ENDOCRINE SOCIETY PRESENTS

Diagnosis and Management of Hypophosphatasia: IMPROVING PATIENT OUTCOMES

SATURDAY, APRIL 1, 2017
7:00 – 9:30 PM
Registration & Meal Service:
6:30 – 7:00 PM
Hyatt Regency Orlando
Regency Ballroom R on the Convention Level

PROGRAM CHAIR
Leanne Ward, MD, FRCPC
Senior Scientist, CHEO Research Institute
Research Chair in Pediatric Bone Health, University of Ottawa
Associate Professor, Faculty of Medicine, University of Ottawa
Director, Pediatric Bone Health Clinical and Research Programs, CHEO

FACULTY
Erik Imel, MD, MS
Assistant Professor of Medicine and Pediatrics, Indiana University, School of Medicine
Linda DiMeglio, MD, MPH
Associate Professor of Pediatrics, Indiana University, School of Medicine

AGENDA
Alkaline Phosphatase in Health and Disease
Clinical Spectrum of Hypophosphatasia
Treatment Options in the Management of Hypophosphatasia

LEARNING OBJECTIVES
Upon completion of this educational activity, participants will be better able to:
• Describe the role of alkaline phosphatase and discuss the genetic underpinnings of hypophosphatasia
• Describe the skeletal and non-skeletal manifestations of hypophosphatasia
• Apply recently approved treatment option in perinatal, infantile and juvenile-onset hypophosphatasia
• Management of ongoing treatment of patients with hypophosphatasia

CME CREDITS: 2.5
AMA PRA Category 1 Credits™

This activity is supported by an educational grant from Alexion Pharmaceuticals, Inc

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SYMPOSIUM AGENDA

Diagnosis and Management of Hypophosphatasia: Improving Patient Outcomes
Saturday, April 1, 2017

7:00 – 7:05 PM  Welcome and Introduction
Leanne Ward, MD, FRCPC

7:05 – 7:45 PM  Alkaline Phosphatase in Health and Disease
Erik A. Imel, MD

7:45 – 8:25 PM  Clinical Spectrum of Hypophosphatasia
Linda A. DiMeglio, MD, MPH

8:25 – 9:05 PM  Treatment Options in the Management of Hypophosphatasia
Leanne Ward, MD, FRCPC

9:05 – 9:10 PM  Summary
Leanne Ward, MD, FRCPC

9:10 – 9:30 AM  Audience Q&A

FACULTY

Leanne Ward, MD, FRCPC – Program Director
Associate Professor, Departments of Medicine and Surgery
University of Ottawa
Medical Director, Pediatric Bone Health Clinical and Research Programs
Children’s Hospital of Eastern Ontario
Ottawa, Canada

Erik A. Imel, MD, MS
Associate Professor of Medicine and Pediatrics
Indiana University School of Medicine
Indianapolis, IN

Linda A. DiMeglio, MD, MPH
Professor of Pediatrics
Director of Career Development and Co-Chair of the Pediatric Protocol Development Team
Indiana University Clinical and Translational Science Institute
Indianapolis IN
**FACULTY BIOGRAPHY**

**Leanne Ward, MD, FRCPC – Program Director**

Dr. Leanne Ward is an Associate Professor of Pediatrics at the University of Ottawa where she has held a Research Chair in Pediatric Bone Health since 2010. She is the Medical Director of the Pediatric Bone Health Clinical and Research Programs at the Children’s Hospital of Eastern Ontario and a pediatric endocrinologist within the Division of Endocrinology and Metabolism. Dr. Ward’s research program is dedicated to the study of bone development and the treatment of bone disorders in children. She has been the principal investigator of the “STOPP” research program (STeroiD-induced Osteoporosis in the Pediatric Population), a pan-Canadian project funded by the Canadian Institutes of Health Research to evaluate the effect of glucocorticoids on bone health in children with chronic illnesses. Dr. Ward actively leads and collaborates on a number of clinical trials for children with osteogenesis imperfecta, rickets and chronic illness osteoporosis. She has served as an endocrinology and bone health advisor to various national and international organizations on various aspects of skeletal health in children, including the Centres for Disease Control Clinical Care Guidelines for Duchenne Muscular Dystrophy and the International Conference on Children’s Bone Health. Dr. Ward has received a number of awards for her work in pediatric bone health, including a Canadian Child Health Clinician Scientist Career Development Award, a Canadian Institutes for Health Research New Investigator Award, a Canadian Child Health Clinician Scientist Career Enhancement Award, and two, five-year Research Chairs in Pediatric Bone Health (University of Ottawa, 2010 and 2015).

**Erik A. Imel, MD, MS**

Dr. Imel is an Associate Professor of Medicine and Pediatrics at the Indiana University School of Medicine and Riley Hospital for Children. He is Board Certified in both adult endocrinology and pediatric endocrinology. His clinical and research focus is in metabolic bone disorders in children and adults, especially rare bone disorders including disorders of phosphate metabolism.

