Pediatrics Metabolic Bone Disorders

with focus on

Hypophosphatasia (HPP)

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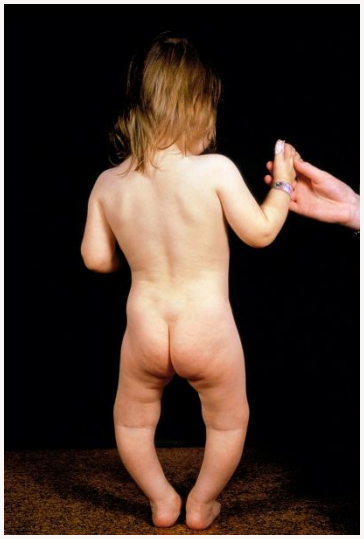
Rickets

- Rickets is a disorder of growth plate mineralization and ossification, in which bones are weakened due to abnormal calcium metabolism
- Can be inherited or acquired:
  - Lack of dietary vitamin D leads to vitamin D deficiency rickets
  - X-linked hypophosphatemia (XLH), or vitamin D–resistant rickets

Clinical manifestations:

- Bowed legs (pictured)
- Misshaped skulls
- Low calcium and phosphorus levels
- Increased PTH levels
- Increased ALP levels



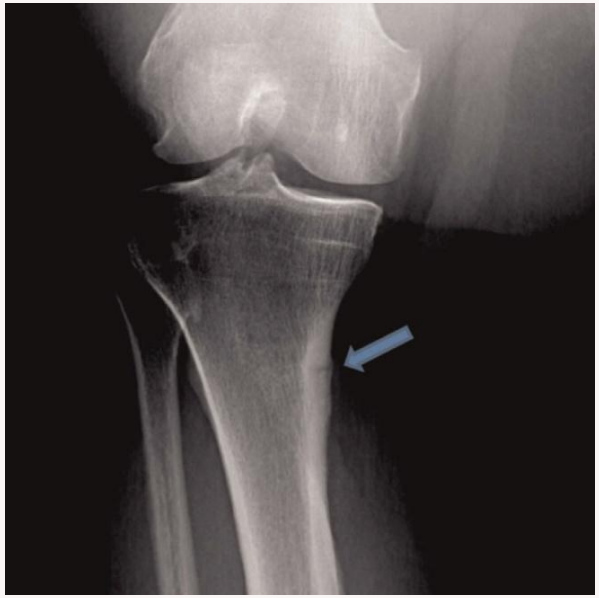
- Nutritional vitamin D deficiency rickets is treated with vitamin D and calcium supplementation.

XLH

- XLH is a type of rickets characterized by excessive loss of phosphate unrelated to calcium levels
  - Caused by a mutation in the phosphate-regulating gene (PHEX)
  - Leads to impaired renal tubular reabsorption of phosphate

Clinical Manifestations:

- Growth retardation (short stature)
- Bowed legs
- Lower extremity insufficiency fractures
- Arthritis and Osteomalacia (adults)
- Low blood phosphate and vitamin D
- Raised urine phosphate
- Raised serum ALP in children
- Normal serum calcium



XLH is treated with Vitamin D metabolites (calcitriol) and phosphate

Osteogenesis Imperfecta

- **Osteogenesis imperfecta or "brittle bone disease" is a genetic condition characterized by fragile bones that break easily**
  - OI is caused by a mutation in the type I collagen genes, affecting the body's normal production of collagen leading to fragile bones

Clinical manifestations:

- Short stature
- Blue sclerae (pictured)
- Dentinogenesis imperfecta
- Wormian bones
- Hearing loss
- Osteopenia

There is no cure for OI, but treatment focuses on:

- Minimizing fractures
- Maximizing mobility, function, general health

Bisphosphonates are prescribed for OI

Hypophosphatasia (HPP)

Hypophosphatasia[1]

- Hypophosphatasia (HPP) is a rare metabolic disease caused by inactivating mutations in the gene encoding tissue-nonspecific alkaline phosphatase (TNSALP).
- The biological hallmark of HPP is low TNSALP activity.
- First described by Rathbun (1948) in 9 weeks old infant [2]

Objectives :

- Review HPP pathophysiology and mechanism of disease
- Review the various forms of HPP as classically defined
- Review the clinical manifestations of HPP
- Highlight the importance of accurate diagnosis

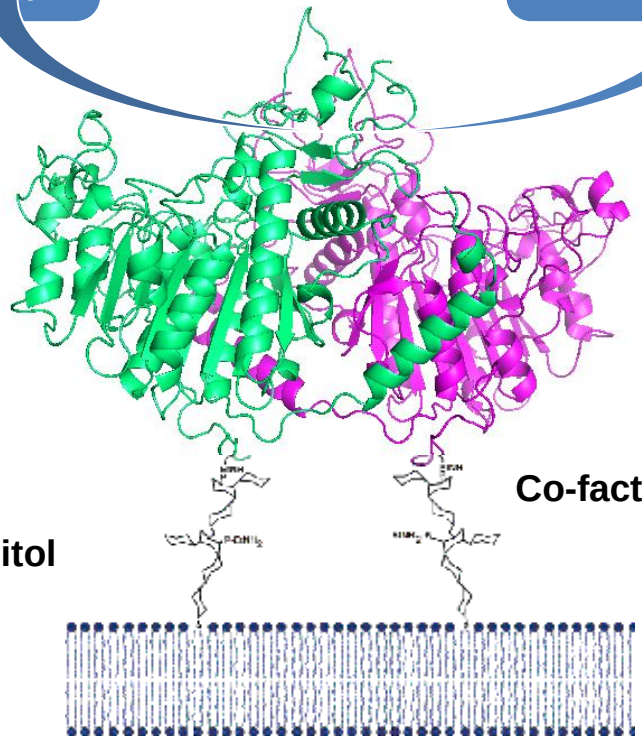
1. Whyte, M. (2012) 2. Rathburn, J (1948)

The tissue-nonspecific alkaline phosphatase (TNSALP)[1,2,3]

Key substrates

Inorganic pyrophosphate (PPi)
Pyridoxal 5'-phosphate (PLP)
Phosphoethanolamine (PEA)

Inorganic phosphate (Pi) + Pi
Pyridoxal (PL) + Pi
Ethanolamine (EA) + Pi



Alkaline phosphatase homodimer

Co-factors: Zn^{2+}, Mg^{2+}

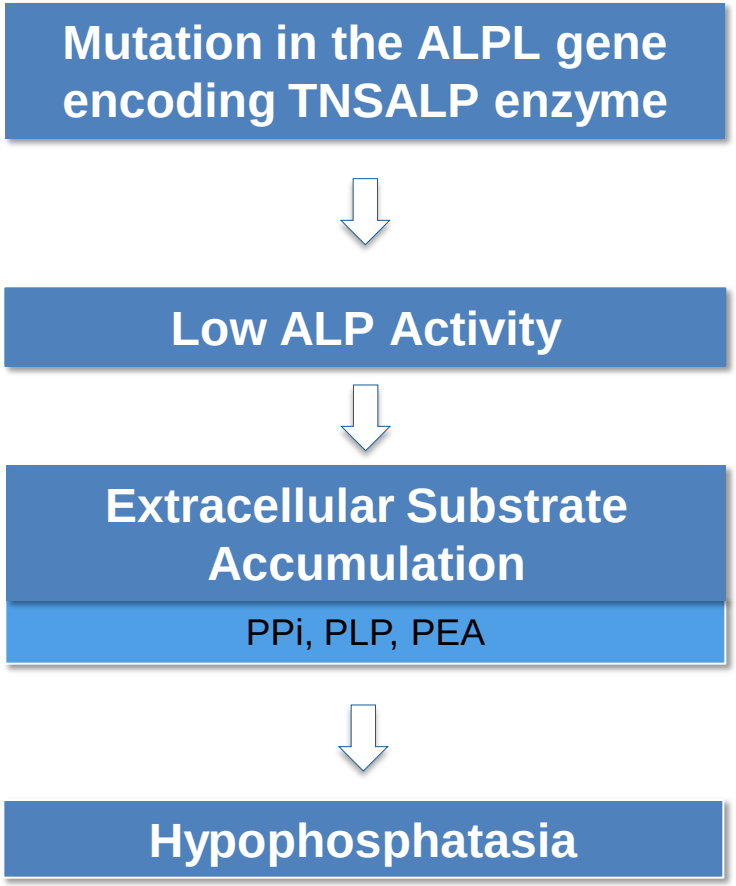
Glycophosphatidylinositol (GPI) anchor

Cell membrane

Mutations in the catalytic domain or other sites within the TNSALP protein can lead to decreased TNSALP activity and HPP

