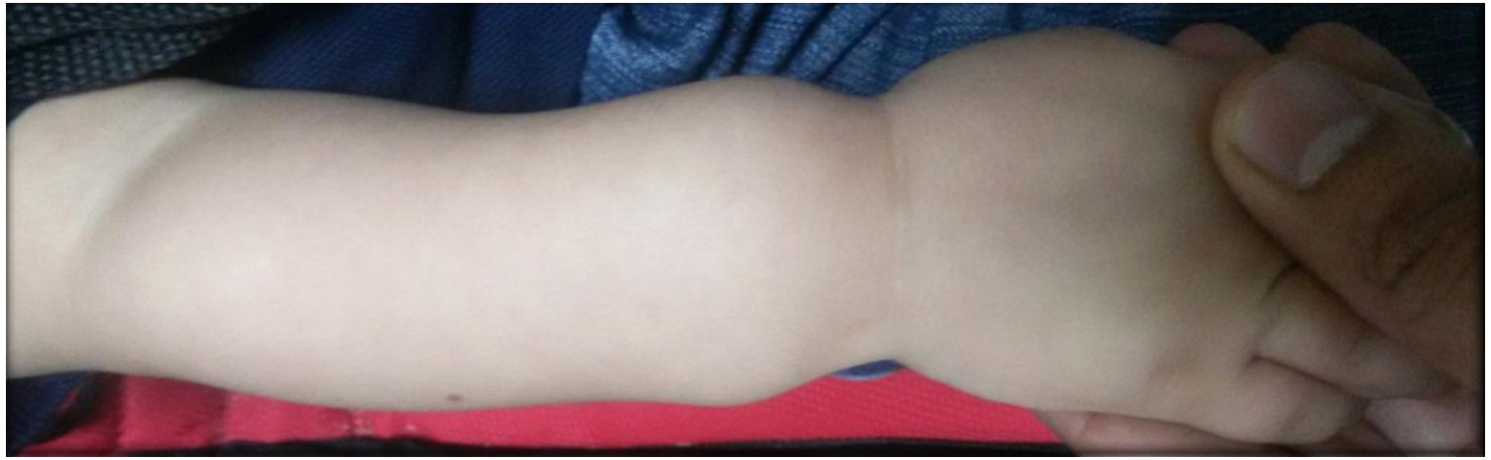
# NOT AS EASY AS IT SEEMS

*Prof. Abdulmoeen Agha*

# History

Mohammed, 1.9 m year, Saudi boy brought to my endocrine clinic for the evaluation of skeletal changes of rickets



# History

Mohammed is an outcome of SVD FT , with uncomplicated pregnancy

Teeth didn’t erupt till age of 9 months
Skeletal changes noticed at age of 10 months as enlarged epiphysis and bowing of the back
didn’t roll over till age of 1 year and 1 month

# History

Past medical : unremarkable

Past surgical : unremarkable

Current Developmental :

Gross : can pull to stand = 6-9 m

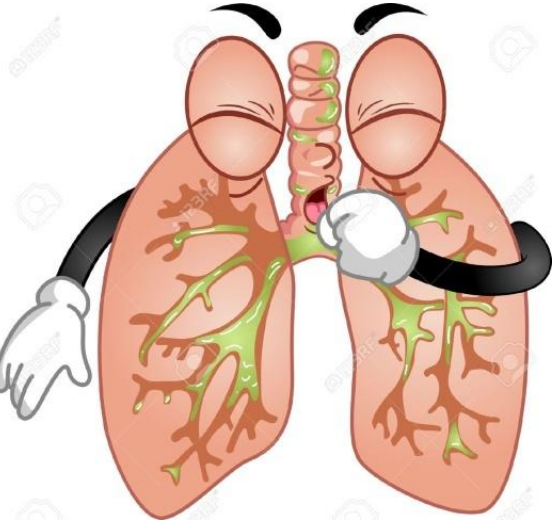
fine : can pincer grasp = 9m

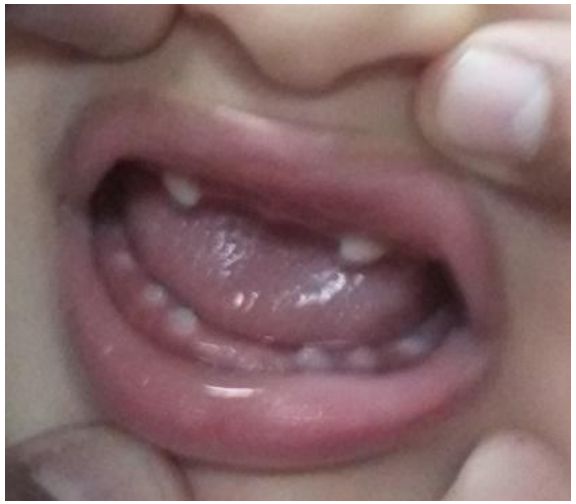
social : can follow simple tasks = 15 m

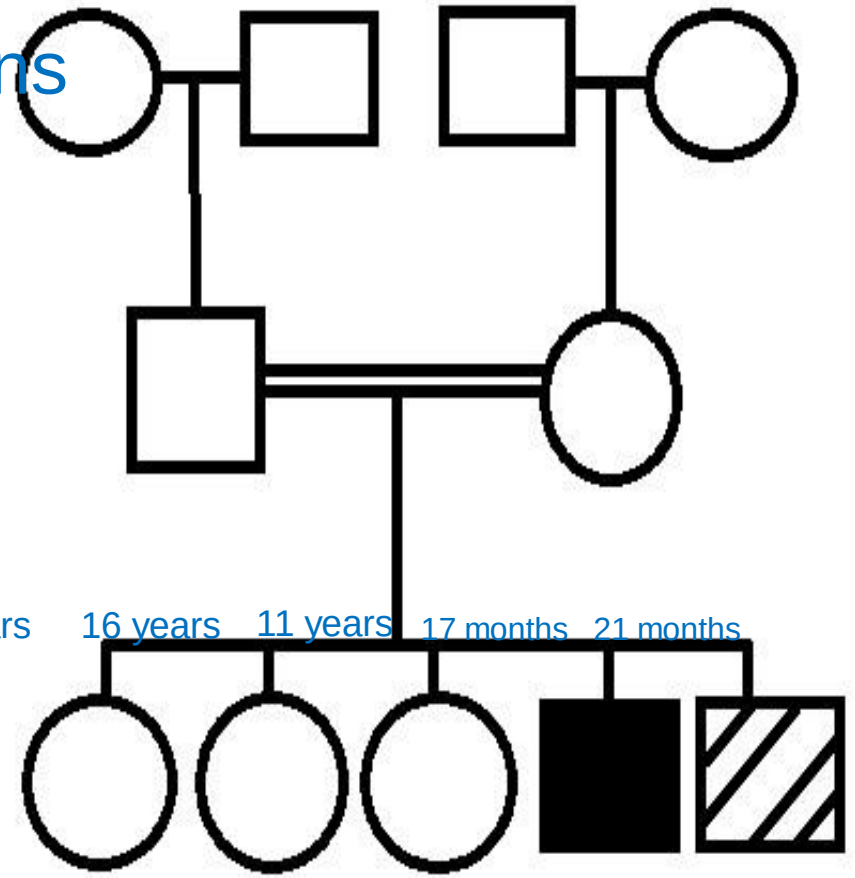
Language : can put 2 words together = 2 years

