HPP-from lethal to “asymptomatic” disease

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האיגוד הישראלי לנפרולוגית ילדים
ISPN The Israeli Society of Pediatric Nephrology

קווים משיקים ברפואת ילדים
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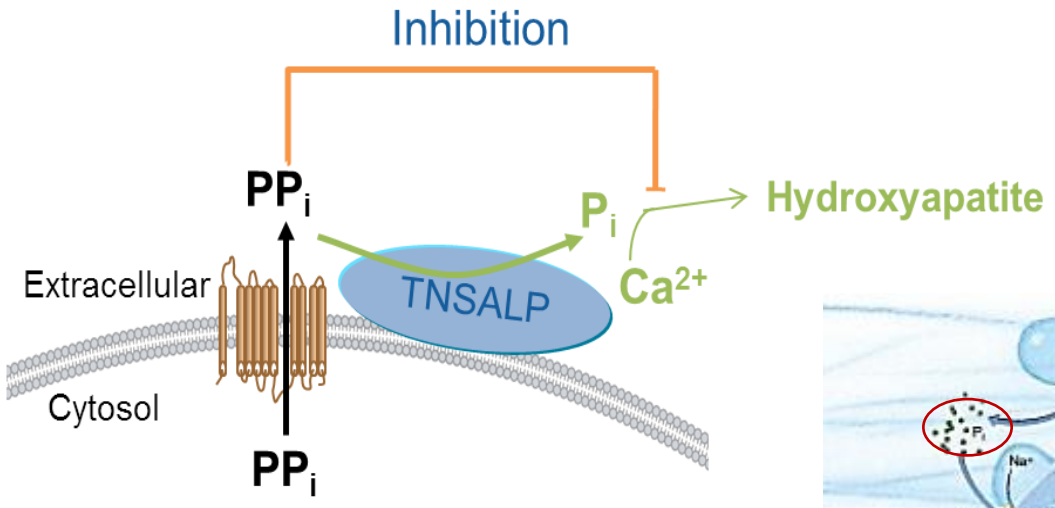
מרכז רפואי שמיר

HPP

A rare, inherited, potentially life-threatening disorder of bone mineralization.

Inactivating mutation in tissue non specific alkaline phosphatase gene (ALPL; OMIM# 171760) → low ALP activity.