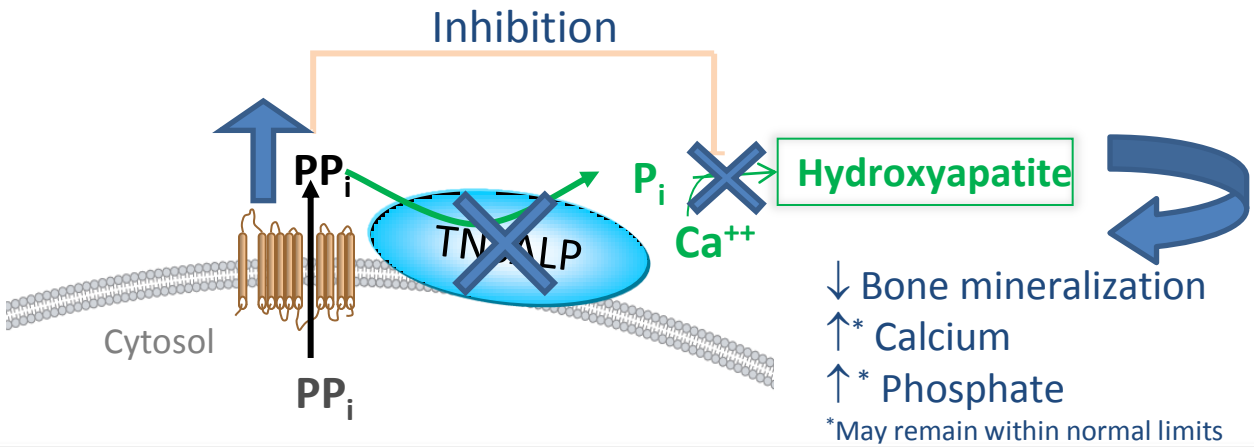
1. Le Du, M. (2001); 2. Mornet, E. (2001); 3. Fauvert, D. (2009)

Mechanism of Disease[1]



1. Rockman-Greenberg, C. (2013)

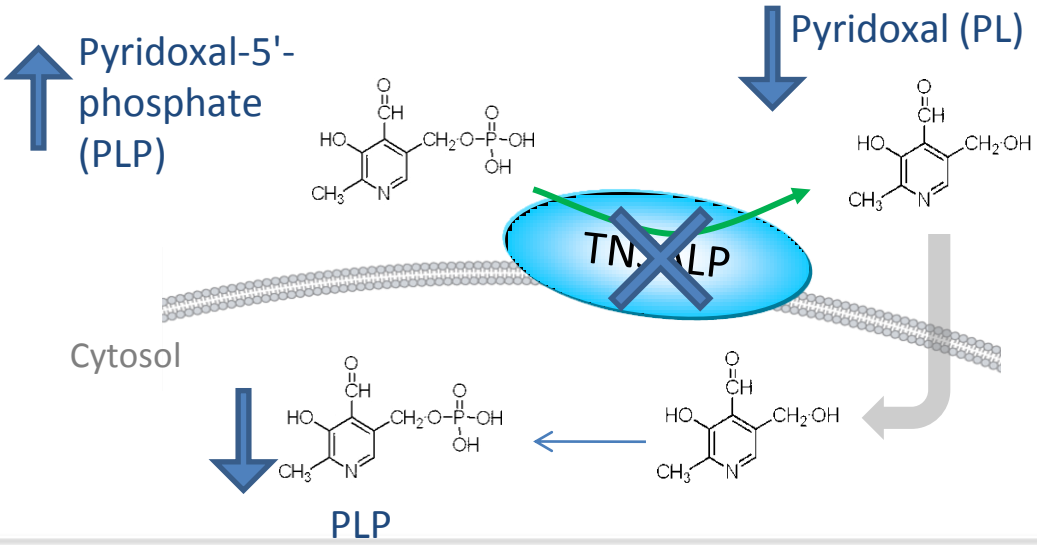
HPP Pathophysiology: Bone[1,2]



- During normal bone mineralization, TNSALP dephosphorylates inorganic pyrophosphate (PPi) on osteoblast membranes, producing inorganic phosphate (Pi).
  - Pi and Ca^{++} form hydroxyapatite crystals
- In HPP, low TNSALP activity leads to extracellular accumulation of PPi
  - PPi is a potent inhibitor of bone mineralization

1. Millán, J. (2008); 2. Rockman-Greenberg, C. (2013)

HPP Pathophysiology: CNS[1,2,3]



- Pyridoxal-5’-phosphate (PLP) is the active form of vitamin B6
- In normal circumstances TNSALP dephosphorylates PLP, producing pyridoxal (PL)
  - PL crosses the cell membrane and is re-phosphorylated into PLP
  - Intracellular PLP is involved in neurotransmitter synthesis (e.g. GABA, dopamine, serotonin, etc.)
- PLP deficiency in the brain may result in seizures[1]

1. Millán, J. (2008); 2. Millán, J. (2006); 3. Rockman-Greenberg, C. (2013)

Genetics of HPP

- The gene for TNSALP is located on the short arm of chromosome 1 (1p36.1-34)[1]
  - 12 exons over approximately 50kb
- At least 280 distinct mutations have been described[2]
  - Missense mutations 75%
  - Small deletions 11%
  - Splicing mutations 6%
  - Nonsense mutations 4%
  - Small insertions 2%
  - Other 2%
- Prevalence of specific genetic mutations is higher in some populations[3]
  - Canada (Manitoba Mennonites) – c.1001G > A
  - United States – c.1133A >T
  - Europe –c.571G > A
  - Japan –c.1559delT
- Inheritance may be either autosomal dominant or autosomal recessive[4]
  - Perinatal or infantile HPP nearly always results from autosomal recessive inheritance
  - Childhood, adult and odontohypophosphatasia may result from autosomal dominant or autosomal recessive inheritance
- There can be considerable variability in the presentation/severity of HPP among siblings, even those who share the same mutation(s)[4]

1. Greenberg, C. (1990); 2. Mornet E. (2014); 3. Mornet, E. (2007); 4. Whyte, M. (2013)

Forms of Hypophosphatasia

- HPP is classically described as having the following clinical forms [1,2,3]

Disease Form	Age at First Signs/Symptoms
Perinatal	In-utero and at birth
Infantile	< 6 months
Childhood/Juvenile	≥ 6 months – 18 years
Adult	≥ 18 years
Odontohypophosphatasia	Any age Only clinical abnormality is dental disease
Prenatal benign	In utero Postnatal course ranges significantly from infantile form to odontohypophosphatasia

- There is increasing awareness that[4]
  - These definitions are somewhat arbitrary
  - There is a spectrum of severity both across and within these categories

1. Rockman-Greenberg, C. (2013); 2. Whyte, M. (2013); 3. Wenkert, D. (2011); 4. Whyte, M. (2013)

Prevalence and Incidence of HPP[1-6]

- Prevalence and Incidence rates for HPP are not well characterized
- Studies to date are primarily focused on severe (perinatal & infantile) HPP
- Methods and populations differ greatly
- Most commonly referenced rates are:
  - 1:100,000 live births in Toronto, based on the birth rate locally for Ontario, Canada
  - 1:300,000 in France, based on molecular diagnosis during 2000-2009.
- Additional reports include:
  - 1:300,000-500,000 (incidence in Japan)
  - 4:500,000 (incidence in Germany)
  - 1:538,000 (prevalence in Europe)
- Data related to founder mutations:
  - 1:2500 among the Mennonite population in Manitoba, Canada (c.1001G > A)
  - 1:900,000 prevalence of a founder mutation in Japan (c.1559delT)
- All data supports a classification of HPP as a rare (Manitoba Mennonite) or ultra-rare disease