# History

Family history : Death of previous child at age of 11 moths, 4rd child “ Abdulrahman “
presented at age 9 months with
skeletal deformities , delay eruption , chest infections







# History

Social history: father works in company , house wife “house wife

Vaccination : up to date

Nutritional history

Breast fed till age of  8months, artificial formula

milk intake about 120ml , 5 times per day till today ,

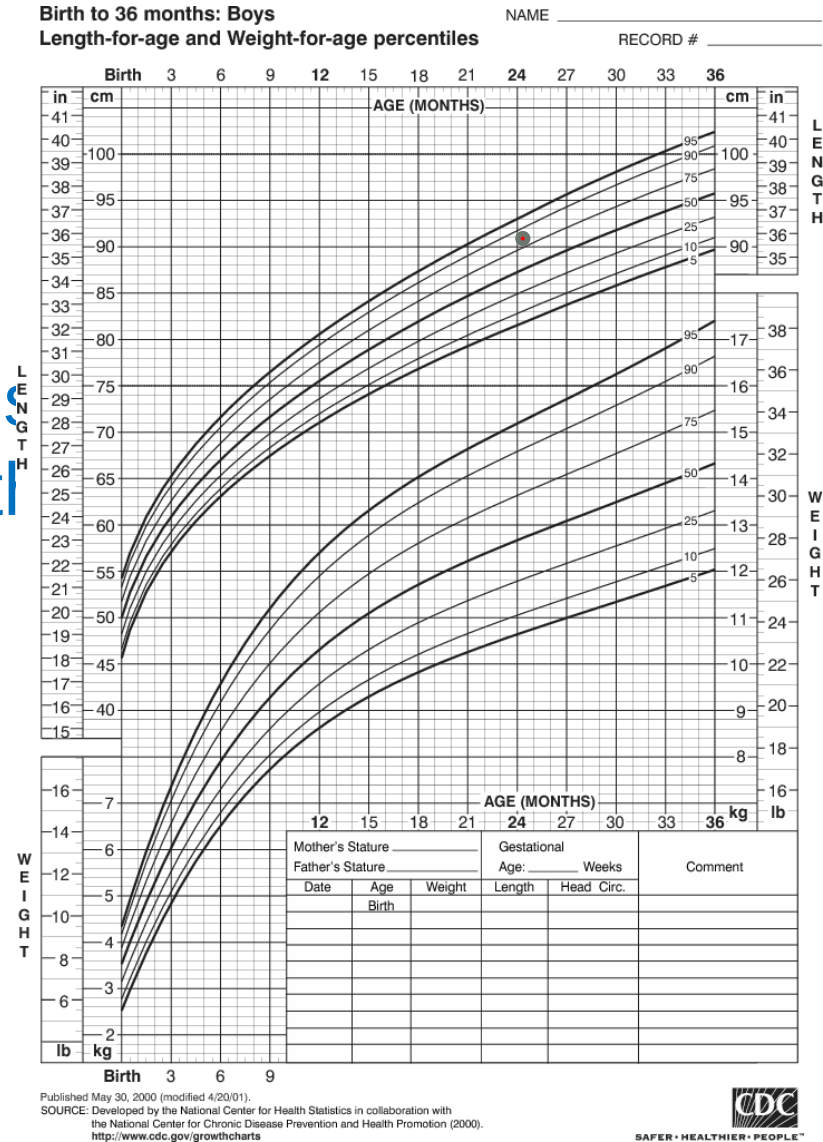
caring about exposing child to sun 30 min /day


# Examination :

On his initial clinical assessment:
was alert ,conscious , active , playful

Anthropometric measures:
weight  8 kg below 5th centile responding to 7 months
Height 71 cm below 5th centile responding to 7 month
Head circumference 47cm between 25th and 10th centile

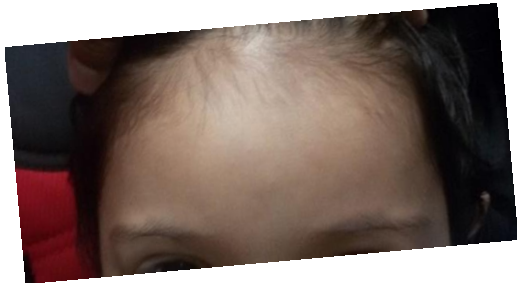
Not jaundiced , not pale ,
not cyanosed , not dysmorphic ,
not in pain , not dehydrated ,
not distressed .

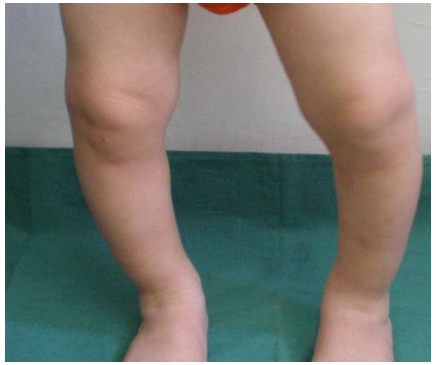


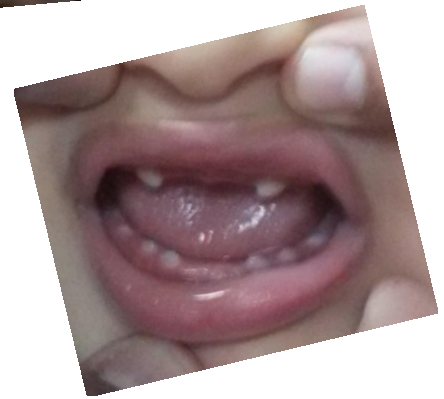
MSK examination :

Prominent forehead , deciduous teeth , enlarged epiphysis at both wrists and ankles , varus deformity of lower limb , kyphoscoliosis of the back , with generalized Hypotonia

AF and PF closed , no rachitic rosary , no harrison groove , no chest wall deformity , head is not large , no craniostynosis , no enlarged sutures

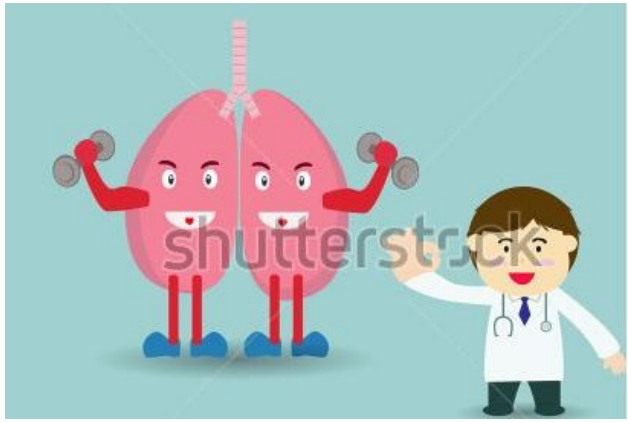






# Examination :

CNS examination : unremarkable
Respiratory examination : no evidence of chest infection
CVS examination : unremarkable
Abdomen examination :
distended abdomen with soft lax no organomegaly



- Course of the disease:

