis, and targeted effective treatments. These clinical vignettes highlighted some real-world themes and challenges to managing patients presenting with these diverse conditions, especially the hidden burden of disease. In sharing these cases, we hope to raise awareness of these conditions, promote best practice in genetic diagnosis and management, and further advocate for reimbursement equity for effective therapies.

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CRediT authorship contribution statement

Deepti Chaturvedi: Data curation, Writing – original draft, Writing – review & editing. **Taif EmadEldin Mehasi:** Data curation, Writing – original draft, Writing – review & editing. **Assia Benbrahim:** Data curation, Writing – original draft, Writing – review & editing. **Lubna ElDeeb:** Data curation, Writing – original draft, Writing – review & editing. **Asma Deeb:** Conceptualization, Data curation, Funding acquisition, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

Data availability

Data will be made available on request.

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