Diagnosis and Management of X-linked Hypophosphatemia (XLH)

August 10, 2018

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## Disclosures

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<td>Stock ownership/ Corporate</td>
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Agenda

- Pathology, Diagnosis and Natural history of XLH
- Historical standard of care for XLH
- Innovations in care of patients with XLH
Albright provided the classical description of the disease now known as XLH in 1937\(^1\), although “rachitis tarda” was described much earlier in cases of resistance to treatments such as cod-liver oil.

- This paper describes a 16 year old patient with 15 years of rickets resistance to physiologic vitamin D and heliotherapy.

- Individual fractures were assisted in healing by extremely high vitamin D dosages.
Winters described in 1958 a family from North Carolina with chronic hypophosphatemia and rickets\(^2\) and important observations were made:

- Rickets were worse in males than in females
- No instances of male-to-male transmission
- Renal phosphate absorption 50% of normal
- Rickets were resistant to vitamin D effects on phosphorus, but not on calcium
- 5 possible mechanisms were proposed, one of which #4 turned out to be essentially correct
Glorieux and colleagues reported in 1972 the treatment of 8 patients with XLH with phosphate salts and Vitamin D$_3$ and were observed to have improvements in growth and resolution of rickets.

- Improvement in serum phosphorus was noted.
- With some refinements, this treatment modality has been our standard of care for the past forty-plus years.
XLH at birth

Patients with XLH tend to be

- normal at birth
- and have a rather variable phenotype

- Hypophosphatemia is present from birth, but obvious signs and symptoms will develop over the first year of life
- Patients without known family history will typically escape detection somewhat longer than those with a family history
Short stature is not universal, but is common and more significant in males as compared to females.

Bowing often develops as children grow and begin to walk in the first two years of life, and severity can be estimated by medial knee distance or by radiographic measurements\(^4\).
Pediatric Diseases – Metaphyseal Changes

Widened and frayed metaphyses are common findings of XLH

The distal femur, proximal tibia, and the distal aspect of the radius and ulna are locations which are frequently affected by rickets\(^5\)

Carpenter et al, 2011
Dental manifestations in XLH are common and include:6,7

- Enamel hypoplasia and discoloration
- Thinning of dentin with enlargement of pulp chambers
- Chronic or recurrent dental abscesses

Foster et al, 2014
Souza et al, 2010
Pediatric Disease - Skull

- Craniosynostosis
  - Sagittal suture appears most common\(^2^2\)
- Frontal Bossing with dolichocephaly
- Flattened Cranial Base
- Decreased depth of posterior fossa
- Chiari I Malformation – 44\% of patients\(^2^3\)
Pediatric Disease - Other

- Motor delay
- Stiffness and pain
- Alteration to walking and running gait
Adult Disease - Osteomalacia

- Osteomalacia can be seen in adults with XLH\(^8\), and can contribute to:
  - Fractures
  - Bone Pain
  - Stiffness
  - Early-onset Arthritis

Carpenter et al, 2011
Enthesopathy is a common finding (30-84%) in patients with XLH and is the result of excessive mineralization of the enthesis fibrocartilage.

These lesions are frequently painful and can limit mobility.

Liang et al, 2009
Dental Abscess – 86% of patients

Hearing Loss

Joint Pain – 82% of patients

Muscle pain and weakness, can occur due to hypophosphatemia for any reason

Poor exercise and activity tolerance
What are Rickets?

Any condition which results in the failure of bone mineral (hydroxyapatite) to accumulate properly into the bone

Historically, have occurred for nutritional reasons, but now this is uncommon in the United States

London during the Industrial Revolution
Phosphate Utilization

- Diets are generally rich in phosphate, of which approximately 60-70% is absorbed by the small intestine
  - Process regulated by 1,25-hydroxyvitamin D
- Phosphate is filtered by the glomerulus and then reabsorbed by sodium phosphate transporters in the proximal tubule
  - These transporters can be downregulated by FGF23 and PTH
Function of FGF23

- Predominantly produced by the osteocytes
- Two main mechanisms of action\textsuperscript{26}
  - Inhibit renal tubular phosphate reabsorption
  - Suppress 1-alpha hydroxylase activity
- Requires FGFR And Klotho coreceptors for activity
Nature of Renal Phosphate Wasting

Pathogenic PHEX variant

Upregulation

FGF23

Effect on Sodium/Phosphate Effect
- Increases Phosphate Excretion

Effect on 1 alpha hydroxylase
- Decreases Phosphate Absorption
There are several different types of hypophosphatemic rickets, which can differ in phenotype and inheritance pattern.

Today, we are discussing X-linked hypophosphatemic rickets:

- X-linked dominant disorder, which is uncommon
- Caused by loss of function pathogenic variants in the \textit{PHEX} gene, which is a phosphate-regulating endopeptidase
Between 57%-78% of the variants detected have been on sequencing analysis.

This leaves 22%-43% of variants detected on deletion/duplication analysis.