**Linda A. DiMeglio, MD, MPH**

Dr. DiMeglio is a Professor in the Department of Pediatrics, Section of Pediatric and Diabetology at the Indiana University School of Medicine. After graduating from Harvard University with honors, Dr. DiMeglio obtained her MD from the University of Pennsylvania in Philadelphia, PA and performed her residency in Pediatrics at Children’s Memorial Hospital (Northwestern University) in Chicago, IL. She completed her fellowship in Pediatric Endocrinology and received her Master’s in Public Health from Indiana University-Purdue University, Indianapolis. Dr. DiMeglio has been working in clinical and translational research with a focus on novel technologies and therapies for type 1 diabetes and therapies for metabolic bone disease and since her fellowship. She performed the first randomized, controlled trial of insulin pump therapy for very young children and is currently the principal investigator for a multisite study designed to optimize the use of continuous glucose monitors in children with diabetes under the age of 8. She also is an active clinician, sees patients with endocrine disorders and diabetes in clinics and teaches medical students, residents, and fellows.
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The Endocrine Society is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

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LEARNING OBJECTIVES

Upon completion of this educational activity, learners will be better able to:

- Describe the role of alkaline phosphatase and discuss the genetic underpinnings of hypophosphatasia
- Describe the skeletal and non-skeletal manifestations of hypophosphatasia
- Apply recently approved treatment option in perinatal, infantile and juvenile-onset hypophosphatasia
- Management of ongoing treatment of patients with hypophosphatasia

TARGET AUDIENCE

This continuing medical education activity should be of substantial interest to endocrinologists and endocrine fellows, pediatric endocrinologists and pediatric endocrine fellows, and other healthcare professionals caring for patients with metabolic bone disorders.

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Linda A. DiMeglio, MD: Investigator, Alexion
Leanne Ward, MD: Advisory Group Member, Alexion; Investigator, Novartis Pharmaceuticals

The faculty reported the no relevant financial relationship: Erik A. Imel, MD

The following SPC member who reviewed content for this activity reported relevant financial relationships:

E Michael Lewiecki, MD: Consultant, Amgen, Merck, Eli Lilly, Radius Health, Shire, Abbvie and Alexion; Speaker, Alexion, Shire; Research Grant Support, Amgen, Eli Lilly, Merck
Joan Han, MD: Research Support, Rhythm Pharmaceutical

The following SPC Committee members reported financial relationships:

Zahid Ahmad, MD: Research Support, Regeneron, FH Foundation; Consultant, Regeneron; Speaker, Amgen, Genzyme, Sanofi
Andrew Ahmann, MD: Research Support, Dexcom, Lexicon, Medtronic, Novo Nordisk; Consultant, Dexcom, Novo Nordisk, Trividia Health
Giuseppe Barbesino, MD: Spouse, employee of Genzyme
John Carmichael, MD: Research Support, Novo Nordisk, Chiasma, Novartis, Pfizer, Strongbridge Biopharma; Speaker, Novartis; Advisory Board, Pfizer, Chiasma, Ionis Pharmaceuticals
Natalie Cusano, MD: Research Support, Shire; Speaker, Shire
Alan Kelly, MD: Speaker, Eli Lilly
Lisa Nachtigall, MD: Consultant, Ipsen, Novartis, Corcept; Grant Support/Investigator, Chiasma
Neda Rasouli, MD: Research Support, Novo Nordisk, Calibra, INTARCIA Therapeutics, GlaxoSmithKline, Bristol Meyer Squibb, AstraZeneca /Amylin, Ionis Pharmaceuticals, Boehringer Ingelheim

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The following SPC members reported no relevant financial relationships: Connie Newman, MD, Amy Rothberg, MD

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Alkaline Phosphatase
in Health and Disease

Erik Allen Imel, M.D.
Alkaline Phosphatase in Health and Disease

Erik Allen Imel, M.D.
Associate Professor of Medicine and Pediatrics
Endocrinology
Indiana University School of Medicine
April 1, 2017

Disclosures

• None
• No off-label medication discussions.

Objectives

• Review the role of alkaline phosphatase
  – Gene
  – Protein function and substrates
• Identify conditions associated with abnormal alkaline phosphatase levels
  – High
  – Low
• Identify consequences of low alkaline phosphatase
• Describe genetic abnormalities causing hypophosphatasia

Clinical case question

This 6 month old infant has seizures, hydrocephalus, nephrocalcinosis and rachitic changes. Which abnormality, if present, would differentiate her cause of rickets most specifically from other types of rickets?

A. Low serum phosphorus
B. High pyridoxal 5’-phosphate
C. Low serum calcium
D. Low urinary calcium
E. High bone specific alkaline phosphatase

Image from Imel, in Pediatric Endo Board Review 2013, The Endocrine Society

Alkaline phosphatase gene and protein

• In humans 4 genes encode alkaline phosphatase
• 3 “Tissue-specific” ALPs on chromosome 2q34-37
  – Intestinal ALP
  – Placental ALP
  – Germ-cell placental-like ALP
• 1 “Tissue-nonspecific” ALP (TNSALP) expressed in liver, kidney, bone
  – encoded by the ALPL gene on 1p36.1-p34
  – >50kb, 12 exons, 11 translated
  – 507 amino acids
  – Tissue-specific glycosylation (Bone ALP has O-glycosylation)

Alkaline phosphatase enzyme function

• Works at physiologic pH
• Dimerizes
  – Each monomer binds 4 metal ions
  – 2 Zn, 1 Mg, 1 Ca
• An ectoenzyme
• Anchored to cell membranes or membrane vesicles by glycosyl phosphatidylinositol (GPI)
• Also released into circulation

**ALP substrates**

- Dephosphorylates phosphoesters and inorganic pyrophosphate (PPi)
- ALP competitively inhibited by inorganic phosphate (Pi)

**Intestinal ALP**

- Component of the gut mucosal defense
- Prevents bacterial invasion through gut mucosa
- Can detoxify endotoxin (LPS) by removing a Pi group
- In mice, different isoforms have different effects on fat absorption.