1. Rockman-Greenberg, C. (2013); 2. Mornet, E. (2011); 3. Fraser, D. (1957); 4. Watanabe, A. (2011); 5. Taketani, T. (2013); 6. Beck C. (2009)

Systemic Manifestations of Low TNSALP Activity Overview

Presentation and severity of HPP varies among patients

SKELETAL[1,2,4-11, 20-22]

- Hypomineralization
- Craniosynostosis
- Rickets, skeletal deformities
- Osteomalacia
- Fractures
  - Non-traumatic
  - Recurrent
  - Non-healing
- Bone pain
- Chronic bone inflammation
- Short stature

RESPIRATORY[1,10,12-14]

- Respiratory failure
- Respiratory insufficiency requiring support

MUSCULAR[1,3,4,19]

- Hypotonia
- Non-progressive proximal myopathy
- Muscle pain
- Immobility requiring assistive device (e.g., cane, crutches, walker, wheelchair)
- Delayed or missed motor milestones

NEUROLOGIC[1,2,]

- Seizures
- Increased intracranial pressure

RENAL[6,10,12,15,16,23]

- Nephrocalcinosis

RHEUMATOLOGIC[17]

- Chondrocalcinosis
- CPPD* deposition
- Calcific periarthritis
- Pseudogout
- Joint pain

*calcium pyrophosphate dihydrate

DENTAL[5,20]

- Premature loss of teeth
- Poor dentition

OTHER[5,18,19]

- Hypercalcemia†
- Hypercalciuria†
- Failure to thrive

†May remain within normal limits

1. Balasubramaniam, S. (2010); 2. Collmann, H. (2009); 3. Seshia, S. (1990); 4. Beck, C. (2011); 5. Whyte, M. (2012); 6. Barvencik, F. (2011); 7. Coe, J. (1986); 8. Kozlowski, K. (1976); 9. Moulin, P. (2009); 10. Whyte, M. (2012); 11. Weinstein, R. (1981); 12. Baumgartner-Sigl S. (2007); 13. Silver, M. (1988); 14. Teber, S. (2008); 15. Mohn, A. (2011); 16. Eade, A. (1981); 17. Chuck, A. J. (1989); 18. Whyte, M. (2012); 19. Seefried L. (2014); 20. Caswell, A. (1991); 21. Berkseth, K. E. (2013); 22. Schlesinger, B. (1954); 23. Auron, A. (2005)

Systemic Manifestations of Low TNSALP Activity Perinatal/Infantile (first symptoms at birth to < 6 months)

Presentation and severity of HPP varies among patients

SKELETAL[1,2,4-11, 20-22]

- Hypomineralization
- Craniosynostosis
- Rickets, skeletal deformities
- Osteomalacia
- Fractures
  - Non-traumatic
  - Recurrent
  - Non-healing
- Bone pain
- Chronic bone inflammation
- Short stature

RESPIRATORY[1,10,12-14]

- Respiratory failure
- Respiratory insufficiency requiring support

MUSCULAR[1,3,4,8,19,20]

- Hypotonia
- Non-progressive proximal myopathy
- Muscle pain
- Immobility requiring assistive device (e.g., cane, crutches, walker, wheelchair)
- Delayed or missed motor milestones

NEUROLOGIC[1,2]

- Seizures
- Increased intracranial pressure

RENAL[6,10,12,15,16,23]

- Nephrocalcinosis

RHEUMATOLOGIC[17]

- Chondrocalcinosis
- CPPD* deposition
- Calcific periarthritis
- Pseudogout
- Joint pain

*calcium pyrophosphate dihydrate

DENTAL[5,8,20]

- Premature loss of teeth
- Poor dentition

OTHER[5,18,19]

- Hypercalcemia†
- Hypercalciuria†
- Failure to thrive

†May remain within normal limits

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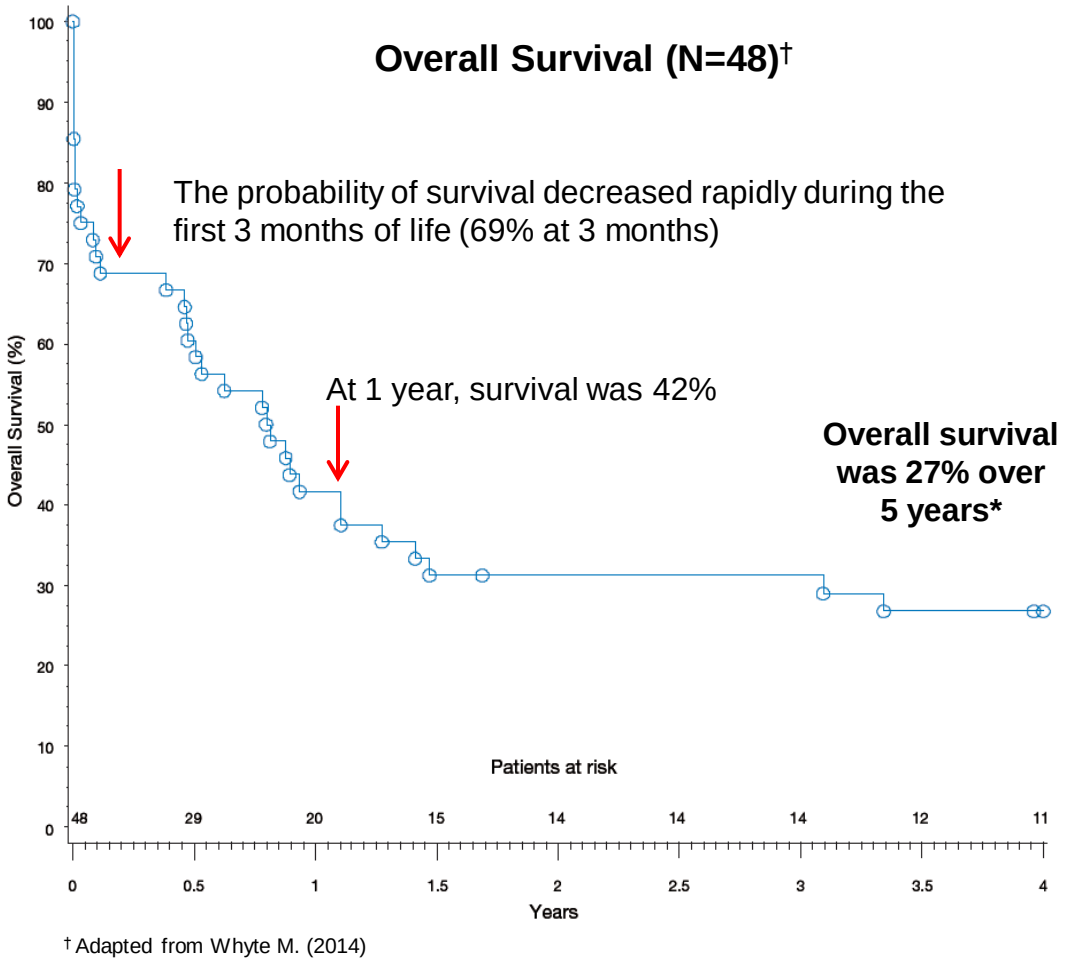
Mortality: Perinatal and Infantile HPP[1-5]

- Perinatal HPP is characterized by extreme hypomineralization
  - survival is rare[1,2]
- In a mixed severe perinatal/infantile HPP population overall mortality was 73% over 5 years (n=48)[5]
- Respiratory failure is the most common cause of death in infants[1,2,4]



† Adapted from Whyte M. (2014)

*No change observed after 4 years figure truncated

1. Rockman-Greenberg, C. (2013); 2. Chodirker, B. N. (1990); 3. Baumgartner-Sigl S. (2007); 4. Whyte, M. (2013); 5. Whyte M. (2014)

Systemic Manifestations of Low TNSALP Activity Juvenile/Childhood (first symptoms ≥ 6 months to 18 y/o)

Presentation and severity of HPP varies among patients

SKELETAL[1,2,4-11,20-22]