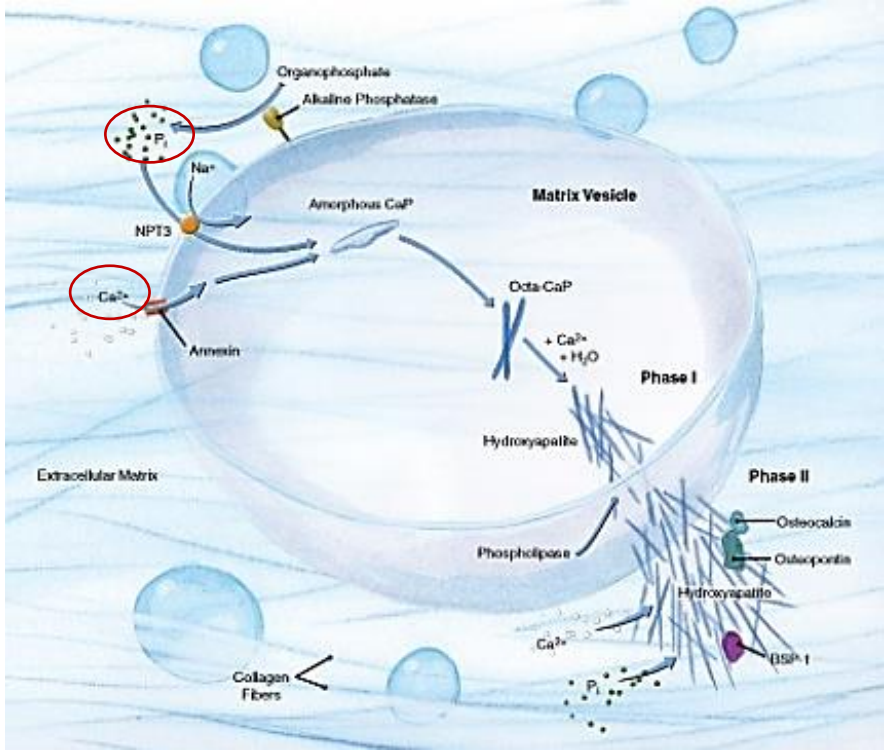
ALP function in bone mineralization



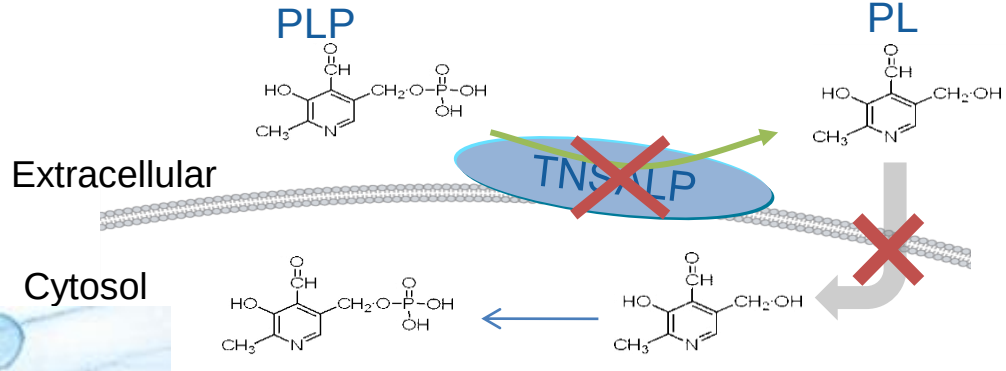
In HPP, low TNSALP activity leads to extracellular accumulation of PPi