**Placental and Placental-like**

- Uncertain function
- May be expressed in some tumors.

**Kidney ALP**

- Present in kidney proximal tubule
- Regulates PPi metabolism
  - (though PPi is excreted primarily downstream of the proximal tubule)
- Can detoxify endotoxin (LPS) by removing a Pi group

**Liver ALP**

- Expressed in hepatocytes and cholangiocytes and secreted into bile
- Inhibits ductal bile secretion
  - By decreasing activity of the basal Cl-/HCO3- exchanger
- May act as ATPase and modulate purinergic signaling
- Dephosphorylates and inactivates CFTR
  - In experimental conditions
- Can detoxify endotoxin (LPS) by removing a Pi group

**Bone ALP and PPi**

- Bone ALP is expressed in hypertrophic chondrocytes and osteoblasts.
- Hydroxyapatite (HA) crystals form in membrane vesicles and are propagated on the collagen matrix.
- Bone ALP cleaves PPi, releases Pi, and facilitates crystal growth.
- Formation of HA
  - Optimal at Pi/PPi ratio >140
  - Inhibited at ratio <70
  - Calcium Pi dehydrate (CPPD) precipitates at ratio <6.
Bone ALP and PPI

- This process is also important for mineralization of teeth.
- Cementum and dentin are under mineralized in HPP.

Bone ALP and PPI

- ALP increases to minimize PPI and to optimize Pi at the mineralization front in:
  - Conditions of impaired mineral availability
    - Nutritional rickets
    - Hypophosphatemic rickets
    - Etc.
  - Increased bone formation
    - Physiologic (childhood and adolescence)
    - Osteoporosis induced by anabolic bone agents
    - Pathologic (fibrous dysplasia, Pagets, etc.)
    - Etc.

Bone ALP, HPP and PPI

- Without ALP, PPI accumulates, binds hydroxyapatite
- Inhibits propagation of crystals.
- Hydroxyapatite formation within membrane vesicles seems relatively preserved.

Bone ALP, HPP and PPI

- Without ALP, mineralization is impaired
  - Disruption of the growth plate
  - Rickets and osteomalacia
  - Skeletal deformity
  - Accumulation of extracellular calcium and Pi
    - Levels often high normal or high
    - Hypercalcemia
    - Nephrocalcinosis
  - Amorphous calcium pyrophosphate deposition
    - Pseudogout
    - Pyrophosphate arthropathy
    - Chondrocalcinosis

Bone ALP in vessels

- PPI inhibits calcification in vessels.
- TNSALP overexpression in vascular smooth muscle causes calcification.

Pyridoxal 5'-phosphate (PLP)

- Major form of vitamin B6
- PLP cannot cross plasma membranes.
  - Must be dephosphorylated to pyridoxal by TNSALP
  - Then rephosphorylated intracellularly to PLP.
- Without TNSALP, extracellular PLP increases.
- HPP does not typically cause full B6 deficiency syndromes (dermatitis, stomatitis, neuritis, anemia)
ALP is expressed in CNS

- In the CNS, PLP is a cofactor for synthesis of certain neurotransmitters.
- However, in severe HPP:
  - Low intracellular PL and PLP
  - Seizures
  - Can suppress seizures by taking pyridoxal (PL), the hydrophobic form of B6

Intracellular Synthesis of GABA, serotonin, etc.

ALP influences in CNS

- Production of neurotransmitters, mediated by PLP
- May influence neural cell differentiation
- May contribute to accumulation of dephosphorylated tau protein in Alzheimer's disease.

Phosphoethanolamine (PEA)

- Part of the glycosyl phosphatidyl inositol (GPI) protein anchor complex

\[
\text{HO-PO}_2\text{-NH}_2
\]

Phosphoethanolamine (PEA)

- The specific source of high circulating PEA is uncertain in HPP
  - PEA may come from degrading these protein anchor complexes
  - Impaired breakdown by liver
  - TNSALP may breakdown PEA
  - PLP is a cofactor for O-PEA-phospho-lyase:
    - Converts PEA to acetaldehyde, Pi, and NH₃

PEA

Alkaline phosphatase measurement

- The total alkaline phosphatase assay measures enzyme activity.
  - Colorimetric substrates at a non-physiologic high pH
  - Detects all ALP forms in serum
  - Cannot be measured accurately in EDTA-plasma, binds divalent cations

Total ALP normal range varies with age, sex and laboratory

- Many labs only give adult ranges.
- Know if your laboratory is giving you appropriate normal values.
- Inappropriate normal ranges lead to misdiagnosing conditions of high or low alkaline phosphatase.
Alkaline phosphatase isoenzyme assay

- Measure enzyme activity with and without heating > 65°C
  - Placental and placental-like ALP
  - Intestinal ALP
  - Liver ALP
  - Bone
- Reported as % of total ALP

- Children:
  - Mostly Bone ALP
- Adults:
  - Bone ALP ≈ Liver ALP
- Pregnancy:
  - Placental ALP expressed

High alkaline phosphatase

- Rickets/osteomalacia
  - Vitamin D deficiency
  - Hypophosphatemic
  - Calcium deficiency
  - Other vitamin D related defects
- Hyperparathyroidism
- Pagets disease of bone
- Fibrous dysplasia of bone
- Transient hyperphosphatasemia
- Biliary disease
- Some cancers
- Others

Source of high ALP?