- According to parents, that their son “Mohammed”, have been diagnosed by many physicians as nutritional rickets and despite of repeated courses of Vitamin D and calcium supplements, clinically Mohammed was deteriorating

# Deferential Diagnosis:

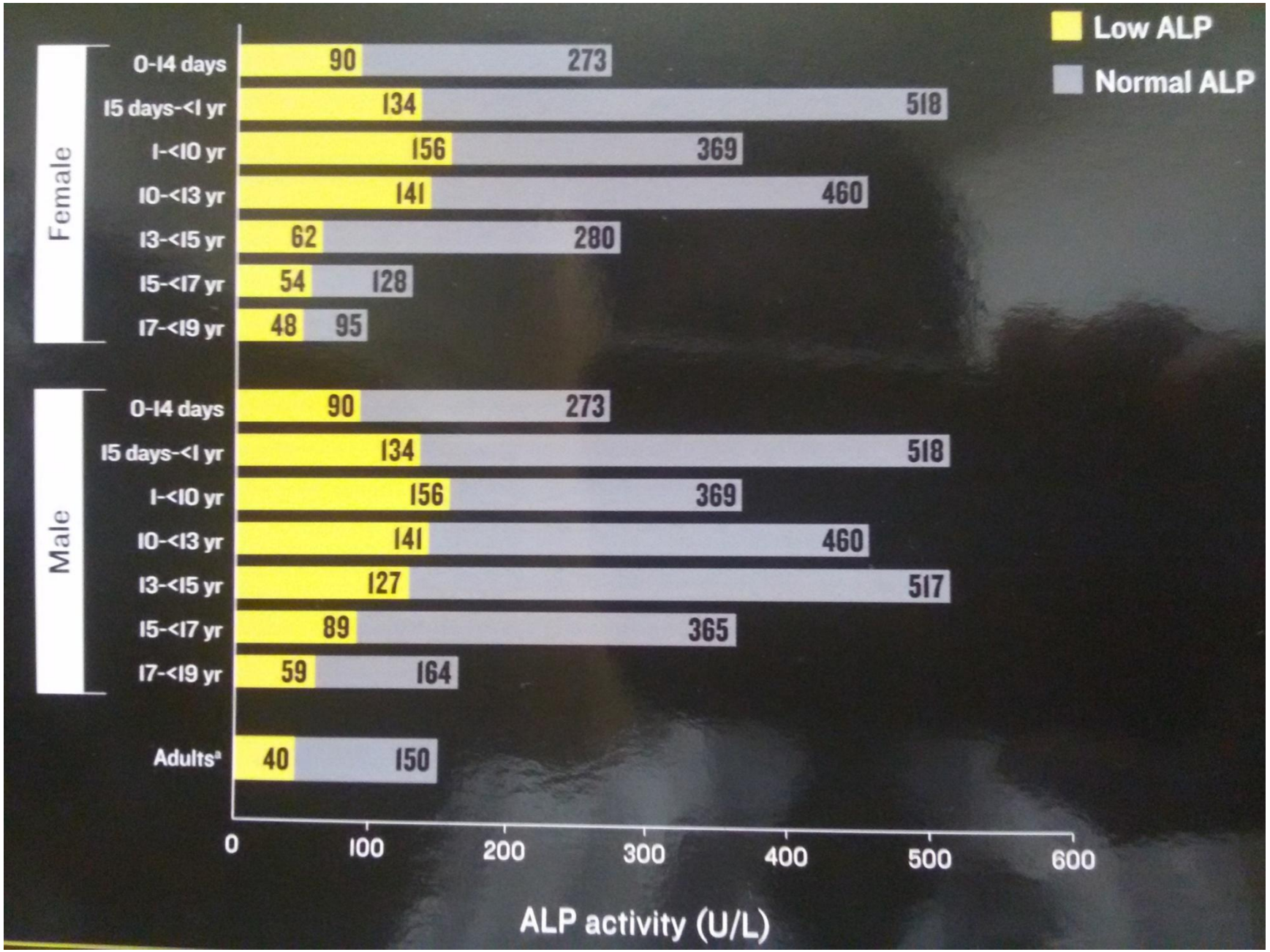
Rickets Vitamin D dependent Rickets
Vitamin D resistant Rickets
Hypophosphatemic Rickets
Rickets due to various “ renal “ or “ Hepatic “
Hypophosphatasia
Osteogensis imprefecta
Skeletal dysplasia
Hypophosphatasia

# Investigations :

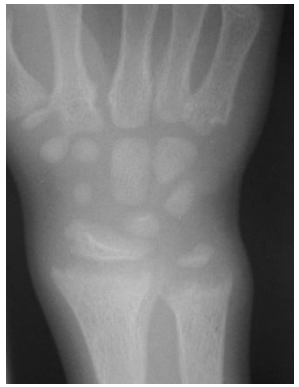
| | | |
|---|---|---|
| Ca | 2.65 mmol/L | “ high “ |
| Phosphate | 2.00mmol/L | “ high “ |
| vitamin D3 | 108 nmol/L | “ very high “ |
| PTH | low | |
| Renal function | Normal | |
| Liver function test | Normal | |