- PPi is a potent inhibitor of bone mineralization

Matrix vesicle



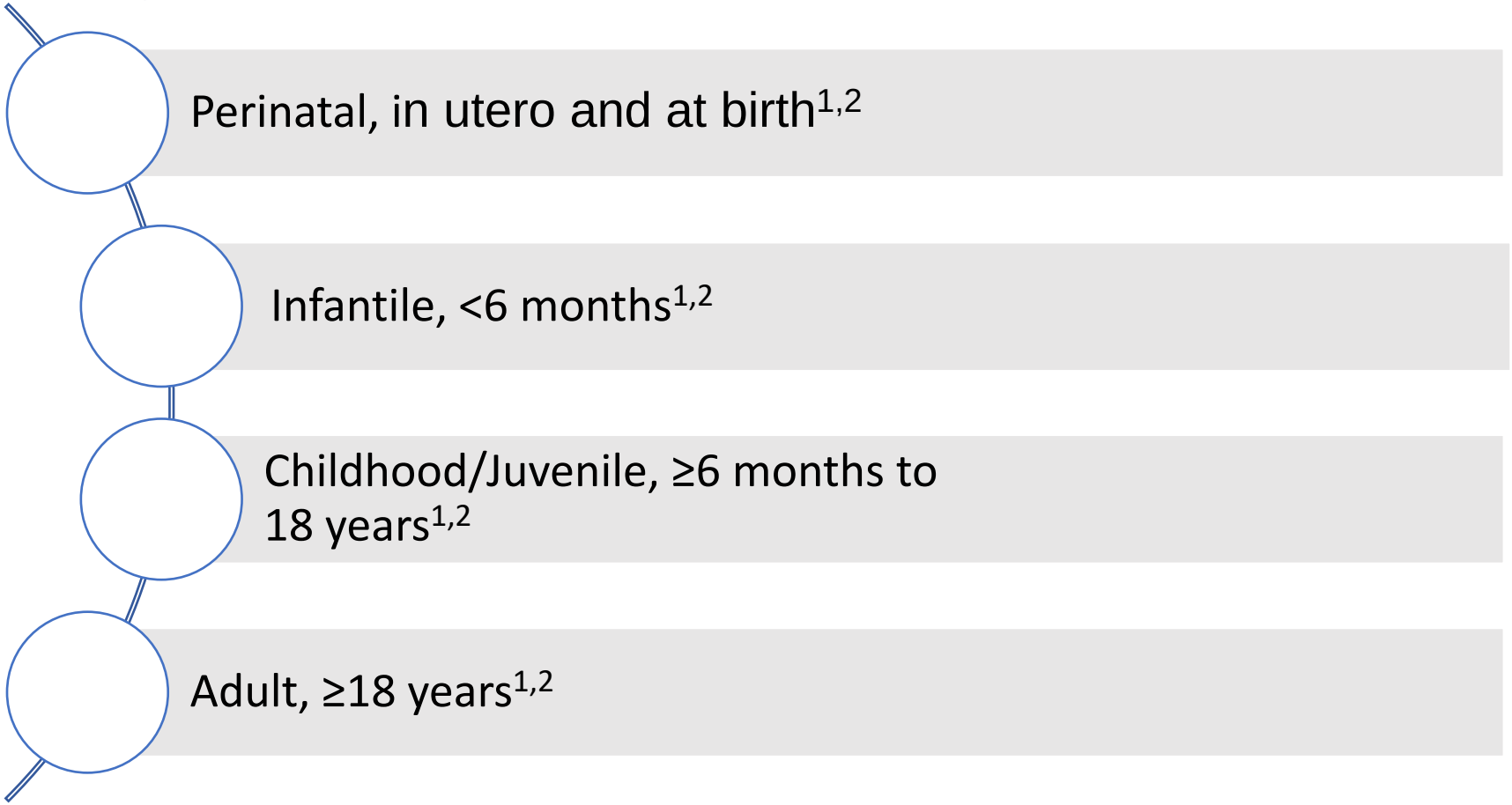
ALP function in brain



TNSALP dephosphorylates pyridoxal 5'-phosphate (PLP, or vitamin B_6) into pyridoxal (PL)>>> crosses the plasma membrane into the CNS.

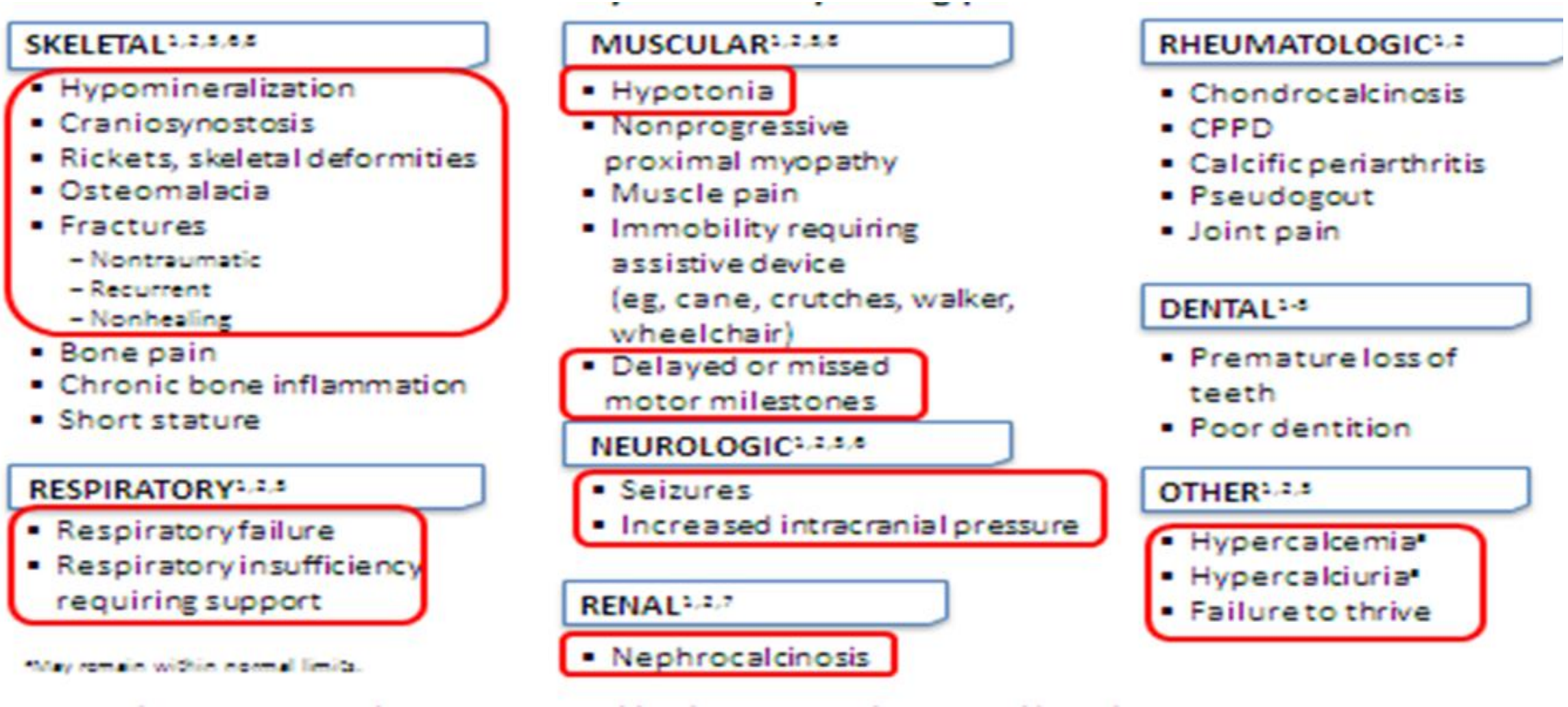
1. Fraser et al. *Am J Med*. 1957
2. Mornet et al. *Ann Hum Genet*. 2011