Studies vary on total yield of PHEX analysis, but suffice to say it is substantially below 100%.¹⁰

– Normal testing does NOT rule out XLH in a patient with appropriate clinical and biochemical findings.
Epidemiology and Prevalence of XLH

- XLH is a rare disease, which means that it affects fewer than 200,000 Americans\textsuperscript{11}
- The incidence of XLH is generally believed to be approximately 1 in 20,000 to 1 in 25,000 which makes it approximately as common as osteogenesis imperfecta
Diagnosis of XLH

- Personal history of Rickets
  - Can get murky pretty quickly; patients may have been told that they had nutritional rickets or another skeletal disorder

- Family history
  - Helpful if present, but about 30% are new dominant mutations\(^ {12} \)
Diagnosis of XLH

- Serum phosphorus – Low
- Urine phosphorus - High
- Serum calcium – Normal
- Urine calcium – Normal
- Alkaline phosphatase – High
- 25-OH Vitamin D – Normal
- PTH – Can be elevated or normal
- FGF23 – Typically elevated
Conventional Treatment in XLH

Conventional medical treatment has been administration of:

- **oral phosphate supplementation**
- **and calcitriol supplementation**

**Phosphorus 20-40 mg/kg/day**

Will be ineffective unless calcitriol is coadministered

**Calcitriol 20-30 ng/kg/day**
Conventional Treatment in XLH

- Phosphate supplements generally must be divided into several (3-5) doses a day
- Calcitriol supplements generally can be given two times per day
- In both cases, it pays to start at doses much lower than target doses and slowly move up
Safety

- Serum phosphorus, serum and urine calcium, renal ultrasound, PTH
  - Do not attempt to normalize phosphorus
  - Avoid hypercalcemia, hypercalciuria, nephrocalcinosis
  - Avoid hyperparathyroidism
Monitoring Conventional Therapy

Efficacy

• Alkaline phosphatase, radiology
  • Decrease in alkaline phosphatase level into high normal range suggests healing of rickets
• For pediatric patients, rickets survey will show improvement in metaphyseal changes and bowing over time
• Improvement in growth for children, reduction in pain for children and adults
Rationale for Treatment

- Renal phosphate wasting due to increased phosphate excretion and decreased absorption
  - Decreased absorption related to 1-alpha hydroxylase downregulation targeted by calcitriol supplementation
  - Increased phosphate excretion has historically been difficult to address, but has been indirectly supported by exogenous phosphate administration
Additional Treatment of XLH

- Surgical Treatment is sometimes required, and can be much more conservative with good medical therapy
  - For children, this may be mean leg straightening surgeries or craniosynostosis surgeries
  - For adults, rodding after fracture, arthroplasty, and dental procedures may be necessary
Benefits of Conventional Treatment in Children

- Consistent treatment during growth results in\(^5,^{13}\)
  - Correction of rickets
  - Partial correction of skeletal abnormalities
  - Decrease in need for surgical intervention
  - Improved final height
Benefits of Conventional Treatment in Children

- Additional study has also suggested\(^1^4\)
  - Increase in growth velocity, especially during early phase of treatment
  - Improvement (but not normalization) of serum phosphorus levels
Benefits of Conventional Treatment in Adults

- Adults with XLH can have:
  - Osteomalacia
  - Fractures
  - Enthesopathy
  - Dental Disease
  - Pain
  - Decreased mobility
Benefits of Conventional Treatment in Adults

- Sullivan and colleagues\textsuperscript{15} found that supplementation improved
  - Experience in musculoskeletal symptoms
  - Biochemical parameters related to XLH
  - Osteoid volume and mineral apposition rates
- Adverse events including hyperpara and renal insufficiency were noted
Conner and colleagues\textsuperscript{16} found additionally that extent of therapy did not predict the extent of enthesopathy, but that the extent of therapy was correlated with the extent of dental disease.

Treatment in adulthood may not promote or prevent enthesopathy; however, it may be associated with a lower risk of experiencing severe dental disease.
Limitations of Treatment

Mechanistically, treatment with phosphorus and calcitriol is only a partial treatment

Doesn’t address central *PHEX* problem of FGF23-driven phosphaturia

As a practical matter, **adherence** is really difficult for this disorder

- Phosphate supplementation required between three and five times per day and calcitriol twice per day which is difficult to remember
- Phosphate supplementation causes stomach upset and diarrhea, which can further impact adherence
Limitations of Treatment

- Conventional therapy can improve growth, but patients still do not catch up completely\(^2\)\(^4\)
  - XLH patients in one study had decreased stature (-3.3 SDS), which
  - Leg length (-3.8 SDS) was most impaired
  - Sitting height (-1.7 SDS) was relatively more normal

- Overtreatment can cause hyperpara, nephrocalcinosis, chronic kidney disease
Conventional treatment of XLH has been incomplete

Ideal treatment would address underlying mechanism of disease

– Restoration of PHEX activity – HARD
– Inhibition of FGF23 activity – EASIER?
Burosemab for treatment of XLH

- KRN23 is a monoclonal antibody that binds to and inactivates FGF23
- Phase 1 study in humans showed
  - Increase in serum phosphorus
  - Increase in serum 1,25-dihydroxyvitamin D
  - Increase in TmP/GFR
- Biochemical responses were quicker in the IV group, but longer lasting in the SC group