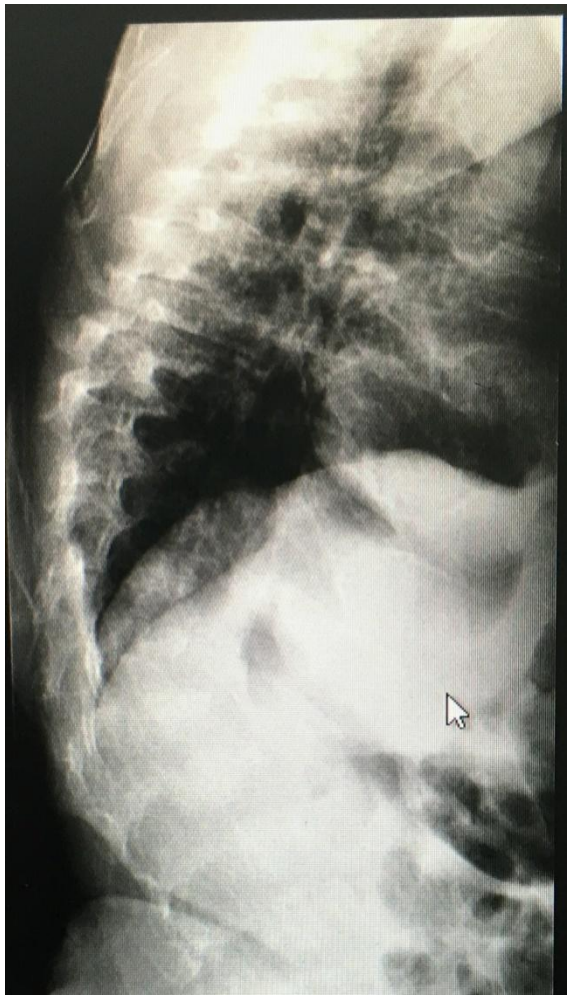
ALP results 41u/L “VERY low “

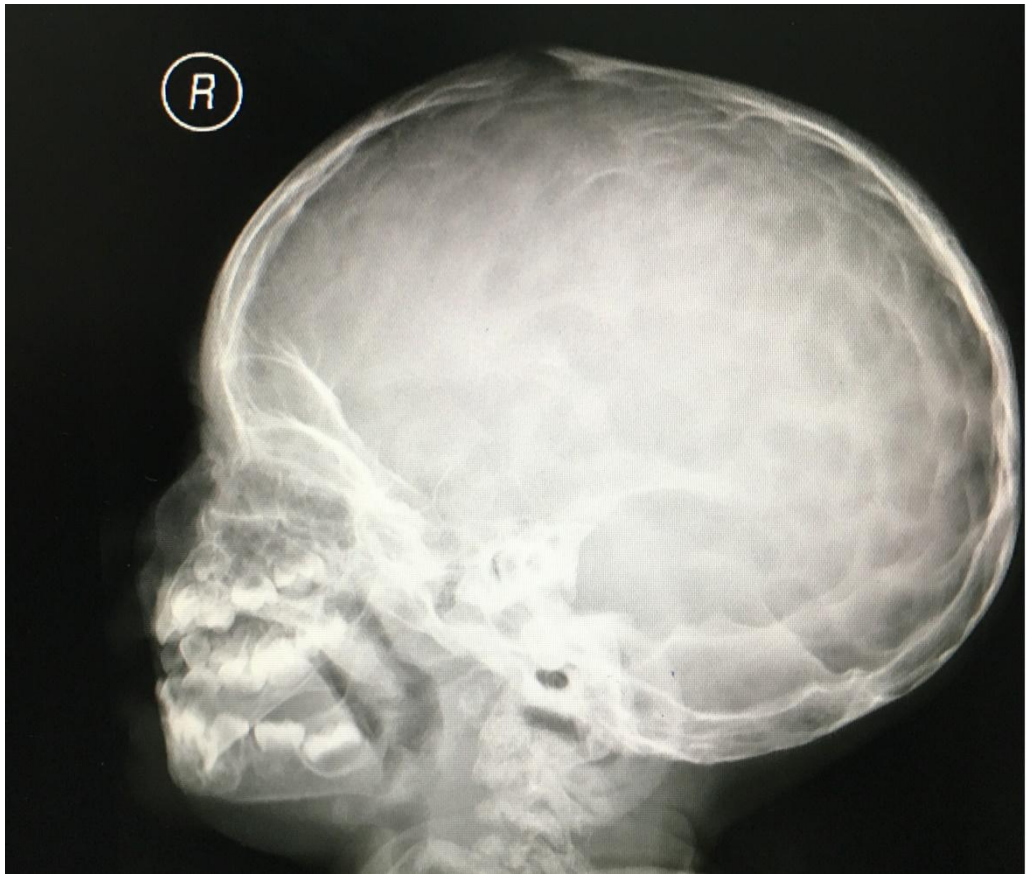
# ALP Levels According To Age



# Investigations :







Based on Low Alkaline Phosphatase of 41 IU/ L (156-369) together with clinical manifestations, initially diagnosis of Hypophosphatasia was started

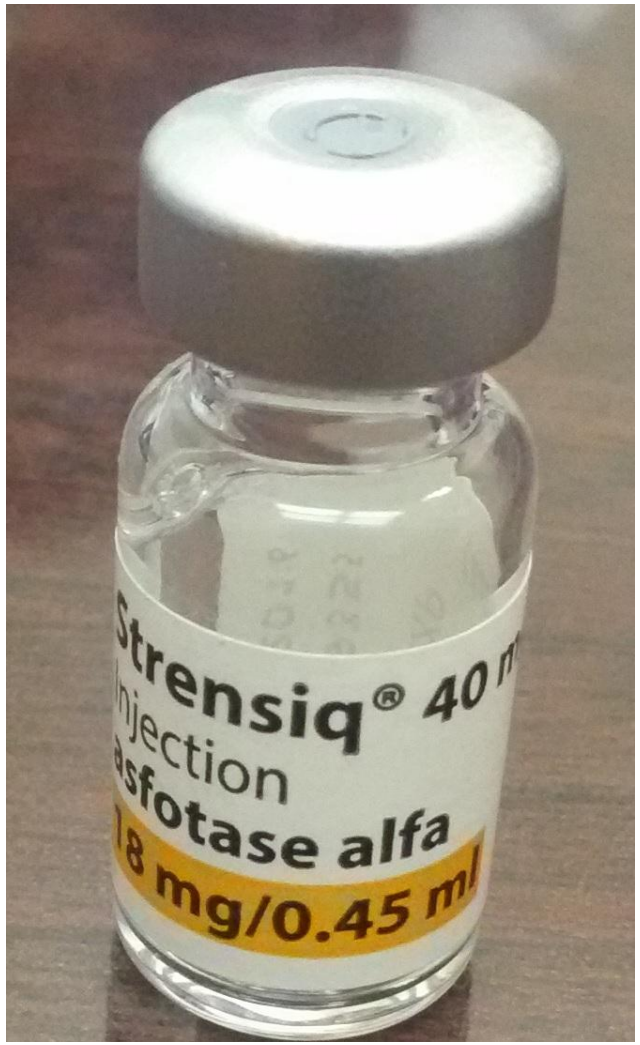
# Management :