Classically Defined Forms of HPP and Age at Symptom Onset



Whyte. In: Thakker et al, eds. *Genetics of Bone Biology and Skeletal Disease*. 2013:337-360.

Clinical manifestations of HPP Infantile form

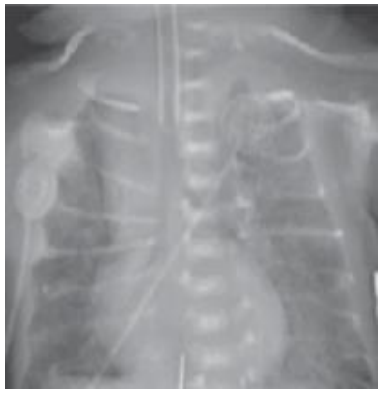


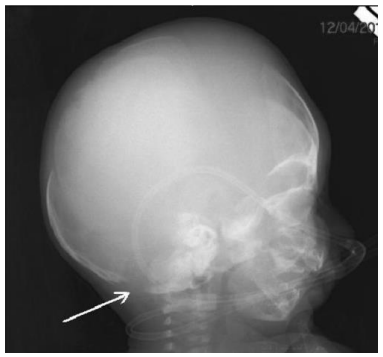
HPP-infantile form: first described case on severe neonatal hypophosphatasia in Israel

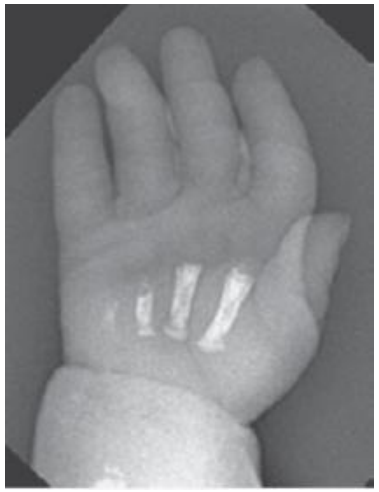
- 5 mo male, bulging fontanel, no fever
- Term, AGA, 1st baby in consanguineous Bedouin family
- At age of 2 days-seizures, controlled only on pyridoxine

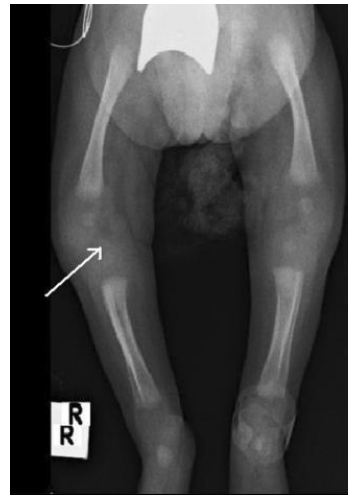
- Alert, bulging fontanel, pectus excavatum, severe hypotony, sternal retractions
- Persistent hypercalcemia
- Persistent very low ALP
- Severe hypomineralization
- Nephrocalcinosis
- Homozygous mutation in gene TNSAP (c.1171C>T[p.R391C])- missense mutation that changes the protein function.