- Clinical signs of rickets or bone disease
- Other biochemical markers of mineral metabolism
- Plain radiographs for rickets or bone lesions?
- Clinical signs of liver disease
- Other liver function tests, especially bilirubin
- Liver imaging?
- If uncertainty remains, check bone ALP (direct assay)

Low alkaline phosphatase

- Lab artifact (EDTA, citrate, oxalate tubes)
- Bone disorders
  - Hypophosphatasia
  - Cleidocranial dysplasia
  - Osteogenesis imperfecta type II
  - Adynamic renal osteodystrophy
- Endocrine issues
  - Hypothyroidism
  - Glucorticoid excess
- Deficiencies
  - Vitamin C
  - Vitamin B12 /pernicious anemia
  - Zinc
  - Magnesium
  - Celiac disease
  - Starvation
- Toxicities
  - Vitamin D toxicity
  - Milk Alkali syndrome
  - Copper (Wilson's disease)
  - Heavy metal
- Medications
  - Clofibrate
  - Glucocorticoids
  - Antiresorptives
- Other:
  - Cardiac bypass surgery
  - Trauma, surgery
  - Massive transfusion
  - Multiple myeloma
  - Some cancers and chemotherapy

Reason for low ALP?

- Most of these are identifiable from the clinical picture
- Review medications, history
- However may require testing for other causes:
  - Creatinine
  - Zinc, Magnesium, Copper
  - Vitamins C, D, B12
  - Endocrine abnormalities
- If suspect HPP:
  - Check Bone ALP, PEA, PLP
  - Other biochemical markers of mineral metabolism
**ALP substrates**

- PPI
- PLP
- PEA
- LPS
- ATP
- Others?

**PLP and PEA**
- PLP levels are sensitive and specific to HPP
- Vitamin B6 supplement falsely elevates level
- High PEA in 24 hour urine collection is useful as a marker of HPP
  - Normalize to creatinine
  - Range varies by age

**Serum total alkaline phosphatase in HPP**

**Hypophosphatasia**

Consequences of HPP vary by severity of the enzyme defect

- Odonto
- Adult
- Child
- Infantile
- Perinatal

More severe enzyme dysfunction

**HPP effects**

**Skeletal**
- Demineralized skeleton
- Rachitic changes at growth plate
- Fractures
- Wide-appearing sutures due to ossification defect, but premature fusion
- Functional craniosynostosis, increased intracranial pressure
- Premature deciduous tooth loss, defective cementum

**Non-skeletal**
- Hypercalcemia, hyperphosphatemia
- Hyperuricemia
- Nephrolithiasis
- Calcium pyrophosphate arthropathy, ossification of ligaments
- Muscle weakness, delayed motor milestones, poor feeding
- Seizures

**HPP Genetics**

- 1:300,000 in Europe
- 1:100,000 in Canada
- 1:2500 in Mennonites from Manitoba, Canada
- Rare, but described in African ancestry
- More moderate or mild forms may be more common (up to 1:6000).
- The more severe forms (perinatal, infantile) are autosomal recessive.
- The milder forms can be autosomal recessive or dominant.
HPP Genetics

- >330 different disease-causing mutations reported
  - 71% Missense
  - 3% Large deletions
  - 11% Small deletions
  - 6% Splice site
  - 5% Nonsense mutations
  - 5% Small Insertions
  - 1% Other
- New mutations continue to be reported

Mutation effects vary:
- Inactivate the enzyme
- Cause intracellular accumulation
- Low protein expression
- Dominant negative effects on the dimer

Mutation database:
- http://www.sesep.uvsq.fr/03_hypo_mutations.php
  Curated by Etienne Mornet at the Universite de Versailles

Clinical case question

This 6 month old infant has seizures, hydrocephalus, nephrocalcinosis and rachitic changes.
Which abnormality, if present, would differentiate her cause of rickets most specifically from other types of rickets?

A. Low serum phosphorus
B. High pyridoxal 5’-phosphate
C. Low serum calcium
D. Low urinary calcium
E. High bone specific alkaline phosphatase

Summary

- ALP removes Pi groups from multiple substrates including ATP, LPS, PPI, PEA, PLP
- ALP facilitates mineralization by decreasing local concentrations of the mineralization inhibitor PPI.
- ALP level (whether high or low) is an important marker for multiple diseases.
- Recognizing the forms of ALP and the clinical conditions leading to high or low ALP levels will facilitate appropriate further testing and diagnosis.

Thank you!
Clinical Spectrum of Hypophosphatasia

Linda A. DiMeglio, MD, MPH
Clinical Spectrum of Hypophosphatasia

Linda A. DiMeglio MD, MPH
Professor of Pediatrics

Objectives

• Describe different HPP presentations, including key laboratory findings
• Contrast HPP presentation with other metabolic bone disorders

Milestones in Hypophosphatasia (HPP)

• 1907 Suzuki et al. describe phosphatase enzyme
• 1923 Robinson and Soames describe “bone phosphatase”
• 1948 Hypophosphatasia identified as a syndrome
• 1955 Increased urinary phosphoethanolamine (PEA) described in HPP
• 1965 Increased pyrophosphate (PPI) described in HPP
• 1985 Increased pyridoxal 5’-phosphate (PLP)
• 1988 First TNSALP mutations causing HPP identified
• 1990s Mouse models for HPP developed
• 2012 First publication of successful enzyme replacement therapy in HPP
• 2015 Asfotase alfa therapy approved by multiple regulatory bodies