**Replacement of the enzyme as SC**

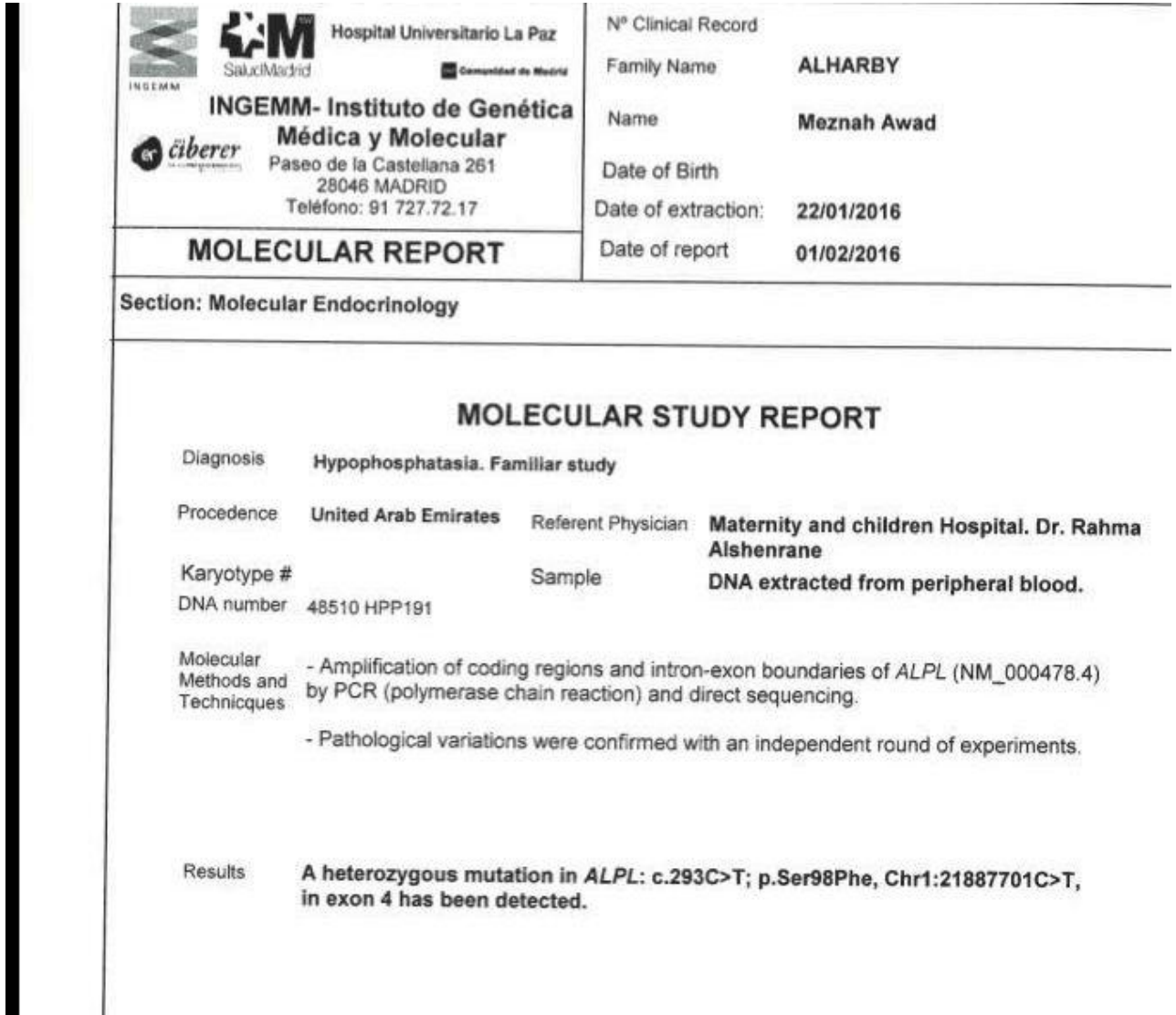
**3 times /week**

**Dose = 2mg /kg**

**Each vial contain 18mg as 0.45ml**



# Genetic testing result has been received after therapy



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Paseo de la Castellana 261
28046 MADRID
Teléfono: 91 727.72.17

| | |
|---|---|
| Nº Clinical Record | |
| Family Name | ALHARBY |
| Name | Meznah Awad |
| Date of Birth | |
| Date of extraction: | 22/01/2016 |
| Date of report | 01/02/2016 |

**MOLECULAR REPORT**

**Section: Molecular Endocrinology**

## MOLECULAR STUDY REPORT

| | | | |
|---|---|---|---|
| Diagnosis | **Hypophosphatasia. Familiar study** | | |
| Procedence | **United Arab Emirates** | Referent Physician | **Maternity and children Hospital. Dr. Rahma Alshenrane** |
| Karyotype # | | Sample | **DNA extracted from peripheral blood.** |
| DNA number | 48510 HPP191 | | |

Molecular Methods and Technicques

- Amplification of coding regions and intron-exon boundaries of *ALPL* (NM_000478.4) by PCR (polymerase chain reaction) and direct sequencing.
- Pathological variations were confirmed with an independent round of experiments.

Results

**A heterozygous mutation in *ALPL*: c.293C>T; p.Ser98Phe, Chr1:21887701C>T, in exon 4 has been detected.**

# Post 3 months of therapy

- Video to reveal clinical improvement
- Lab:

- Calcium 9.7 (8.8- 10.2 mg/dl)
- ALP 5019 (156-369)
- Vitamin D 322 ng/ml (30 -100)

# Take Home Massage

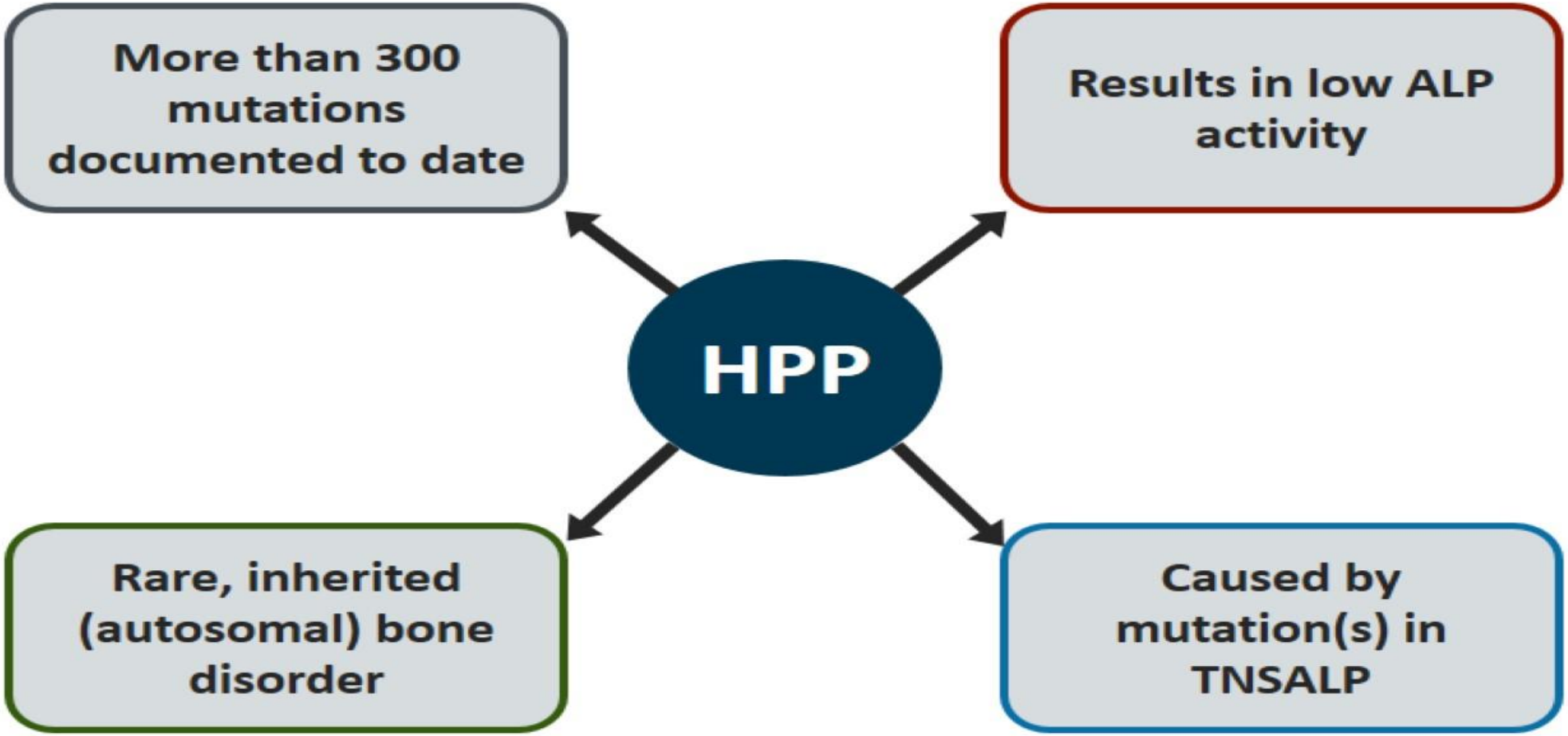
most of these cases misdiagnosed as rickets or skeletal dysplasia and so we need to increase awareness of this rare disease as it is lethal disease