- Hypomineralization
- Craniosynostosis
- Rickets, skeletal deformities
- Osteomalacia
- Fractures
  - Non-traumatic
  - Recurrent
  - Non-healing
- Bone pain
- Chronic bone inflammation
- Short stature

RESPIRATORY[1,10,12-14]

- Respiratory failure
- Respiratory insufficiency requiring support

MUSCULAR[1,3,4,8,19, 20]

- Hypotonia
- Non-progressive proximal myopathy
- Muscle pain
- Immobility requiring assistive device (e.g., cane, crutches, walker, wheelchair)
- Delayed or missed motor milestones

NEUROLOGIC[1,2,]

- Seizures
- Increased intracranial pressure

RENAL[6,10,12,15,16,23]

- Nephrocalcinosis

RHEUMATOLOGIC[17]

- Chondrocalcinosis
- CPPD* deposition
- Calcific periarthritis
- Pseudogout
- Joint pain

*calcium pyrophosphate dihydrate

DENTAL[5,8,20]

- Premature loss of teeth
- Poor dentition

OTHER[5,15, 18,22-23]

- Hypercalcemia†
- Hypercalciuria†
- Failure to thrive

†May remain within normal limits

1. Balasubramaniam, S. (2010); 2. Collmann, H. (2009); 3. Seshia, S. (1990); 4. Beck, C. (2011); 5. Whyte, M. (2012); 6. Barvencik, F. (2011); 7. Coe, J. (1986); 8. Kozlowski, K. (1976); 9. Moulin, P. (2009); 10. Whyte, M. (2012); 11. Weinstein, R. (1981); 12. Baumgartner-Sigl S. (2007); 13. Silver, M. (1988); 14. Teber, S. (2008); 15. Mohn, A. (2011); 16. Eade, A. (1981); 17. Chuck, A. J. (1989); 18. Whyte, M. (2012); 19. Seefried L. (2014); 20. Caswell, A. (1991); 21. Berkseth, K. E. (2013); 22. Schlesinger, B. (1954); 23. Auron, A. (2005)

Systemic Manifestations of Low TNSALP Activity Adult (first symptoms ≥ 18 y/o)

Presentation and severity of HPP varies among patients

SKELETAL[1,2,4-11,20-22]

- Hypomineralization
- Craniosynostosis
- Rickets, skeletal deformation
- Osteomalacia
- Fractures
  - Non-traumatic
  - Recurrent
  - Non-healing
- Bone pain
- Chronic bone inflammation
- Short stature

RESPIRATORY[1,10,12-14]

- Respiratory failure
- Respiratory insufficiency requiring support

MUSCULAR[1,3,4,8,19,20]

- Hypotonia
- Non-progressive proximal myopathy
- Muscle pain
- Immobility requiring assistive device (e.g., cane, crutches, walker, wheelchair)
- Delayed or missed motor milestones

NEUROLOGIC[1,2,]

- Seizures
- Increased intracranial pressure

RENAL[6,10,12,15,16,23]

- Nephrocalcinosis

RHEUMATOLOGIC[17]

- Chondrocalcinosis
- CPPD* deposition
- Calcific periarthritis
- Pseudogout
- Joint pain

*calcium pyrophosphate dihydrate

DENTAL[5,8,20]

- Tooth loss
- Poor dentition

OTHER[5,18,19, 21]

- Hypercalcemia†
- Hypercalciuria†
- Failure to thrive

†May remain within normal limits

1. Balasubramaniam, S. (2010); 2. Collmann, H. (2009); 3. Seshia, S. (1990); 4. Beck, C. (2011); 5. Whyte, M. (2012); 6. Barvencik, F. (2011); 7. Coe, J. (1986); 8. Kozlowski, K. (1976); 9. Moulin, P. (2009); 10. Whyte, M. (2012); 11. Weinstein, R. (1981); 12. Baumgartner-Sigl S. (2007); 13. Silver, M. (1988); 14. Teber, S. (2008); 15. Mohn, A. (2011); 16. Eade, A. (1981); 17. Chuck, A. J. (1989); 18. Whyte, M. (2012); 19. Seefried L. (2014); 20. Caswell, A. (1991); 21. Berkseth, K. E. (2013); 22. Schlesinger, B. (1954); 23. Auron, A. (2005)

Systemic Manifestations of Low TNSALP Activity Odontohypophosphatasia[1-4]

- No evidence of skeletal disease
- Characterized by premature exfoliation of fully rooted teeth
  - Anterior deciduous teeth (incisors) most commonly affected, but may involve all teeth
  - Permanent teeth may also be lost
  - Result of poor mineralization of cementum and loss of periodontal ligament attachment
- Additional features include:
  - Reduced alveolar bone
  - Enlarged pulp chambers and root canals
  - Abnormal enamel and dentin formation
  - Abnormalities in tooth shape, structure, eruption
  - Overall poor dentition including severe dental carries

