# Research Review™ SPEAKER SERIES

## XLH: Management from paediatrics through transition and into adult life

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## About the speakers


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This review is a summary of several presentations given at a Kyowa Kirin-sponsored meeting which was live-streamed as part of this year's Australia and New Zealand Bone and Mineral Society (ANZBMS) Virtual Scientific Meeting. The panel of experts, which was chaired by Professor Craig Munns, used a combined bench to bedside approach and case-based format to illustrate the differential diagnosis of patients with X-linked hypophosphatemic rickets (XLH) from other conditions that can cause hypophosphatemia. The experts also reviewed the role of FGF23 in the underlying pathophysiology of the disease and discussed how to manage patients in the transition from child to adult. Several research efforts to improve the identification and lifelong management of XLH patients were also presented.

## Paediatric XLH: Diagnosis and management

### Dr Peter Simm

#### Fictional case study - Part 1

**Diagnosis & initial management**

**Presentation**

- Female
- 3rd child to non-consanguineous parents
- Normal birth weight and early development, walked at 15 months
- Leg bowing noted from 16 months and progressing
- Other evidence of rickets included frontal bossing and flaring at wrists

**Investigations**

- X-ray for bone age
- Labs (ALP, phosphate, vitamin D, PTH, FGF23, urine tubular loss, TmP/GFR)
- Genetics (PHEX)

**Diagnosis**

- X-Linked hypophosphatemic rickets (XLH)

**Management**

- Doses (starting low and building up to avoid gastrointestinal intolerance)
- Phosphate 20-60 mg/kg/day
- Calcitriol 20-40 ng/kg/day
- Allied health input – multidisciplinary care sought including early involvement of physiotherapist and occupational therapist

**8 years of age**

- Has had 5 years of phosphate/calcitriol
- Growth is tracking on the 3rd centile (mid parental height 75th centile)
- Ongoing bowing with an 8 cm intercondylar gap; orthopaedics is considering guided growth (use of 8-plates at condyles), trying to defer osteotomies until skeletal maturation
- Fasting serum phosphate levels remain 0.8-0.9 mmol/L (reference range 0.9-2.0 mmol/L for 4 to <15 years old)
- ALP has remained 400-500 U/L (within reference range)
- Nephrocalcinosis is present but stable
- Persistent mild rickets evident on bone age X-rays
- Feels left out compared with peers, less able to participate in activity, and pain is a significant limiting factor

**18 years of age**

- Has been non-compliant with oral therapy for much of adolescence
- ALP now 300 (within reference range)
- Fasting phosphate levels remain at 0.8-0.9 mmol/L
- Nephrocalcinosis did not progress but is still evident
- Height is 167 cm (mid parental height was 180 cm), epiphyses fused
- Has pain with activity so minimises strenuous activity, even walking is limited
- Time for transition to adult care

## Pathophysiology of XLH & the role of FGF23

While the gut plays a role in the absorption of phosphate, the kidney is the primary organ for phosphate metabolism. Approximately 90-95% of phosphate is resorbed by the kidney, predominantly via fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH) mechanisms. FGF23 lowers serum phosphate by decreasing phosphate reabsorption and decreasing the hydroxylation of 25OH Vitamin D which in turn decreases phosphate absorption (**Figure 1**).

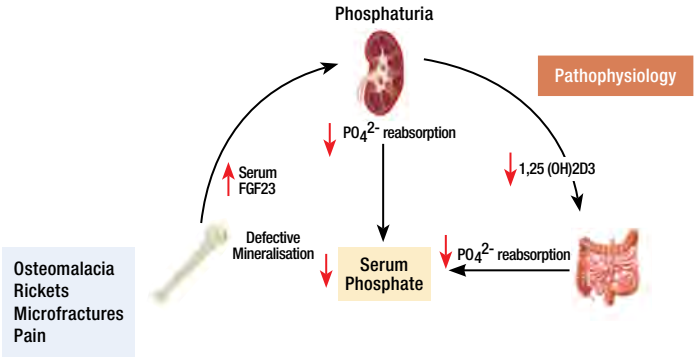


**Figure 1.** The pathophysiology of FGF23-related hypophosphatemia.

The most common form of hypophosphatemia is X-linked hypophosphatemia, which is due to inactivating mutations in the *PHEX* gene and occurs at a rate of 1:20,000 to 1:25,000.[1,2] From a biochemistry perspective, X-linked hypophosphatemia is characterised by low serum phosphate, elevated alkaline phosphatase (ALP), reduced TmP/GFR, normal or mildly elevated PTH, normal serum calcium, normal 25OH vitamin D, low 1,25(OH)2 vitamin D and elevated FGF23.[1-4]

## Causes, management and treatment outcomes

Hypophosphatemic rickets can be FGF23-mediated and non-FGF23 mediated. It has a variable phenotype in children, with symptoms such as rickets, delayed walking, limb bowing and bone pain (**Table 1**).