ALP range in the hospital is not age dependant and part of missing the diagnosis is misunderstanding the ALP range

*Take home message

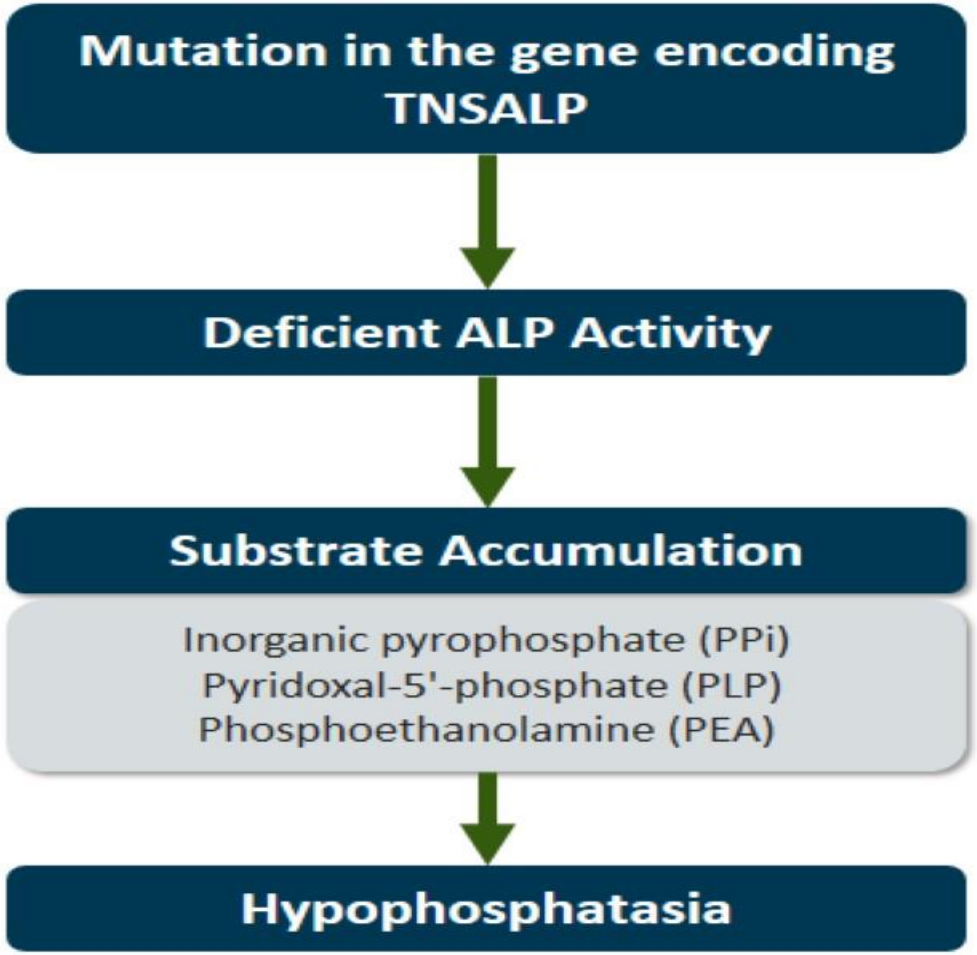
# HYPOPHOSPHATASIA

# What is HPP?




Bianchi ML. *Osteoporos Int*. 2015;26:2743-2757.

# Mechanism of HPP

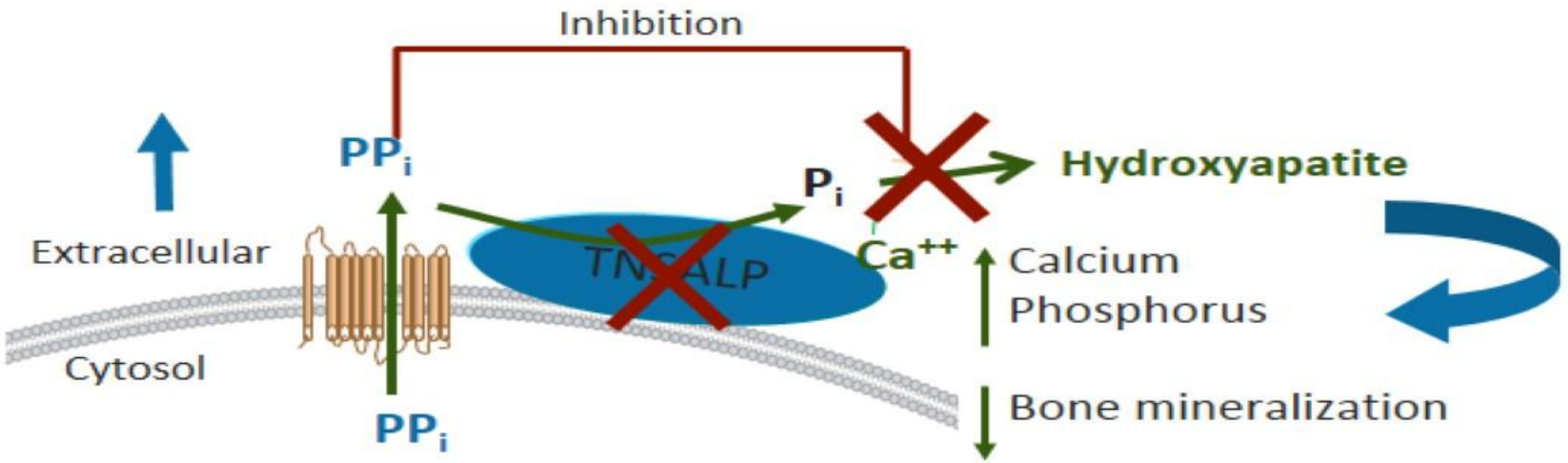



Orimo H. *J Nippon Med Sch*. 2010;77:4-12.

# Pathophysiology in Bone

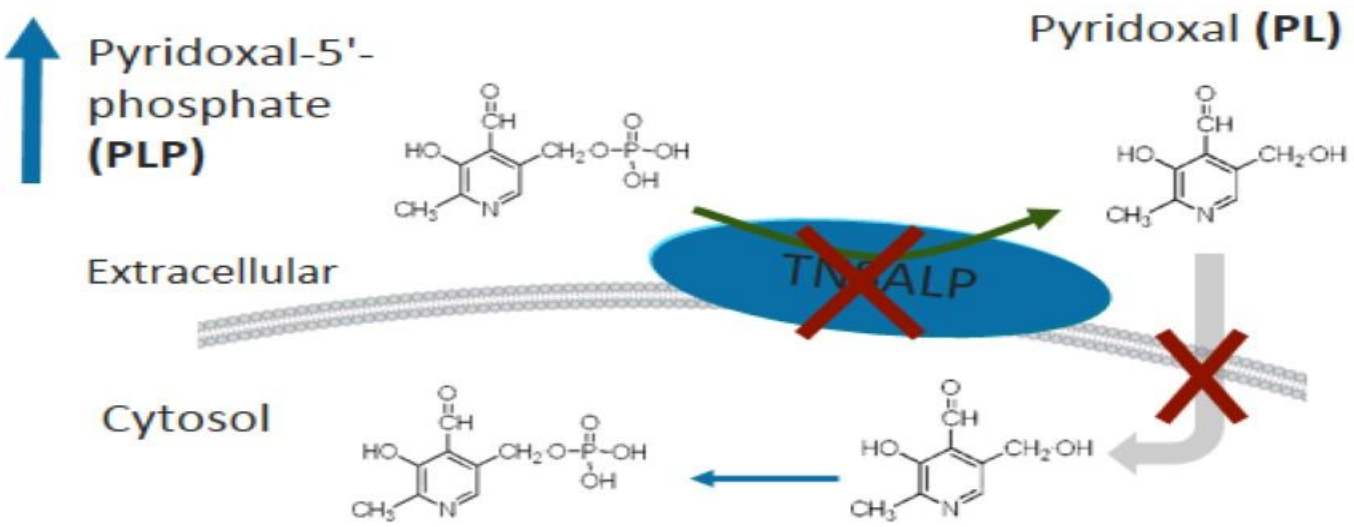
**Bone**

Low TNSALP activity leads to extracellular accumulation of PPi, and inhibition of mineralization