1. Whyte, M. (2013); 2. Mornet, E. (2007); 3. Beumer, J. (1973); 4. Reibel A. (2009)

Differential diagnosis based on lab values

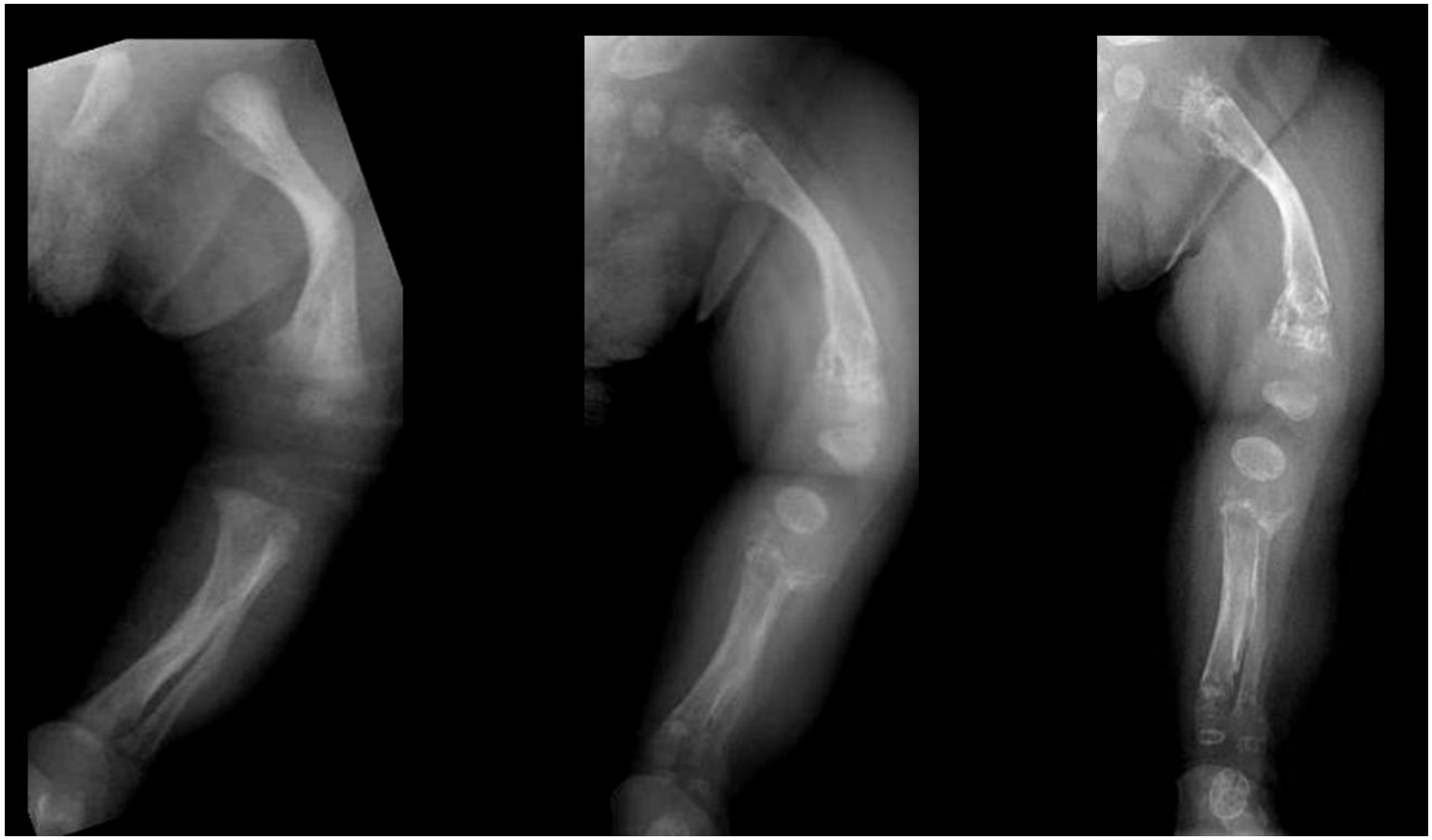
- **Low ALP is the hallmark of HPP**

Lab Values for differential diagnosis[1]				
Disease	**HPP**	**Nutritional rickets**	**X-linked hypophosphatemic rickets**	**Osteogenesis imperfecta**
Serum ALP	↓	↑	↑	normal
Ca/P	↑ or normal	↓	↓	normal
PTH	↓ or normal	↑	↑	normal
Vitamin D	normal	↓	↑	normal

While the clinical symptoms and presentation are similar, low ALP activity will distinguish HPP from other bone diseases

Radiographic Findings of HPP[1]: Progressive Skeletal Demineralization (example 1)

Birth | 5 months old | 7 months old



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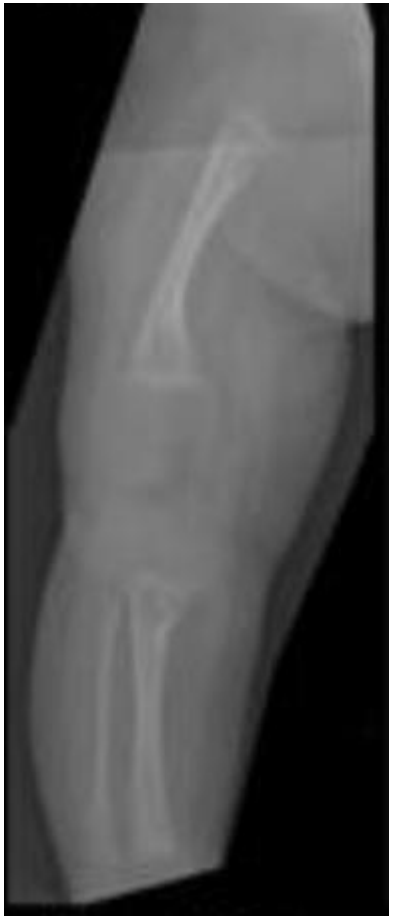
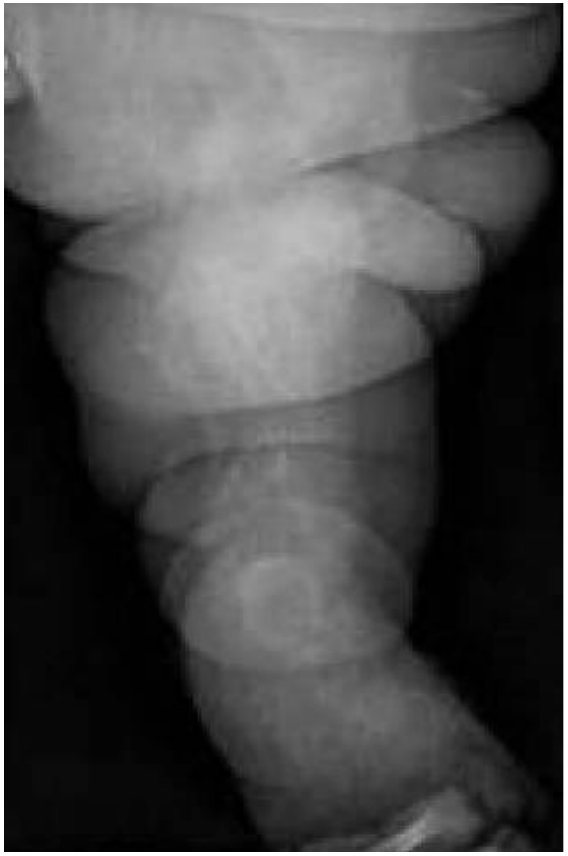
1. Whyte, M. (2012)

Radiographic Findings of HPP[1]: Progressive Skeletal Demineralization (example 2)

7 weeks old



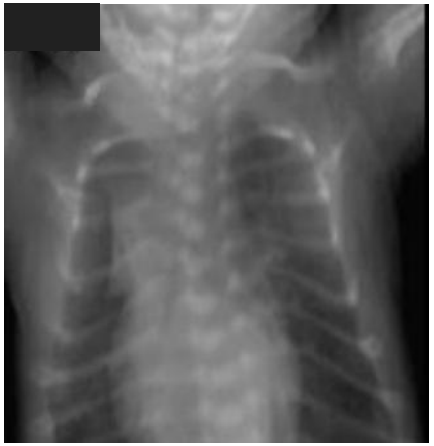
33 months old



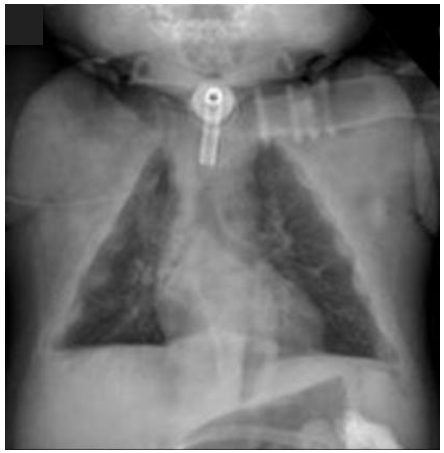
1. Whyte, M. (2012)

Radiographic Findings of HPP[1]: Progressive Skeletal Demineralization (example 3)