The treatment was offered (in Germany-was not available in Israel), the family refused
Two weeks after discharge the infant died



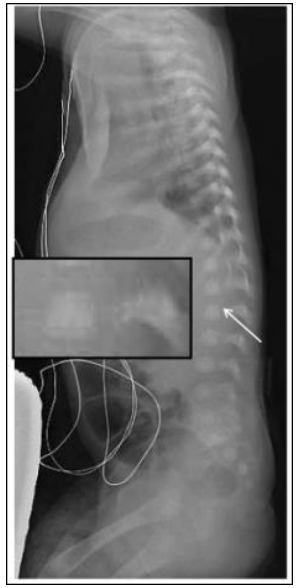


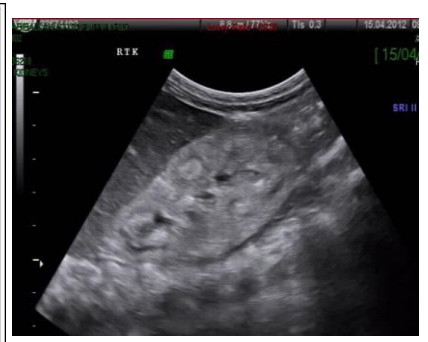




Blood ALP

תוצאה	יחידות	טווח
16	U/L	0 - 462
15	U/L	0 - 462
7	U/L	0 - 462
5	U/L	0 - 462
9	U/L	0 - 462
8	U/L	0 - 462
16	U/L	0 - 462
14	U/L	0 - 462
18	U/L	0 - 462
5	U/L	0 - 462
5	U/L	0 - 462
5	U/L	0 - 462





Gurevich & Landau, Harefuah 2017

Clinical manifestations of HPP Childhood/juvenile form

SKELETAL[1,2,3,6,8]

- Hypomineralization
- Craniosynostosis
- Rickets, skeletal deformities
- Osteomalacia
- Fractures
  - Nontraumatic
  - Recurrent
  - Nonhealing
- Bone pain
- Chronic bone inflammation
- Short stature

RESPIRATORY[1,2,3]

- Respiratory failure
- Respiratory insufficiency requiring support

*May remain within normal limits.

MUSCULAR[1,2,3,8]

- Hypotonia
- Nonprogressive proximal myopathy
- Muscle pain
- Immobility requiring assistive device (eg, cane, crutches, walker, wheelchair)
- Delayed or missed motor milestones

NEUROLOGIC[1,2,3,6]

- Seizures
- Increased intracranial pressure

RENAL[1,2,7]

- Nephrocalcinosis

RHEUMATOLOGIC[1,2]

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

DENTAL[1-3]

- Premature loss of teeth
- Poor dentition

OTHER[1,2,3]

- Hypercalcemia*
- Hypercalciuria*
- Failure to thrive

CPPD, calcium pyrophosphate dihydrate crystal deposition disease; HPP, hypophosphatasia; PPi, inorganic pyrophosphate

Laboratory diagnosis

serum ALP activity –persistent, sex and age adjusted!