Orimo H. *J Nippon Med Sch*. 2010;77:4-12.

# Why is Vitamin B6 Elevated?
## *HPP Pathophysiology in the CNS*




**CNS**

Low TNSALP activity results in PLP (active Vitamin B6) deficiency in the CNS, leading to seizures

Orimo H. *J Nippon Med Sch*. 2010;77:4-12.

# HPP
## *Common Presentation*

- Diagnosis can occur at any age
- Symptoms and severity depend greatly on age of onset
- However, at any age, there is a wide variety of clinical severity
- Classically, HPP is categorized by the age at presentation of symptoms

Mornet E. *Orphanet J Rare Dis*. 2007 Oct 4;2:40.

# Perinatal HPP

- Presents in utero
- Characterized by extreme skeletal abnormalities
- Respiratory problems are common in perinatal HPP and can be life-threatening
- Intractable seizures may also occur
- Perinatal HPP (lethal)
- Perinatal HPP (benign)

Mornet E. GeneReviews® [Internet]. 2007.

# Infantile HPP

- Presents between birth and 6 months of age
- Patients have failure to thrive with poor feeding and inadequate weight gain
- Hypotonia and developmental delay
- Patients may have pseudocraniosynostosis
- Radiographic findings of osteopenia, rickets, bowing
- Respiratory distress
- Vitamin B6 responsive seizures
- Hypercalcemia can lead to nephrocalcinosis and renal failure
- Mortality rate of approximately 50%

Mornet E. GeneReviews® [Internet]. 2007.

# Childhood HPP

- Symptoms begin > 6 months of age
- Early tooth loss is a common first indication of the disorder
- Spectrum of severity
  - Skeletal findings: frequent fractures, widened wrists, rachitic chest changes, bowing
  - Muscle weakness, pain, and early fatigue leading to delay of motor skills development (walking, carrying a backpack, jumping, getting onto a school bus)
  - Waddling gait

Mornet E. GeneReviews® [Internet]. 2007.

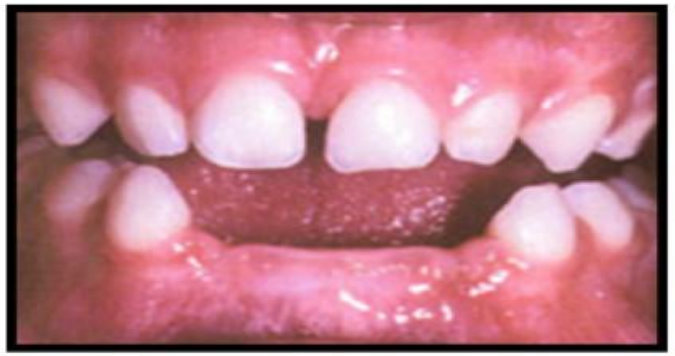
# Adult HPP

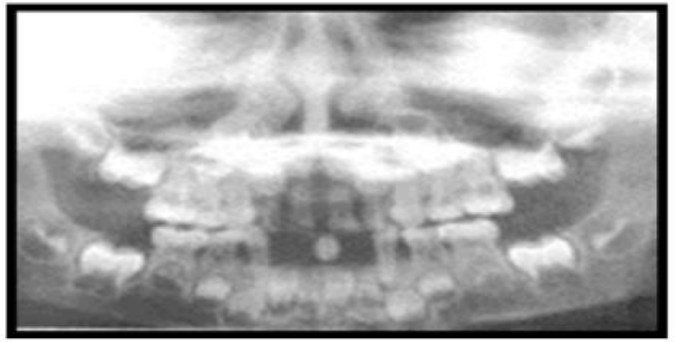
- Variable presentation
- Osteomalacia and osteopenia
- Pain/weakness due to muscle pain that can lead to immobility
- Pseudogout
- Early loss of adult dentition

Mornet E. GeneReviews® [Internet]. 2007.

# Odontohypophosphatasia

- Isolated dental disease
- Diagnosed at any age
- No evidence of osteomalacia by radiograph and/or bone biopsy
- Premature loss of deciduous teeth





Images courtesy of Jill H. Simmons, MD.
Mornet E. GeneReviews® [Internet]. 2007.

# HPP
## *Disease Burden*

| Burden of HPP |
| --- |
| Pain |
| Fractures |
| Impaired mobility |

**HPP is "not just broken bones"**

Mornet *E. Orphanet J Rare Dis*. 2007 Oct 4;2:40.

# Diagnosis of HPP

| Differential Diagnoses |
| --- |
| Nutritional rickets |
| Hypophosphatemia |
| Osteoporosis/osteopenia |
| Osteogenesis imperfecta |
| Osteoarthritis |
| Rheumatologic diseases |

Mornet E. *Orphanet J Rare Dis*. 2007 Oct 4;2:40.

# Diagnosis
## *ALP Levels*

| Age | Lowest Normal Total Serum or Plasma ALP Activity (U/L) | |
|---|---|---|
| | Male | Female |
| 0-30 days | 60 | 60 |
| 1-11 months | 70 | 70 |
| 1-3 years | 125 | 125 |
| 4-11 years | 150 | 150 |
| 12-13 years | 160 | 110 |
| 14-15 years | 130 | 55 |
| 16-19 years | 60 | 40 |
| ≥ 20 years | 40 | 40 |

Mornet E. GeneReviews® [Internet]. 2007.

# Diagnosis

## *Vitamin B6/PLP/PPi/PEA Levels*


- Elevated serum calcium and phosphorus levels may be present, but are not necessary
- Genetic testing is not always required, but may be helpful, depending upon your patient's situation

Mornet E. GeneReviews® [Internet]. 2007.

# HPP
## *Treatment*

**Prior to 2015, treat symptoms and some complications**

- Hypercalcemia: restrict dietary calcium and calciuretics
- Vitamin B6 for seizures
- Respiratory support (ventilator, tracheostomy)
- Surgical release of craniosynostosis
- Fractures may require prolonged casting or stabilization
- Dental hygiene

Mornet E. GeneReviews® [Internet]. 2007.