Table 1. **Clinical features of hypophosphatemic rickets**

| | |
|---|---|
| • Rickets | • Enthesopathies (more in adults) |
| • Delayed walking/waddling gait | • Midface hypoplasia/frontal bossing |
| • Limb bowing (post weight bearing) | • Muscle weakness |
| • Bone pain | • Dental problems - abscesses |
| • Short stature | |

It is important to investigate the cause of any phosphate loss. Because phosphate levels are variable and can change with time of day, meals, and age, the ideal approach is to perform a paired urine and serum test after an overnight fast. To document renal phosphate loss, tubular maximum resorption for phosphate (TmP/GFR) should be calculated.

Growth is a big consideration in the treatment approach. Up to 60% of children with hypophosphatemic rickets fall short of expected final heights even with therapy. Evidence suggests that commencing treatment before a child turns 1 year old can reduce orthopaedic complications and improve height outcomes.[5]

The standard therapies for hypophosphatemic rickets include:

- Phosphate replacement - regular dosing is key to overcoming reduced TmP/GFR, which rapidly increases with phosphate dosing but is back to baseline levels within 90 minutes; the recommended dose is 20-60mg/kg/day, which is best divided up to 5-7 times per day
- Calcitriol - recommended dose of 20-40 ng/kg/day to prevent secondary hyperparathyroidism; note there is no need for calcitriol for non-FGF23-mediated disorders
- Growth hormone therapy - not recommended as routine therapy due to a lack of efficacy data
- Allied health input and support from the time of diagnosis.

Treatment for hypophosphatemic rickets can have complications. Normalising serum phosphate is difficult to achieve without exacerbating other problems, and children need to be monitored (**Table 2**). Complications can include diarrhoea and intolerance to high phosphate doses, nephrocalcinosis, secondary/tertiary hyperparathyroidism and incomplete resolution of growth issues, pain or other skeletal changes such as bowing. In addition, children with hypophosphatemic rickets may develop lower limb deformity, with around two thirds requiring some operative intervention. They can also develop dental abscesses, craniosynostosis, osteotomies, Arnold/Chiari malformations and hearing issues.

Table 2. **Suggested monitoring plan for children with hypophosphatemic rickets**

| 3-monthly | 6-monthly | Yearly | As needed |
|---|---|---|---|
| • Growth<br>• Se ALP<br>• Se PTH<br>• Urine Ca/Cr ratio | • Dental review | • Renal ultrasound<br>• Bone age<br>• 6-minute walk test (over age 5) | • Ongoing multidisciplinary therapy (e.g. physiotherapy and occupational therapy)<br>• Orthopaedic input if significant bowing<br>• Low threshold for MRI if headaches, persistent vomiting or abnormal skull shape |

**Ca/Cr** = calcium/creatinine; **MRI** = magnetic resonance imaging; **Se ALP** = serum alkaline phosphatase; **Se PTH** = serum parathyroid hormone

There are challenges associated with the treatments for hypophosphatemic rickets. Conventional therapy is difficult to comply with given the frequency of dosing required and the possible side effects, and most patients with residual deformities will require intervention and have reduced final height.

## Genetic disorders of phosphate metabolism: How to manage the transition to optimal lifelong adult care

Professor Richard Prince

### Fictional case study - Part 2

#### Outcomes (32 years of age)

**Presentation**

- Has had a stress fracture right hip which was pinned
- Underwent a total right knee replacement
- Had non-healing stress fractures in the right and left midshaft femora
- Suffers from anxiety and depression
- Now has right thigh pain

**Investigations**

- There is an oblique band of moderately intense uptake of tracer in the right proximal femoral shaft in the subtrochanteric region; on SPECT/CT imaging this is at the anterior cortex of the proximal femur and has an oblique orientation
- In the left proximal femur, there is a further less intense focus of uptake involving the medial cortex; no definite cortical abnormality can be seen on the correlative slices of the low dose CT study
- Biochemistry - Fasting phosphate 0.87 mmol/L (ref range 0.75 -1.5), TmP/GFR 0.63 mmol/L GF (ref range 0.75 - 1.35), ALP 167 U/L (ref range 30-110), eGFR, PTH and 25-OH Vit D within reference range,

**Management**

- Heal insufficiency fractures with pain control and optimisation of fracture callus mineralisation through increased dietary phosphate, continued calcitriol and optimised vitamin D
- Long-term management to prevent excessive osteomalacia and reduce nephrocalcinosis risk
- Liaise with expert dentist
- Review joint status

## Diagnosing XLH in adults

Some patients with XLH will be diagnosed for the first time as an adult. A recently reported study suggests that approximately 11% of XLH cases are diagnosed after the age of 18.[6] When diagnosing XLH in adults it is important to:

- Manage vitamin D deficiency
- Exclude hyperparathyroidism-induced phosphate wasting
- Exclude Fanconi type syndromes
- Determine whether there is FGF23 dependent disease.