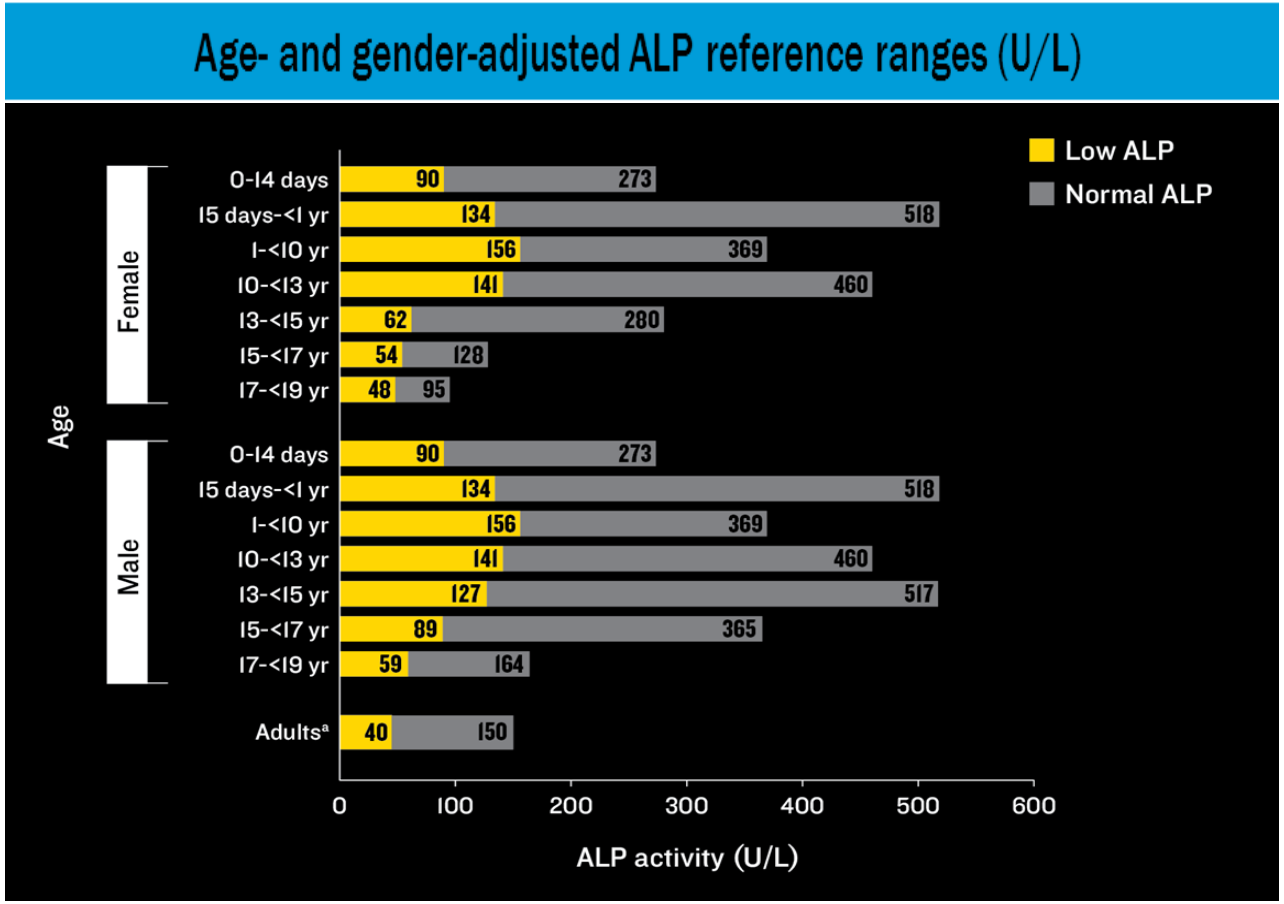
(Hypercalcemia & hyperphosphatemia)

(PTH is suppressed)

Elevated plasma pyridoxal 5-phosphate (PLP)

elevated urine PPI

Genetic testing



The ALP lower limit of normal is significantly higher in children than in adults

ACTA PÆDIATRICA 2020

High prevalence of hypophosphatasia in Southern Israel

Evgenia Gurevich, Eli Hershkovitz, Shaked Yarza, Daniel Landau

Retrospective study

The aim: To diagnose new cases of HPP and to ascertain its prevalence in Southern Israel

Screening of the SUMC Biochemistry lab database serum ALP results over a 14-year period (2002-2016) was performed

Inclusion criteria

Age 0-17 years

repeatedly low ALP levels (<100 U/L)

Exclusion criteria

Previous normal levels of ALP

Other causes of low ALP activity

Family doctors of positive-screened patients were contacted for repeat ALP and PLP levels sampling, followed by radiographs and genetic testing.

Results

658,725 patients analyzed for ALP/ 14 yrs

↓

51,032 had one ALP result lower than age and sex adjusted normal values

↓

2007 patients had ≥ 2 low ALP samples

↓

923 were children (< 18 y)

↓

40 of them had persistent ALP <100 U

↓

12 –pathogenic variants in TNSALP gene were found

Case#1

7 y.o. girl
Premature teeth loose at age 4
Late fontanelle closure, FTT resolved
Normal X-Ray

Alkaline phosphatase

תאריך	מדבקה	תוצאה	יחידות	טווח	טווח גרפי	גורם שולח
10/04/2018...	721319439	65	U/L	69 - 325	*[.....]	רהט א מרכ
18/07/2017...	721228152	71	U/L	69 - 325	[.*.....]	רהט א מרכ
09/11/2015...	720864862	45	U/L	96 - 297	*[.....]	רהט א מרכ
07/05/2015...	720734374	38	U/L	96 - 297	*[.....]	רהט א מרכ
03/05/2015...	12530042	32	U/L	96 - 297	*[.....]	ילדים א סור
02/05/2015...	12300700	45	U/L	96 - 297	*[.....]	ילדים א סור
01/05/2015...	12300131	42	U/L	96 - 297	*[.....]	מיון ילדים ס
04/06/2012...	720021139	66	U/L	108 - 317	*[.....]	רהט א מרכ
VITAMIN B6 STATUS		70	ug/L	9 - 27	[.....]*	