Clinical Spectrum

• Can present at all ages
• Highly variable among patients, even with same mutation(s)
Perinatal Hypophosphatasia
- Manifests in utero or at birth
- Severe hypo-mineralization of the skeleton and/or rachitic changes
- Fractures are often present
- Craniosynostosis
- Hypoplastic lungs and respiratory compromise
- Shortened limbs
- Babies or stillborn or die in the neonatal period

Perinatal “Benign” Hypophosphatasia
- Detected in utero by ultrasound or at birth
- Similar presentation to the perinatal form, but slowly improves and evolves into a milder form of the disease

Case #1: Presentation
- Normal growth and development until 4 months of age – noted to have hydrocephalus, shunt placed
- At 6 months of age – noted to have difficulty feeding, growth failure
- Work-up done: nephrocalcinosis with elevated serum creatinine
  - Creatinine increased gradually
- At 8 months of age, noted to have hypercalcemia
  - Endocrine consulted, treated with pamidronate...

Then
- Low alk phos (< 5 U/L) noted
- Bone isoform undetectable
- Serum pyridoxal phosphate and urinary pyrophosphate markedly elevated

Case #1
- Developed respiratory problems requiring tracheostomy and mechanical ventilation by 1 year of age.
Genetic analysis

- mutation in one TNSALP allele (stop codon); sequencing of exons showed no other mutations
- second allele either deleted or has a mutation in intron or upstream promoter sequence.

HPP: Systemic Manifestations

Presentation: Skeletal
- Osteoporosis/osteopenia
- Rickets/Osteomalacia
- Fractures
  - Can be low-trauma
  - Can be recurrent
  - Can be slow to heal
- Bone pain

Presentation: Skeletal
- Poor Growth
- Craniosynostosis
- Chronic bone inflammation
Presentation: Dental
- Premature loss of teeth
  - With tooth root still attached
- Poor dentition
- Periodontal disease

Presentation: Respiratory
- Respiratory insufficiency/failure

Infantile Hypophosphatasia

Presentation: Renal
- Nephrocalcinosis
- Hypercalciuria

Presentation: Musculoskeletal
- Weakness
- Low tone
- Proximal myopathy
- Delayed motor milestones in infants
- Muscle Pain
- Immobility requiring wheelchair/other support

Presentation: Rheumatologic
- Chondrocalcinosis
- Pseudogout
- Calcium pyrophosphate dihydrate deposition
- Calcific Periarthritis
- Joint pain
Presentation: Neurologic

- Seizures
  - Due to PLP deficiency
  - B6 responsive
  - Increased intracranial pressure

In HPP

Pyridoxal 5’-phosphate (PLP)

Alkaline phosphatase

Pyridoxal (PL)

Vitamin B6 Deficiency and Seizures

Hypophosphatasa

Hypophosphatiasis

Significant variability in clinical manifestations

- Early deciduous tooth loss – root intact
  - Enlarged pulp chambers noted on dental films
- Delayed motor milestones
- Static myopathy with gait disturbance
- Rachitic changes (wrists, ankles, ribs)
  - Valgus or varus LE deformity

Childhood HPP

Picture courtesy of P. Tebben
Adult Hypophosphatasia

- Frequently recognized in middle age
- Musculoskeletal complaints most frequent presenting symptoms
- Fractures
  - Recurrent, poorly healing metatarsal fractures
  - Sub-trochanteric femoral fractures
- May loose teeth prematurely
- Can have pseudogout
- Some with history of rickets/early deciduous tooth loss as a child

Adult Hypophosphatasia: Presentations

- Age at dx – 49 years (Range 35 – 73)
  - Age at onset of symptoms – 44 (30 – 73)
- Features:
  - Musculoskeletal pain - 41%
  - Fracture - 18%
    - Any history of fracture – 54%
    - Hip/femur fx – 23%
  - Chondrocalcinosis – 27%
  - Pseudogout – 14%
Odontohypophosphatasia

- Only childhood manifestation is early deciduous tooth loss
- Some may have Adult HPP but have not yet manifest additional features

Low alkaline phosphatase

- Lab artifact (EDTA, citrate, oxalate tubes)
- Bone disorders
  - Hypophosphatasia
  - Cleidocranial dysplasia
  - Osteogenesis imperfecta type II
  - Adynamic renal osteodystrophy
- Endocrine issues
  - Hyperthyroidism
  - Hypothyroidism
- Glucocorticoid excess
- Deficiencies
  - Vitamin C
  - Vitamin B12 (pernicious anemia)
  - Zinc
  - Magnesium
  - Collagen disease
  - Starvation
- Toxins
  - Vitamin D toxicity
  - Milk Alkali syndrome
  - Copper (Wilson's disease)
  - Heavy metal
- Medications
  - Clofibrate
  - Glucocorticoids
  - Antiresorptives
- Other:
  - Cardiac bypass surgery
  - Trauma surgery
  - Massive transfusion
  - Multiple myeloma
  - Some cancers and chemotherapy

Labs

<table>
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<tr>
<th>Test</th>
<th>Case 1</th>
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<tbody>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.8</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>4.5</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.6</td>
</tr>
<tr>
<td>25 OHD (ng/mL)</td>
<td>45</td>
</tr>
<tr>
<td>Alkaline Phosphatase (U/L)</td>
<td>55</td>
</tr>
</tbody>
</table>