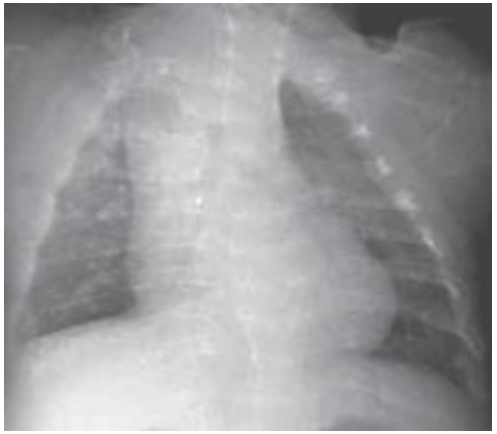
7 weeks old



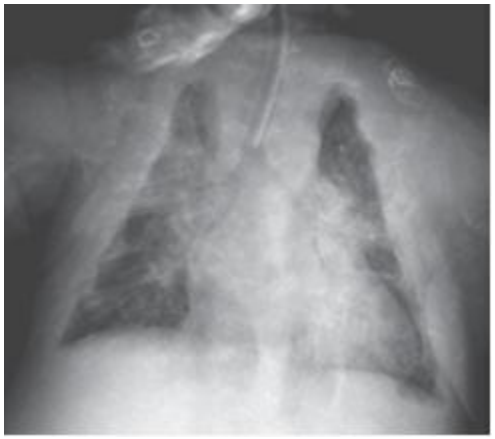
33 months old



7 weeks old



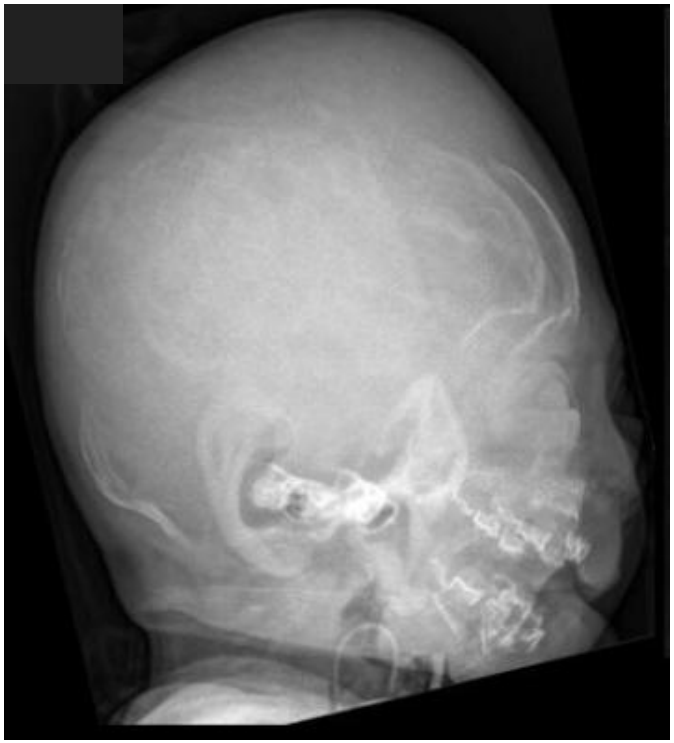
32 months old



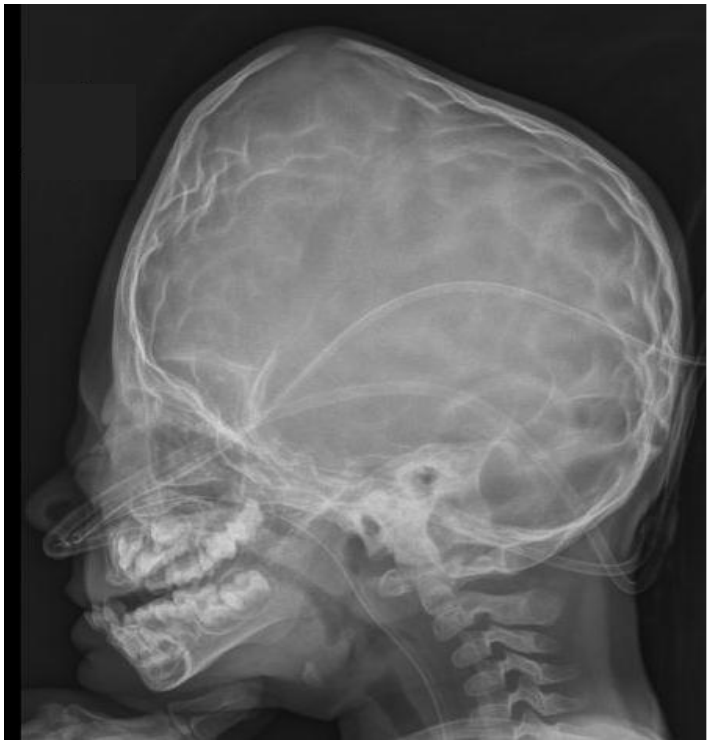
1. Whyte, M. (2012)

Radiographic Findings of HPP: Cranial Vault Abnormality in 2 Patients[1]

20 months old

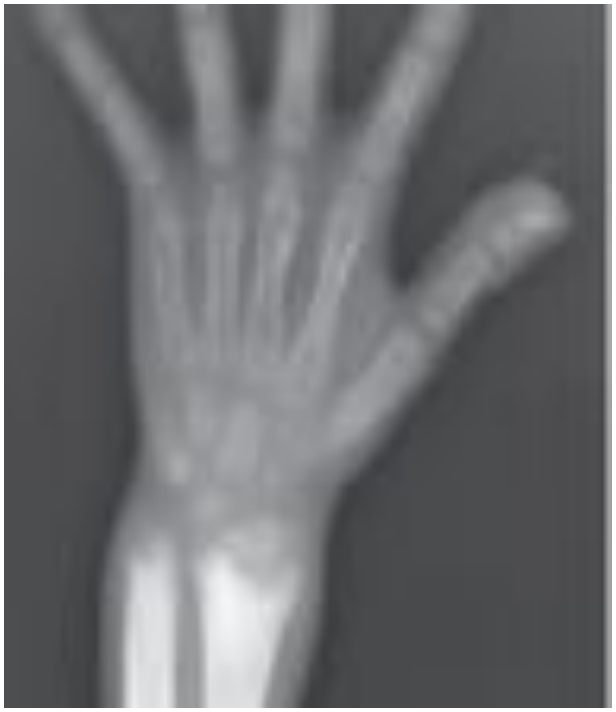


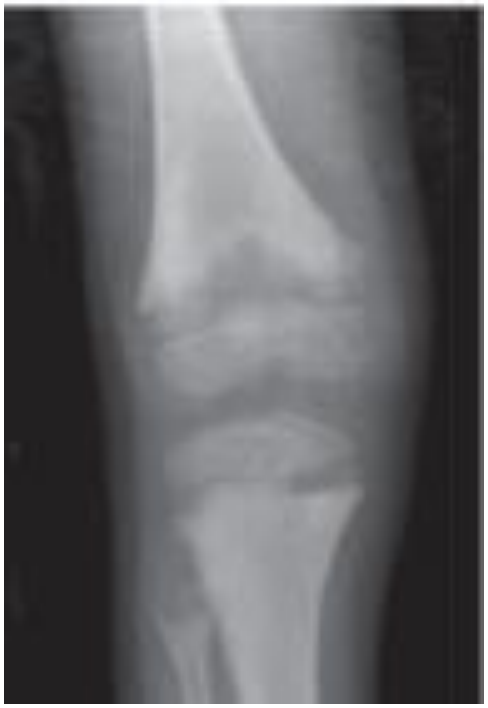
33 months old



1. Whyte, M. (2012)

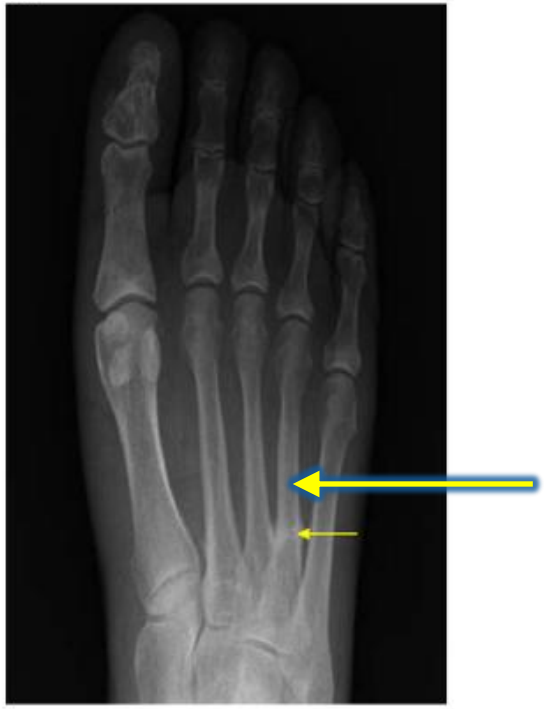
Radiographic Findings in Children with HPP[1]