Case#2

5 y. o. boy (case 1 sibling)
Leg pain for 2 years-referred for orthopedic evaluation
Premature loss of deciduous teeth
Normal X-Ray

Alkaline phosphatase

10/04/2018...	721353983	104	U/L	93 - 309	[.*
04/06/2017...	721173240	79	U/L	93 - 309	*[..
26/02/2017...	721173669	62	U/L	93 - 309	*[..
16/11/2016...	12137047	79	U/L	93 - 309	*[..
VITAMIN B6 STATUS		47	ug/L	9 - 27	

A heterozygous mutation in *ALPL*:NM_000478.5:c.69_74delGAAAGA; p.(Glu23_Lys24del), chr1-21887126-GAAAGA, in exon 3 has been detected.

Not diagnosed based on low ALP by primary physician!!!!!!

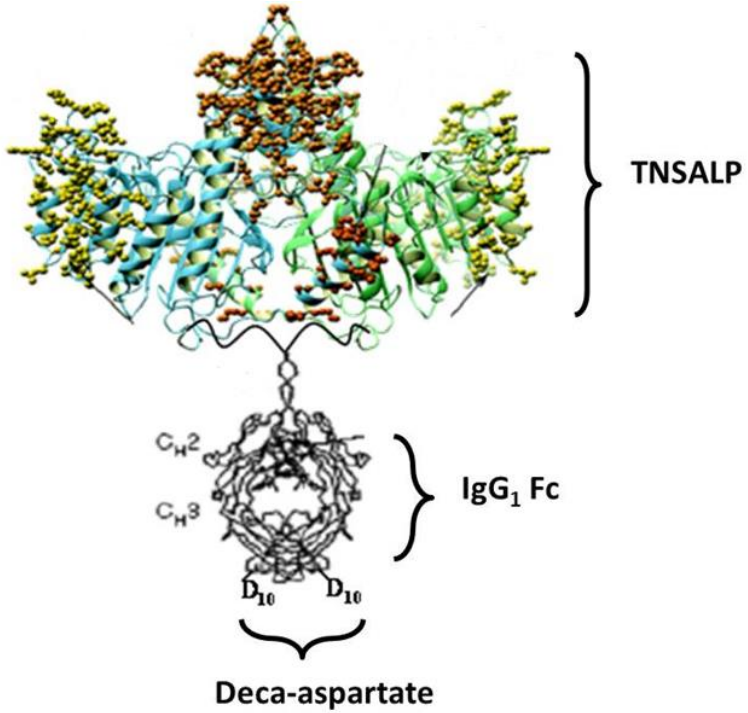
Asfotase Alfa

Strensiq (asfotase alfa) for injection

Asfotase alfa is a human recombinant TNSALP

Each chain consists of the

- Catalytic domain of human TNSALP
- Human immunoglobulin G1 Fc domain
- Deca-aspartate peptide used as a bone- targeting motif



Indication

- Asfotase alfa (Strensiq®) is indicated for long-term enzyme replacement therapy in patients with pediatric-onset hypophosphatasia to treat the bone manifestations of the disease