Note: Alk Phos normal range given as 45-110

4 Steps to Diagnosis

1) Consistent clinical features
2) Low serum alkaline phosphatase
3) Elevated plasma PLP and/or urine PEA
4) Genetic testing

Low alkaline phosphatase

- Lab artifact (EDTA, citrate, oxalate tubes)
- Bone disorders
  - Hypophosphatasia
  - Cleidocranial dysplasia
  - Osteogenesis imperfecta type II
  - Adynamic renal osteodystrophy
- Endocrine issues
  - Hyperthyroidism
  - Hypothyroidism
- Glucocorticoid excess
- Deficiencies
  - Vitamin C
  - Vitamin B12 (pernicious anemia)
  - Zinc
  - Magnesium
  - Collagen disease
  - Starvation
- Toxins
  - Vitamin D toxicity
  - Milk Alkali syndrome
  - Copper (Wilson's disease)
  - Heavy metal
- Medications
  - Clofibrate
  - Glucocorticoids
  - Antiresorptives
- Other:
  - Cardiac bypass surgery
  - Trauma surgery
  - Massive transfusion
  - Multiple myeloma
  - Some cancers and chemotherapy
**HPP Imposters**

**Dental Abnormalities**
- HPP – Early deciduous tooth loss with root intact
- Osteogenesis Imperfecta – Dentinogenesis imperfecta
- X-linked hypophosphatemic rickets – Abscessed teeth

**Radiologic HPP Imposters**

<table>
<thead>
<tr>
<th>Alkaline Phosphatase</th>
<th>HPP</th>
<th>Nutritional Rickets</th>
<th>Hypophosphatemic Rickets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

**Summary**

- HPP can present at a variety of ages with a wide range of clinical findings
- Laboratory hallmark is low serum alkaline phosphatase
  - Differentiates disease from other metabolic/genetic bone disorders

**Questions?**
Treatment Options in the Management of Hypophosphatasia

Leanne Ward, MD, FRCPC
Treatment Options in the Management of Hypophosphatasia

Leanne Ward, MD FRCPC
Director, Pediatric Bone Health Clinical and Research Programs
Children’s Hospital of Eastern Ontario
Research Chair in Pediatric Bone Health
University of Ottawa, Canada

Endocrine Society Satellite Symposium
Orlando, Florida
April 1, 2017

Objectives
- To discuss the treatment options for patients with HPP, spanning:
  - Supportive therapy
    - Multi-disciplinary
  - Bone-honing enzyme replacement therapy
    - Asfotase alfa
  - Therapy to increase production of ALP
    - PTH
    - Anti-sclerostin antibody
    - Bone marrow and mesenchymal stem cell transplant
  - Therapy to increase bone mass
    - Bisphosphonates

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Supportive Therapy for the Systemic Manifestations of Low TNSALP Activity

Juvenile Onset HPP

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowed long bones</td>
<td>59</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>59</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>53</td>
</tr>
<tr>
<td>Limits daily activities</td>
<td>47</td>
</tr>
<tr>
<td>Requiring medication</td>
<td>41</td>
</tr>
<tr>
<td>Bone pain</td>
<td>50</td>
</tr>
<tr>
<td>Limits daily activities</td>
<td>44</td>
</tr>
<tr>
<td>Requiring medication</td>
<td>28</td>
</tr>
<tr>
<td>Muscle weakness limiting daily activities</td>
<td>47</td>
</tr>
<tr>
<td>Myalgia</td>
<td>38</td>
</tr>
<tr>
<td>Limits daily activities</td>
<td>34</td>
</tr>
<tr>
<td>Requiring medication</td>
<td>19</td>
</tr>
<tr>
<td>Fractures</td>
<td>34</td>
</tr>
<tr>
<td>Myopathy</td>
<td>31</td>
</tr>
<tr>
<td>Craniosynostosis</td>
<td>25</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>22</td>
</tr>
</tbody>
</table>

Juvenile Onset HPP Patients Experience Significant Morbidity
- Non–pharmacological interventions: 94%
  - Surgical or medical intervention: 88%
  - Physiotherapy: 34%
  - Occupational therapy: 31%
- Mobility aids
  - Orthotics: 31%
  - Walking aids: 9%
  - Wheelchairs: 6%

Supportive HPP Management

Medical Care
- Neonatology
- Endocrinology
- Bone health
- Respirology
- Pain management
- Rheumatology
- Nephrology
- Genetics
- Nutrition

Surgery and Rehabilitation
- Orthopedics
- Neurosurgery
- Dentistry
- Physiotherapy
- Occupational therapy

Overall Management
As with any complex disorder involving multiple services, a clinician from one of the sub-specialties needs to provide overall leadership, coordination and patient care advocacy.

Mineral Ion Metabolism

Hypercalcemia/hypercalcuria
- Calcium supplementation avoided
- Loop diuretics, hyperhydration, steroids

Hyperphosphatemia
- Pi competitively restricts TNSALP activity and gene expression
- Dietary phosphate restriction
- Phosphate binders

Rickets

Mineral Ion Metabolism with ERT

Pre-ERT
- Hypercalcemia and hyperphosphatemia

Post-ERT
- Hungry bones syndrome!