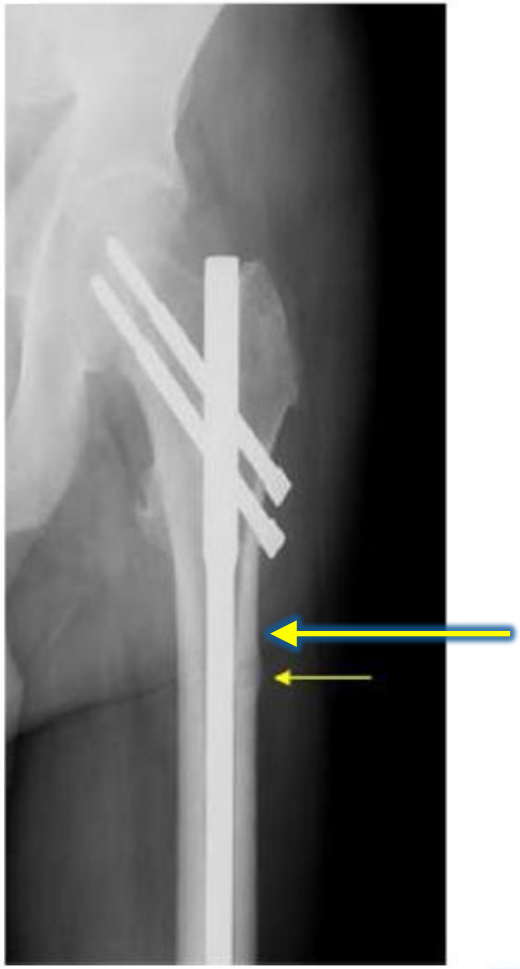




1. Madson, K. (2014)

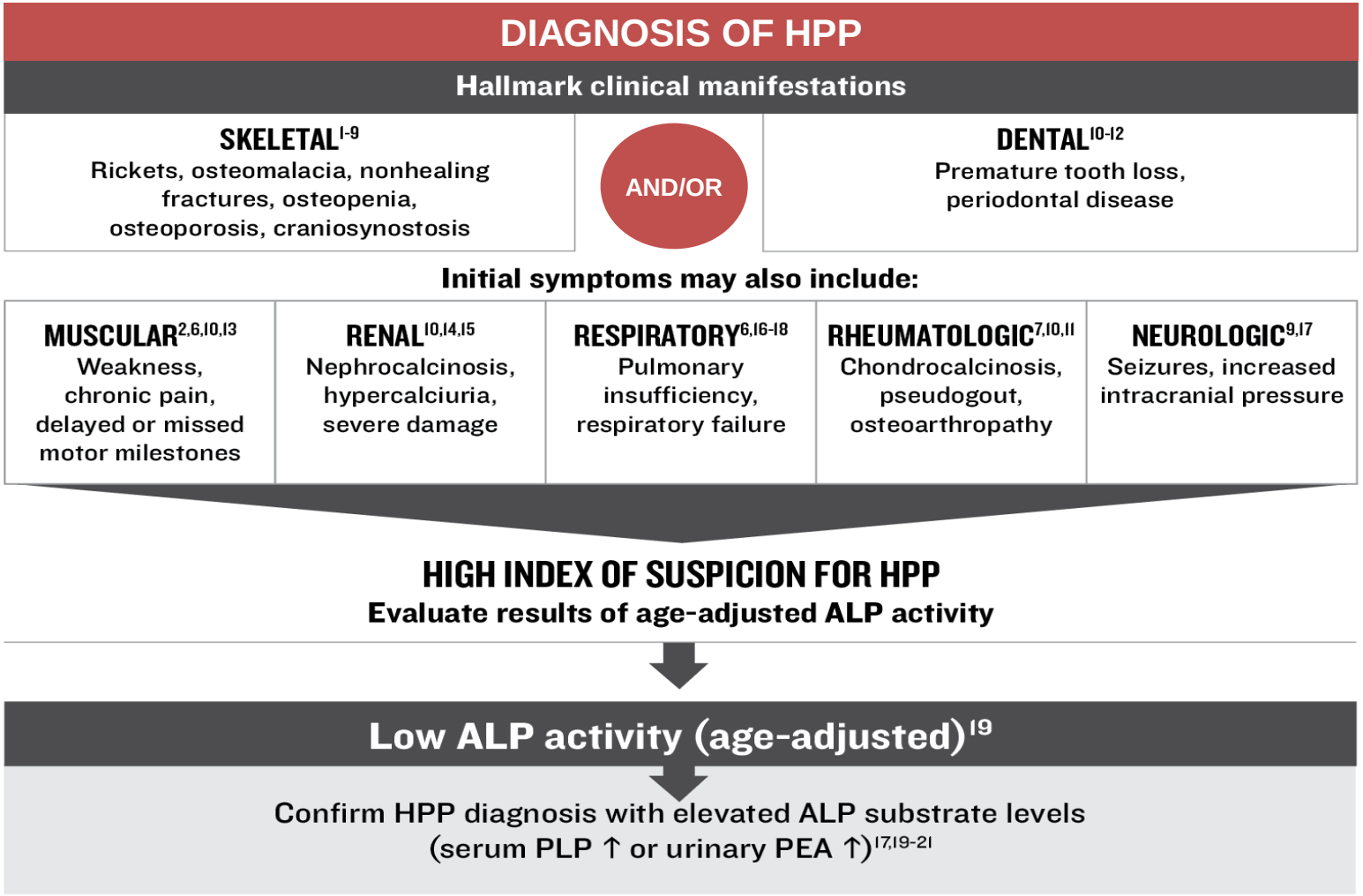
Radiographic Findings in Patients with HPP Diagnosed as Adults[1]





1. Berkseth, K. E. (2013)

Diagnosis of HPP[1-15]

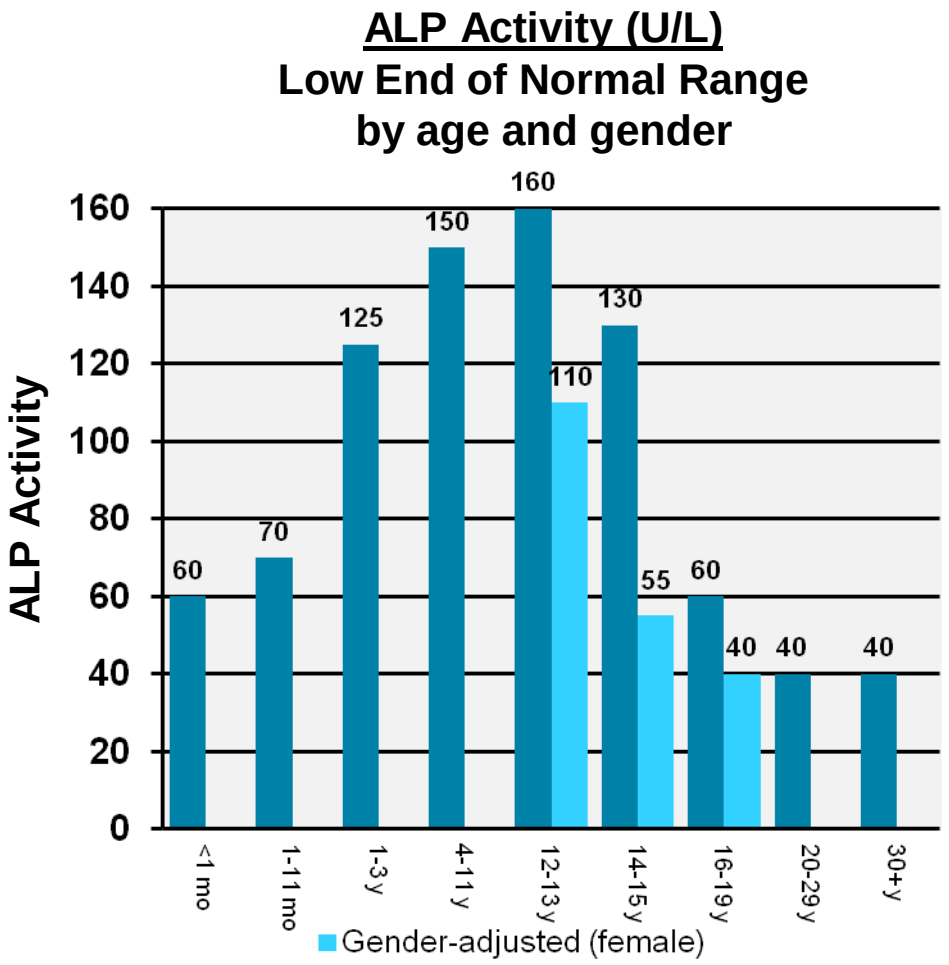


The information is intended as educational information for healthcare professionals. It does not replace a healthcare professional's judgment or clinical diagnosis.