Carpenter et al, 2014
Burosemab for treatment of XLH

- Sequential Phase 1/2 trial involving 28 adults with XLH for 4-month dose escalation\(^1\)\(^8\
- 3.7\% had normal serum phosphorus at baseline
- 88.5\% had normal serum phosphorus by day 7 after fourth dose
- 22 patients continued to 12 month extension study\(^1\)\(^9\)
- Mean peak phosphorus 2.6 – 3.0 mg/dL
- Mean trough phosphorus 2.3 – 2.5 mg/dL

\(\text{Imel et al, 2015}\)
Open-label Phase 2 trial, 52 children with XLH randomly assigned to receive SC burosemab either every 2 weeks or 4 weeks\textsuperscript{19}

- Dose adjusted to achieve serum phosphorus at lower end of normal range
- Primary endpoint was improvement in Thacher Rickets Severity Score
- Radiographic Global Impression of Change was used to compare radiographic appearance at weeks 40 and 64 to baseline
Burosemab for treatment of Pediatric XLH

- Increases in serum phosphorus seen in both groups, but more stable in every two week group
- Renal tubular phosphate reabsorption increases in both groups
- Increased 1,25-dihydroxyvitamin D and decreased ALP seen
- Significant reduction in RSS, denoting overall improvement in rickets
- RGI-C noted improvement in entire cohort, but more marked in subcohort of patients with higher RSS
Burosemab for treatment of Adult XLH

- 133 Patients completed 24 week double-blinded, placebo-controlled Phase 3 RCT\textsuperscript{21}
  - 68.7\% had previous orthopedic surgery
  - 63.4\% had history of osteoarthritis
  - 99.3\% had evidence of enthesopathy
  - 69.4\% had previous conventional therapy
  - 71.6\% had severe pain
Patients who received burosemab had a significantly higher rate of normal serum phosphate both at midpoint of dosing (94.1% vs. 7.6%, p<0.001) and at the end of the dosing interval (67.6% vs. 6.1%)

-5 patients required dose reduction due to Phos level greater than 4.5

TmP/GFR also increased significantly in the burosemab group (1.7+/− 0.4 to 2.7 +/- 0.75), but very little change was seen in the placebo group
Burosemab for treatment of Adult XLH

- 32 (47.1%) subjects in the burosumab group had 65 active fractures at baseline.
- 38 (57.6%) subjects in the placebo group had 91 active fractures at baseline.

- By week 24, 43.1% of patients in the burosemab group had fracture healing compared with 7.7% in the control group.
Burosemab for treatment of Adult XLH

Trend toward improvement in pain for adults with XLH

Significant improvement in WOMAC physical function and stiffness scores

Fig 2. Effect of burosumab on participant-reported outcomes. Data are expressed as least squares mean change from baseline ± standard error. BPI = Brief Pain Inventory; WOMAC = Western Ontario McMaster Universities Osteoarthritis Index.
Dosing of Burosemab

- Burosemab should not be coadministered with phosphate and/or calcitriol supplementation
- Do not use if hypophosphatemia is not present
- Only use if chronic kidney disease is not present
- Pediatric dosage is 0.8 mg/kg SC every two weeks
- Adult dosage is 1 mg/kg SC every four weeks
Surveillance of Burosemab

- In children, serum phosphorus every 4 weeks for the first 3 months of treatment
  - If serum phosphorus is greater than 5 mg/dL, dose should be reduced and reassessed in four weeks
  - If serum phosphorus is below LLN, can be increased
  - If serum phosphorus is normal, continue present dose

- Specific recommendations for dosage adjustment provided in burosemab PI
Surveillance of Burosemab

- In adults, the maximum dose is 90mg
- Serum phosphorus should be measured on a monthly basis, measured 2 weeks post-dose, for the first 3 months of treatment
- If serum phosphorus is above the normal range, withhold the next dose and reassess the serum phosphorus level after 4 weeks
  - The patient must have serum phosphorus below the normal range to be able to reinitiate
## Adverse Events seen with burosemab therapy

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<th>Adult Patients</th>
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<tr>
<td>Headache</td>
<td>Back pain</td>
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<tr>
<td>Injection site reaction</td>
<td>Headache</td>
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<tr>
<td>Vomiting</td>
<td>Tooth infection</td>
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<tr>
<td>Fever</td>
<td>Restless leg syndrome</td>
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<tr>
<td>Pain in arms and legs</td>
<td>Decreased vitamin D levels</td>
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<tr>
<td>Decreased vitamin D levels</td>
<td>Dizziness</td>
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<tr>
<td>Rash</td>
<td>Constipation</td>
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<td>Toothache or infection</td>
<td>Hyperphosphatemia</td>
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<td>Muscle pain</td>
<td></td>
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<td>Dizziness</td>
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Conclusions

XLH is a rare, but significant disease which has multiple impacts on health throughout the lifespan.

Standard treatments have been suboptimal and difficult to comply with.

Burosemab offers therapy which targets hyperphosphaturia and shows efficacy for XLH.
THANK YOU!
References


References


22. Imel EA, Personal Communication.