Patient Support Groups

- Soft Bones Canada
- Soft Bones Foundation (U.S.)
- HPP-Choose Hope (U.S.)
- Hypophosphatasie Europe (France)
- Hypophosphatasie Deutschland (Germany)
- HypoPhosPhatasia Support Association of Japan (HPPSA-J)

Vitamin D Status

Vitamin D Insufficiency
- Should be treated but not zealously

Severe vitamin D deficiency \(\uparrow\) PTH
- Treat to normalize PTH
- 25OHD level 20 ng/mL or 50 nmol/L

Pre-ERT:
- Avoid high dose vitamin D therapy
- Avoid vitamin D analogues
**Nutrition**

• Failure to thrive is a key presenting feature in the infantile and juvenile forms

• Support from a dietician

• Enteral and parenteral nutrition may be required
  – May develop oral aversions over time

• Anti-reflux therapy is often needed

**Dental Care**

• Early intervention:
  • Optimal oral hygiene and regular dental care
  • Dental prosthetics in adults

**Orthopedic Issues**

• Scoliosis

• Osteochondral spurs, syndesmophytes

• Limb deformity

• Fracture and “pseudo-fracture” management
  – Prolonged casting due to delayed healing
  – Stabilization of long bones with intra-medullary rods

**Neurological Management**

• Seizures:
  • B6-dependent seizures may be a presenting sign = a severe phenotype and poor prognosis
  • Treat with a dephosphorylated form of B6

• Craniosynostosis:
  – Neurosurgical release for patients with:
  – Raised intra-cranial pressure, Chiari malformation, hydrosyringomyelia

**Objectives**

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    • Asfotase alfa
  – Therapy to increase production of ALP
    • PTH
    • Anti-sclerostin antibody
    • Bone marrow and mesenchymal stem cell transplant
  – Therapy to increase bone mass
    • Bisphosphonates

**Pain and Physical Activity**

• Pain:
  – Anti-inflammatories are the mainstay of therapy
  – Psychological support and chronic pain management services

• Physical activity/mobility:
  – Muscle weakness++ and pain limit mobility
  – Exercise
  – Physiotherapy and assistive aids may be required
    • Orthotics
    • Walking aids
    • Wheelchairs
Enzyme Replacement

- Infusions of plasma-enriched soluble ALP
  - ALP in the circulation
  - Unsuccessful
- TNSALP needs to be within the skeletal and cartilage matrices, in order to mineralize bone and growth plate
- Recombinant “fusion protein”
  - TNSALP ectodomain plus a deca-aspartate motif for bone targeting

Asfotase alfa

- Human recombinant TNSALP
- First-in-class, bone-targeted enzyme replacement therapy for treatment of HPP
- Fusion protein
  - TNSALP ectodomain
  - IgG1 Fc domain
  - Deca-aspartate
    - Bone-targeting motif
- Routes of administration:
  - SC injection
  - IV

PolyAsp sequence = Decapeptide of 10 amino acids
String of negative charges from all of the carboxylate groups of the amino acids fosters strong binding to hydroxyapatite crystals.

Asfotase Alfa in the Treatment of Severe Infantile Onset HPP

- Ongoing Phase II, multinational, multicenter, open-label study
- Ten study sites: USA (6), UK (2), Canada (1), United Arab Emirates (1)

<table>
<thead>
<tr>
<th>Initial Phase</th>
<th>Extension Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single IV (2.0 mg/kg)</td>
<td>Starting dose = final dose of initial phase</td>
</tr>
<tr>
<td>1.0 mg/kg 3x wk 3C</td>
<td></td>
</tr>
<tr>
<td>11 patients enrolled</td>
<td>9 patients continue treatment</td>
</tr>
</tbody>
</table>
| 10 patients | 1 death
d6

Whyte et al, NEJM, 2012;366::904-913;  Whyte et al, JCEM, 2016
Open-Label Study

- 11 children with life-threatening, perinatal or infantile hypophosphatasia
  - Diagnosis before 6 months of age
  - Age range 1 to 33 months
  - 6 required respiratory support
    - CPAP, O2, tracheostomy and ventilation
    - 4 had respiratory deterioration leading up to treatment
    - 7 tube-fed
    - One baby was on ambient air and fed orally (moderate)
- Observational – no statistical comparisons
- Asfotase 40 mg/ml
  - IV infusion 2 mg/kg
  - 1-3 mg/kg sc 3 times per week

Summary of Results

- Circulating TNSALP substrates diminished
- Increases in PTH as calcium dropped
  - No hypocalcemia, ectopic calcification
- Growth plate healing and skeletal densification
- Pulmonary function improved
- Improved developmental milestones
- Deciduous teeth erupted in all patients
- No obvious impact on craniosynostosis

Primary Endpoint: Improved Bone Mineralization (RGI-C) at 6 Months in Patients Treated With Asfotase Alfa

- Significant improvement was noted as early as Month 3, continued, and was sustained through 3 years

18 month old baby with hypophosphatasia

Withdrew from the study after the initial IV infusion of Asfotase alfa
- Fever, O2 desaturation, rigors and irritability with the infusion
- Radiographs 14 months later shows substantial deterioration

Whyte et al, NEJM, 2012;366::904-913
Upon Arrival

Slide compliments Dr. Cheryl Greenberg

Baseline and 12 weeks following Asfotase alfa therapy

Slide compliments Dr. Cheryl Greenberg

Adverse Events

- No serious adverse events that were considered **definitely drug-related**
- One patient died from sepsis, after 7.5 months of therapy
- One patient withdrew consent after first infusion

Survival at one year:
95% of the treated group, 42% of historical controls

Survival at 5 years:
84% of the treated group, 27% of controls

**5% of the ventilated controls survived, compared to 76% of the ventilated treated patients

Asfotase Alfa Treatment Improves Survival for Perinatal and Infantile Hypophosphatasia