1. Whyte, M. (2012); 2. Beck, C. (2011); 3. Barvencik, F. (2011); 4. Whyte, M. (2012, May); 5. Coe, J. (1986); 6. Whyte, M. (2012); 7. Chuck, A. J. (1989); 8. Sutton, R. (2012); 9. Collmann, H. (2009); 10. Rockman-Greenberg, C. (2013); 11. Whyte, M. (1982); 12. Reibel A. (2009); 13. Seshia, S. (1990); 14. Mohn, A. (2011); 15. Fallon, M. (1985); 16. Baumgartner-Sigl S. (2007); 17. Balasubramaniam, S. (2010); 18. Silver, M. (1988); 19. Mornet, E. (1993); 20. Whyte, M. (2001); 21. Whyte, M. (1985)

The Diagnostic Hallmark of HPP is Low ALP Activity[1-2]

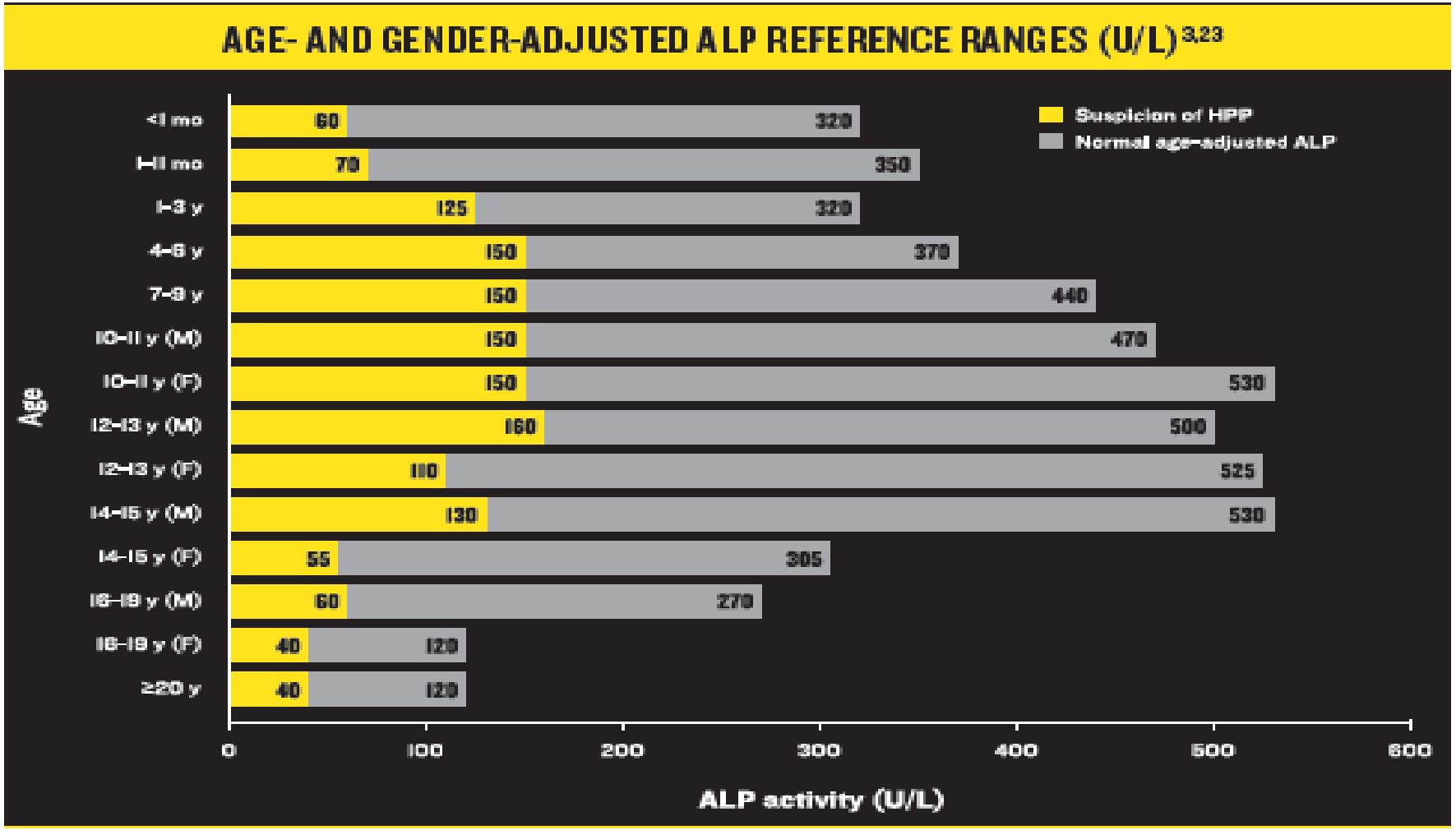
- Normal reference ranges for serum or plasma ALP activity are age-and gender dependent
- Most labs do not flag low ALP activity levels
- When full reference ranges are reported, it is important to note that:
  - Reference values depend on methods
  - Laboratories may vary in their age-and-gender appropriate reference ranges[1]



Adapted from ARUP laboratories. Higher normal ALP activity in children and adolescents compared with adults. Typical lowest normal reference values for serum ALP activity in North America. Methodology: quantitative heat inactivation/enzymatic.

1. Mornet, E. (1993); 2. Rockman-Greenberg, C. (2013)

ALP varies with Age and Gender



ALP activity is higher in infants, children, and adolescents than in adults

Misdiagnosis May Have Undue Consequences in Patients with HPP[1-4]

Bisphosphonates, high dose vitamin D, and calcium supplements may worsen HPP[1,3]

- 11-month-old male with HPP[1]
  - High-dose vitamin D and calcium supplementation for a presumed diagnosis of nutritional rickets
  - This therapeutic regimen led to rapid and severe deterioration of clinical symptoms resembling vitamin D intoxication
  - Patient developed hypercalcemia, growth failure, and bulging anterior fontanelle
  - Hypercalciuria led to severe renal damage with nephrocalcinosis
  - HPP was diagnosed 5 months after initial misdiagnosis.

- 55-year-old female with HPP[3]
  - 4 years of Bisphosphonate therapy for a presumed diagnosis of osteoporosis
  - Patient experienced multiple fractures including, atypical subtrochanteric femoral fractures and recurrent metatarsal stress fractures
  - Patient was asymptomatic until soon after her first Bisphosphonate exposure
  - HPP was diagnosed 6 years after initial misdiagnosis

1. Mohn, A. (2011); 2. Mornet, E. (1993); 3. Sutton, R. (2012); 4. Whyte, M. (2012)

Treatment

- No approved treatment for decades.

Asfotase Alfa (Strensiq) NOW APPROVED.

- S/C injection 3 or 6 times a week.

Summary:

- HPP is a rare, inherited metabolic disorder caused by inactivating mutations in the gene encoding tissue-nonspecific alkaline phosphatase (TNSALP)[1,2]
- The biochemical hallmark of HPP is low TNSALP activity[1,19]
  - Normal range for TNSALP varies by age- and gender
- Clinical manifestations include[1,2,3,4]
  - **Defective mineralization (bone and teeth)[1,3,4,6,9]**
    - Bone deformities, rickets, fractures (multiple, recurrent, poorly healing, non-traumatic), bone pain, and craniosynostosis
    - Premature loss of primary teeth, loss of permanent teeth, overall poor dentition
  - **Multiple systemic effects:[1,3,5,10-15,17,20]**
    - Respiratory compromise, seizures, increased intracranial pressure
    - Non-progressive proximal myopathy, muscle pain, missed motor milestones, immobility requiring wheelchair or other mechanical support
    - Chondrocalcinosis, calcific periarthritis, pseudogout, nephrocalcinosis and/or renal complications
- Presentation/severity of HPP is variable[3]:
  - Patients of all ages may be severely affected by HPP
  - Presentation among patients with the same mutation(s) can be quite different

1. Rockman-Greenberg, C. (2013); 2. Fraser, D. (1957); 3. Whyte, M. (2008); 4. Anderson, H. C. (1997); 5. Baumgartner-Sigl S. (2007); 6. Whyte, M. (2012); 7. Whyte, M. (1985); 8. Beck, C. (2009); 9. Coe, J. (1986); 10. Balasubramaniam, S. (2010); 11. Collmann, H. (2009); 12. Mohn, A. (2011); 13. Barvencik, F. (2011); 14. Eade, A. (1981); 15. Seshia, S. (1990); 16. Moulin, P. (2009); 17.Weinstein, R. (1981); 18. Whyte, M. (2001); 19. Mornet, E. (1993); 20. Skrinar, A. (2010)

THANK YOU!

Questions