# HPP
## *Treatment Challenges*

**Attempts at definitive treatment inadequate or contraindicated**

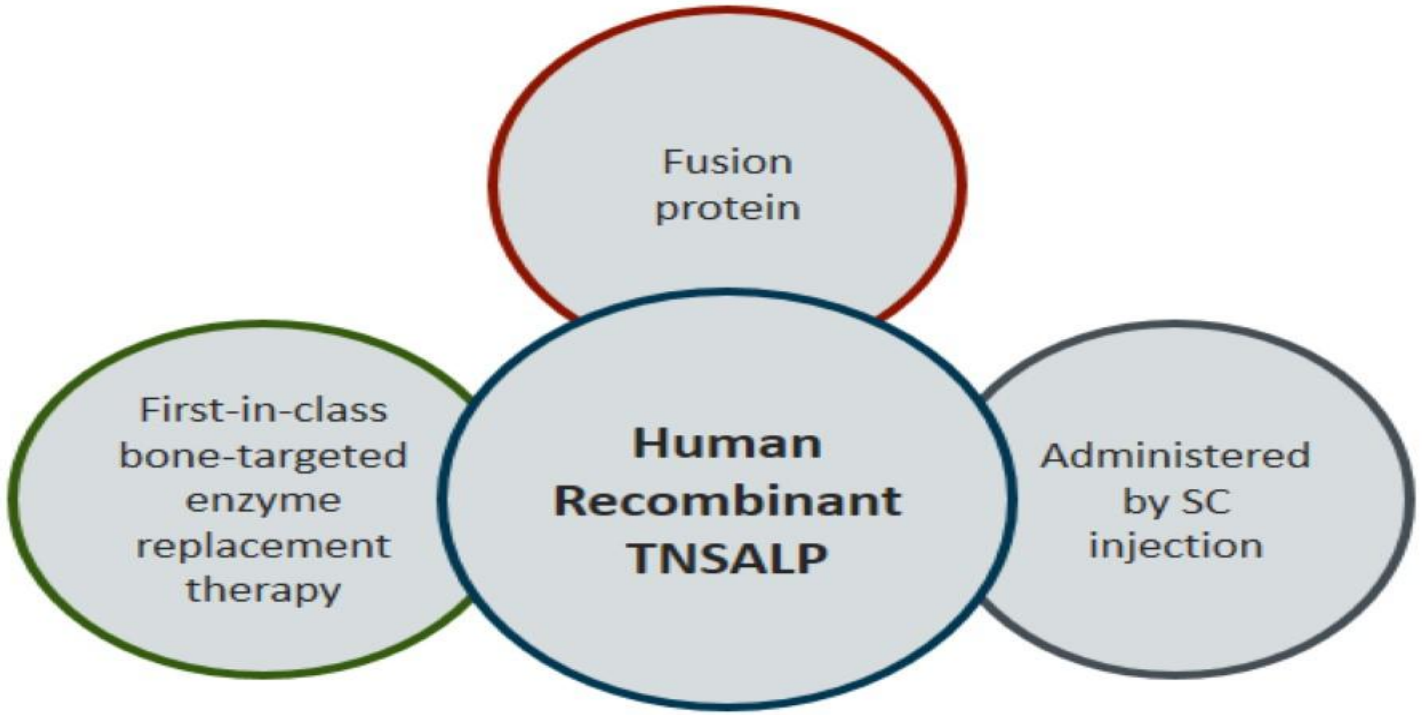
- Bisphosphonates (contraindicated)
- Significant morbidity with bone marrow transplantation
- Variable results with parathyroid hormone, or teriparatide
- Human TNSALP from Paget's disease patients has been unsuccessful

Mornet E. GeneReviews® [Internet]. 2007.

# HPP
## *Current Treatment: Asfotase Alfa*

**October 23, 2015**

- Asfotase alfa is now approved by the FDA in patients who have symptoms (or a history of symptoms) of HPP prior to age 18 years



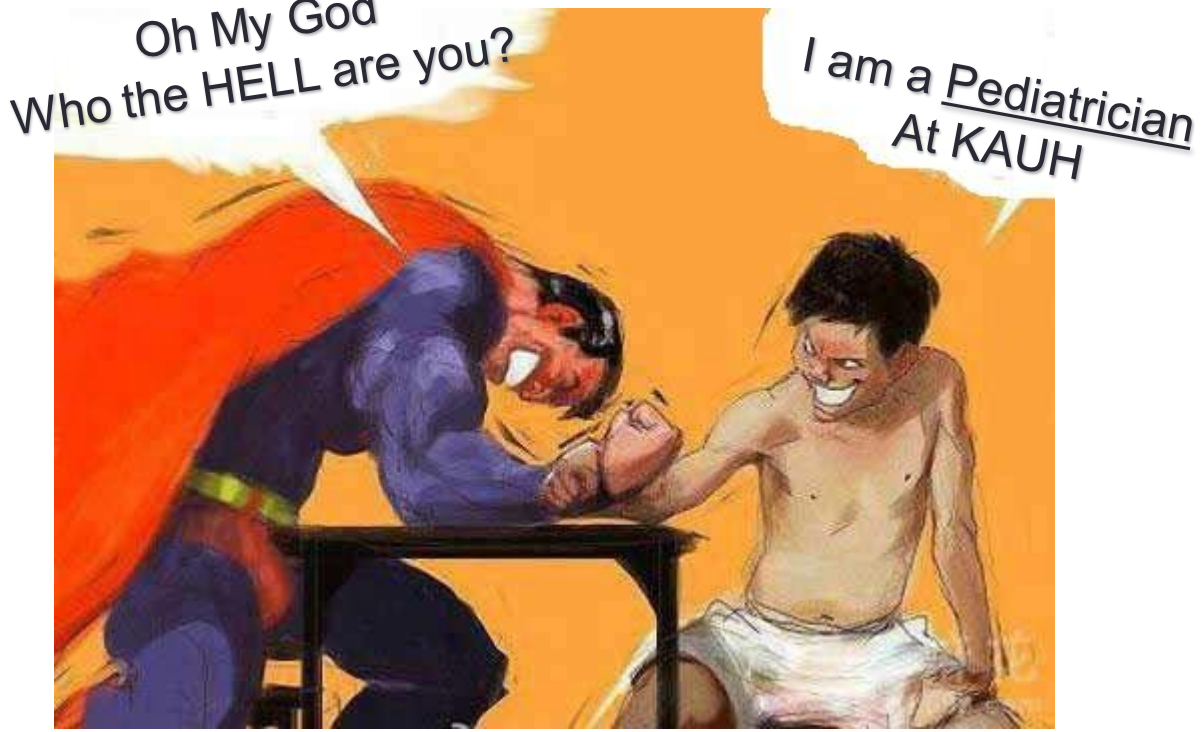

FDA Approves New Treatment for Rare Metabolic Disorder [news release]. Silver Spring, MD: Food and Drug Administration; October 23, 2015.

# Closing Comments

- Manifestations of HPP vary based upon age at presentation and severity of disease
- The morbidity can be significant at any age
- Now, there is a recently approved medication to treat this disease
- Research is needed to determine the appropriate length of treatment with asfotase alfa, long-term effects of treatment, and the effect of treatment upon adults with HPP

# Thank you All

# Thank you Prof Agha for everyting
# &
# Thank you All




Dr.Yaser Bamashmous
Pediatric Resident " R3"