Michael P. Whyte, Cheryl Rockman-Greenberg, Keiichi Ozono, Richard Biese, Scott Moseley, Agustin Melian, David D. Thompson, Nicolas Bishop, and Christine Holm

( *J Clin Endocrinol Metab* 101: 334–342, 2016)

Treated patients: N = 37  
Historical controls: N = 48

Survival at one year:
95% of the treated group, 42% of historical controls

**Survival at 5 years:**
84% of the treated group, 27% of controls

**5% of the ventilated controls survived, compared to 76% of the ventilated treated patients**
Asfotase alfa therapy for children with hypophosphatasia

Michael P. Wherta,3,16 Katherine L. Hobson,3 Deam Phillips,3 Amy L. Reaves,5 William H. Mulkistern,6
Amy Yalnizyan,2,7 Karen E. Mack,8 Kim Hamilton,9 Karl Ragan,10 Kinya P. Fujita,11 David B. Thompson,12
Scott Mesley,13 Torje Orlin13,14 and Eloy Bocanegra-Greenberg15

Asfotase Alfa for the Treatment of Juvenile HPP
Children 6 to 12 years of age

- Phase II, open-label, 2 sites (US, Canada); N = 12

**Initial Phase**
(n=13)
Randomized: 6 mg/kg/week (n=6) 9 mg/kg/week (n=7)

**Extension Phase**
(n=12)
Initial dose: 3 mg/kg/week Increased to 6 mg/kg/week via protocol amendment

**Historical Control** (n=16)
1 patient withdrew* 12 patients continue treatment

<table>
<thead>
<tr>
<th>BL</th>
<th>6</th>
<th>12</th>
<th>24</th>
<th>36*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (Months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*1 mo. treatment; elective surgery

Skeletal Improvement during Asfotase alfa treatment of children with juvenile HPP
Metaphyseal Splaying
Clinically can see improvement

<table>
<thead>
<tr>
<th>Before treatment</th>
<th>After treatment</th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 years</td>
<td>2.5 years</td>
<td>2 years</td>
</tr>
<tr>
<td>6 months</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>4.5 years</td>
<td></td>
<td>4 years</td>
</tr>
</tbody>
</table>

Treatment start

Slide compliments Dr. Cheryl Greenberg

Improved anthropometry during Asfotase alfa treatment in juvenile HP

Height Z-score difference: 0.9
BMI Z-score difference: 0.5

Safety results – injection site reactions

Erythematous reaction: First months of injections, disappears
Purple discoloration: Appears later, persistent
Abdominal lipohypertrophy: 4 years

Slide compliments Dr. Cheryl Greenberg

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**Parathyroid Hormone**

- PTH stimulates synthesis of TNSALP by osteoblasts
- Not an option in children
- Adult Study Outcomes: BMD, pain, mobility, biochemistry, skeletal radiography, bone histology
- Case reports with inconsistent effects, including initial but lack of sustained benefit

**Anti-Sclerostin Antibody**

- IPS104, an anti-sclerostin monoclonal antibody, improves disease biomarkers and markers of bone formation in patients with adult-onset hypophysostasia (HPP)

**Bone Marrow and Mesenchymal Cell Transplant**

- Tried with some success in severe forms
- High risk procedure, limited by pulmonary hypoplasia
- Case reports:
  - 5 patients, severe HPP
  - None died, all with degrees of improvement
  - One patient developed Ph+ leukemia

**Objectives**

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**Bisphosphonate Therapy**

- Bisphosphonates do not rescue the phenotype in severe cases
  - Theoretically contraindicated
    - Analogues of inorganic pyrophosphate (PPI)
    - Mineralization inhibitors
    - No convincing benefit in adults
- Could they play a role in decreasing fractures in children with milder forms of HPP?
- Are there differences in the response to bisphosphonates in children compared to adults that need to be considered?

**Perspective**

**Hypophosphatasia: Enzyme Replacement Therapy Brings New Opportunities and New Challenges**

Michael P Whyte

Department of Internal Medicine, Division of Bone and Mineral Diseases, Washington University School of Medicine, and Center for Metabolic Bone Disease and Molecular Research, Children’s Hospital, St Louis, MO, USA
Effects of Pamidronate on Bone Tissue: Histomorphometric Analysis of Iliac Bone

Iliac Biopsy

Rauch et al., Lancet 2004:369:1377

Bisphosphonate Therapy

- Increases in cortical thickness are expected to occur in any bisphosphonate-treated patient who is growing
- Whether positive effects of newer generation bisphosphonates on cortical bone modeling provide an anti-fracture effect in milder forms has not been formally studied

Summary and Conclusions

- Multi-disciplinary supportive care remains the cornerstone of effective HPP therapy, whether receiving ERT or not
- Asfotase alfa, to date reported in infants and children, targets the underlying pathophysiology with greater precision than any available therapy
- With asfotase alfa now available multi-nationally, further studies are needed to understand the full effects of the drug on the underlying phenotype across the ages and clinical spectrum
- Attempts to alleviate symptoms of the disease through optimization of bone mass or to increase production of osteoblasts and ALP have led to mixed results
- Whether second and third generation bisphosphonates can improve bone strength through their effects on bone modeling in the growing child with HPP is unclear
Acknowledgements

- Dr. Cheryl Greenberg
  - University of Manitoba
- Dr. Marc McKee
  - McGill University
- Dr. Frank Rauch
  - McGill University