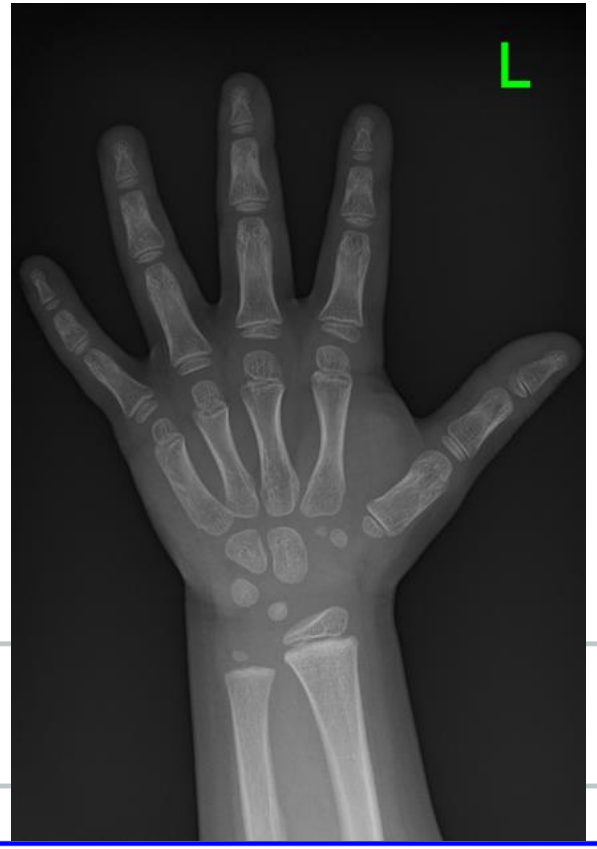
Registration status in Israel:

- Asfotase alfa (Strensiq®) has received marketing autorisations by the Israeli Ministry of Health on 14 February 2016.

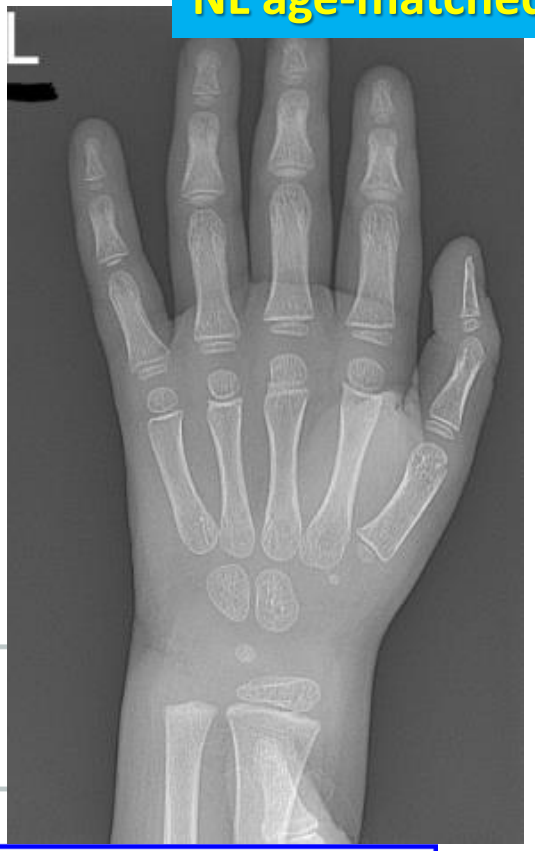
1. Whyte et al. *N Engl J Med*. 2012;366:904-913. **2.** Strensiq [summary of product characteristics]. Alexion Europe SAS; 2015.
3. Madson et al. Slides presented at: 54th European Society for Paediatric Endocrinology Annual Meeting; October 2, 2015; Barcelona, Spain.

D8590C00003 ALXN1850-HPP-305 (Mulberry)

4 y.o. girl
Asymptomatic
ALP 72 U/L (N=150-370)
Ca 9.8 mg/dl
Ca ionized 1.27 mmol/l
(N=1.12-1.23)
P 5.7 mg/dl
Ca/Cr-N
PTH-N



NL age-matched



Pathogenic variant identified

INTERPRETATION

A heterozygous pathogenic variant was identified in the *ALPL* gene. Pathogenic variants in this gene are associated to autosomal recessive and autosomal dominant forms of *ALPL*-related hypophosphatasia. The clinical implication of this result should be evaluated in context of the consultand´s clinical picture and family history.

No further clinically relevant variants were detected.

This variant is described for the infantile, adult and childhood form of Hypophosphatasia in the *ALPL* gene variant database (https://alpImutationdatabase.jku.at).

Conclusions

- HPP is underdiagnosed disease.
- Clinical manifestations are variable and children may be even “asymptomatic” as may have mild clinical signs
- High index clinical suspicion and use of the diagnostic algorithm

may facilitate an early detection and offer life-saving or disease modification treatment by enzyme replacement.

- Appropriate diagnosis may prevent unnecessary and harmful treatments

Thank you