Patients with genetic hypophosphatemic osteomalacia have a range of clinical and functional problems (**Table 3**). A study examining the lifelong impact of XLH found recurrent fractures occurred most often in the femur, feet, and tibia/fibula.[7] XLH can also result in osteoarthritis, osteophytes and enthesophytes, which in turn can affect biomechanical function.[8] Most (almost 100%) of patients with XLH have dental abnormalities, specifically enamel defects.[9]

Table 3. **Clinical and functional problems in patients with genetic hypophosphatemic osteomalacia**

**Structural bone abnormalities**

- Short stature
- Osteomalacia / hyperparathyroidism
- Fractures

**Structural joint abnormalities**

- Enthesopathy
- Joint stiffness
- Spinal stenosis

**Muscle weakness**

**Dental abnormalities**

- Dental abscess

**Renal complications**

**Hearing loss and tinnitus**

**Functional abnormalities**

- Pain
- Ambulation difficulties
- Fatigue
- Loss of balance

## Managing adults with XLH

XLH is a burdensome disease, causing bone pain and joint pain in both adults and children.[7] When considering metabolic treatment for adult patients with XLH, several issues should be considered. These include the reasons for the use of calcitriol and phosphate e.g. stress and completed fracture healing, tooth abscess healing, and/or the prevention of severe osteomalacia based on normalising ALP. Physicians should also consider how to prevent hyperparathyroidism and renal failure.

The patient perspective is also an important consideration. Two surveys conducted in 286 adult patients found:[10]

- Mobility and chronic pain were the symptoms that had the biggest impact on quality of life
- 35% of responders indicated that hypophosphatemia had a severe impact on daily life
- Almost half of the patients (44%) used over the counter medications to relieve pain, and 18% used opioid medications
- The impact of the disease increased over time, having additional impacts for 84% of responders.

## National guidelines

The Australian and New Zealand Hypophosphatemic Management Working Party is an initiative of ANZBMS which aims to improve the health management of hypophosphatemic rickets in adults by developing agreed national guidelines. The guidelines will consider a range of issues in the management of patients, including the need for a consulting expert to manage hypophosphatemic rickets, how to transition from paediatric to adult care, what optimal adult XLH management looks like, and the role of allied health professionals. This is particularly relevant given the polling of the ANZBMS audience showed there were differing views on whether to treat adult XLH patients, when to treat them, and what to treat them with (phosphate monotherapy, calcitriol monotherapy or combined phosphate and calcitriol).

# Current Australian & New Zealand studies

## Studies 1 & 2: Australian & New Zealand paediatric XLH prevalence surveys

### Associate Professor Benjamin Wheeler

**Background:** The Australian and New Zealand Paediatric Surveillance units (APSU and NZPSU) are well placed to investigate rare paediatric diseases such as XLH given their involvement in monitoring and surveillance in both countries.

**Objectives**: To estimate the prevalence of XLH in Australia & New Zealand, and to describe the cases in terms of demographics, family history, biochemistry, clinical features, and treatments.

**Methods:** Observational survey study where one-off XLH report cards will be sent to all paediatric specialists in Australia and New Zealand (mirrored). The report cards are to be completed for children with:

- Radiological evidence of rickets, ALP values above the normal age and gender-matched limits of the local laboratory range, and serum phosphate values below the normal limits of the local laboratory range, and
- Either a pathogenic mutation in the *PHEX* gene, and/or FGF23 levels above the limits of the local laboratory range, and/or family history that supports X-linked inheritance.

The XLH report card will also be sent to physicians of adult patients to capture data on adults with XLH.

## Study 3: Clinical registry to evaluate treatment outcomes in paediatric X-linked hypophosphatemic rickets (XLH) in Australia

### Professor Craig Munns

**Objective:** To establish a REDCap electronic registry that captures longitudinal clinical data and treatment outcomes in Australian children with XLH.

**Methods:** A prospective, longitudinal, patient registry study consisting of a pilot study of approximately 30 paediatric XLH patients currently being managed at the Children's Hospital Westmead, followed by an extension study consisting of approximately 250 paediatric patients. The study will initially run for 18 months with the potential for long-term follow up (>10 years). Clinical, biochemical, radiological, and quality of life data will be collected. Eligible patients will include children with:

- Radiological evidence of rickets, ALP values above the normal age and gender-matched limits of the local laboratory range and serum phosphate values below the normal limits of the local laboratory range, and
- Either a pathogenic mutation in the PHEX gene, and/or FGF23 levels above the limits of the local laboratory range, and/or family history that supports X-linked inheritance.

### Take home messages

- Treating XLH in children can be challenging and close monitoring is required; the standard therapies for XLH in children include phosphate replacement and calcitriol along with involvement from allied health professionals.
- Treating adults with XLH involves thinking about the reasons for the use of calcitriol and phosphate, prevention of hyperparathyroidism and renal failure and consideration of the patient perspective.
- There is a lot of variability in how adults with XLH are managed, highlighting a need for national guidelines and a better approach to the transition from paediatric to adult patients.
- Studies being conducted in Australia and New Zealand will provide insight into the prevalence, characteristics and treatment outcomes of XLH patients.

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