A peculiar case of therapy-resistant Epilepsy

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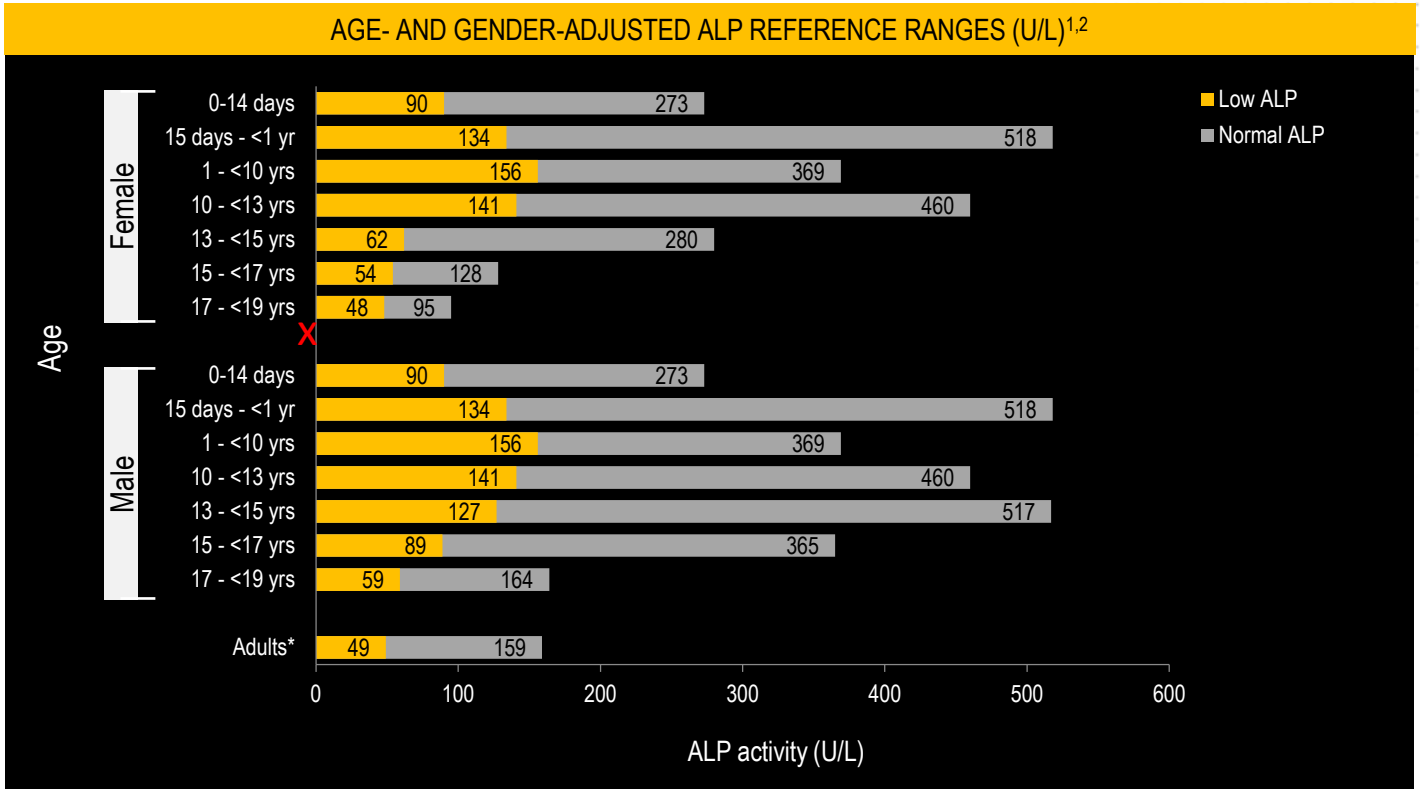
Case presentation

- Turkish girl, consanguineous parents; Family History: -
- At the age of 10 years consult inherited metabolic diseases:
  - Refractory convulsions (generalized tonic/clonic; focal; myoclonic)
  - Mental retardation (total IQ<50)-Cognitive deterioration
  - Dysarthry-active language limited: few words (verbal IQ: ?)
  - Myopathy: limb-girdle/quadriceps femoris
    Gowers sign +; waddling gait; muscle pain
- Muscle biopsy (M Quadriceps femoris, vastus medialis):
  - Fatty degeneration
  - Histology: Ragged fed fibers present (J.J. Martin, UIA)
  - Biochemistry: slightly decreased enzymatic act. Complex 1

Case presentation Ctd

- Therapy-resistant convulsions-myoclonic jerks (esp.in the morning):
  - Topamax 150-100-200 mg/day
  - Tegretol: 200-400 mg/day
  - Vitamine E, zinc sulphate
- Serum alkaline phosphatase (2011-2016): 31-37 U/L (RV: 42-98)
- Plasma PLP: 174 nmol/L (RV: 26-102); plasma AA: normal
- HYPOPHOSPATASIA (diagnosis at age 26 years)
- MRI brain + spectroscopy: normal
- Interictal EEG: normal
- DXA (T-score): L2-L4: +1.60; left hip: +0.01; right hip: +0.85
- No fractures in personal antecedents

The ALP lower limit of normal is significantly higher in children than in adults.[1,2]



Adapted from the Canadian Laboratory Initiative in Pediatric Reference Intervals (CALIPER) project (Colantonio et al, 2012). No variation in ALP based on ethnic differences was observed. Reference ranges shown were established on the Abbott ARCHITECT C8000 analyzer.
[a]Adult range provided by the Abbott ARCHITECT ALP product information sheet is for females >15 and males >20 years of age. For younger ages, Abbott does not provide lower limits of normal.

Reliable assessment of ALP requires age- and gender-adjusted reference ranges.[3,4]

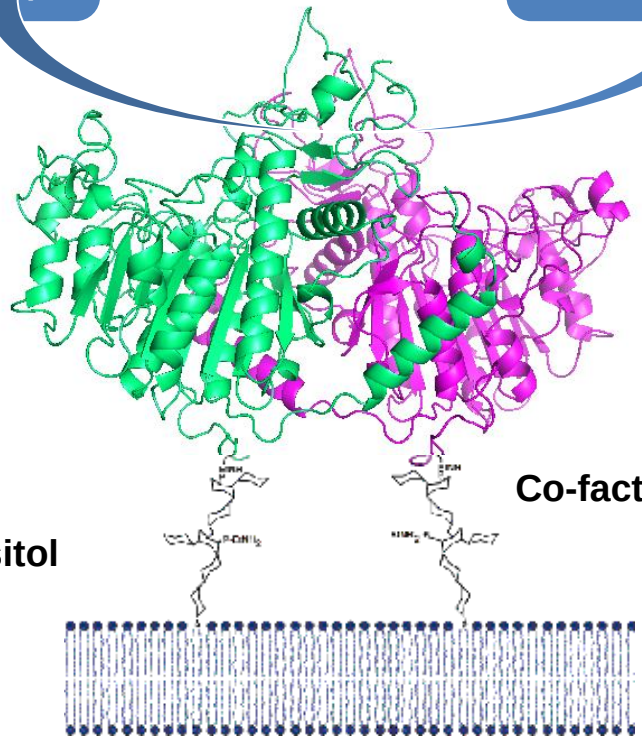
References: **1.** Colantonio et al, *Clin Chem*, 2012. **2.** Architect *c*Systems/Aeroset System alkaline phosphatase assay [package insert], 2007. **3.** Rockman-Greenberg, *Pediatr Endocrinol Rev*, 2013. **4.** Mornet et al, *GeneReviews,* 2007.

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)

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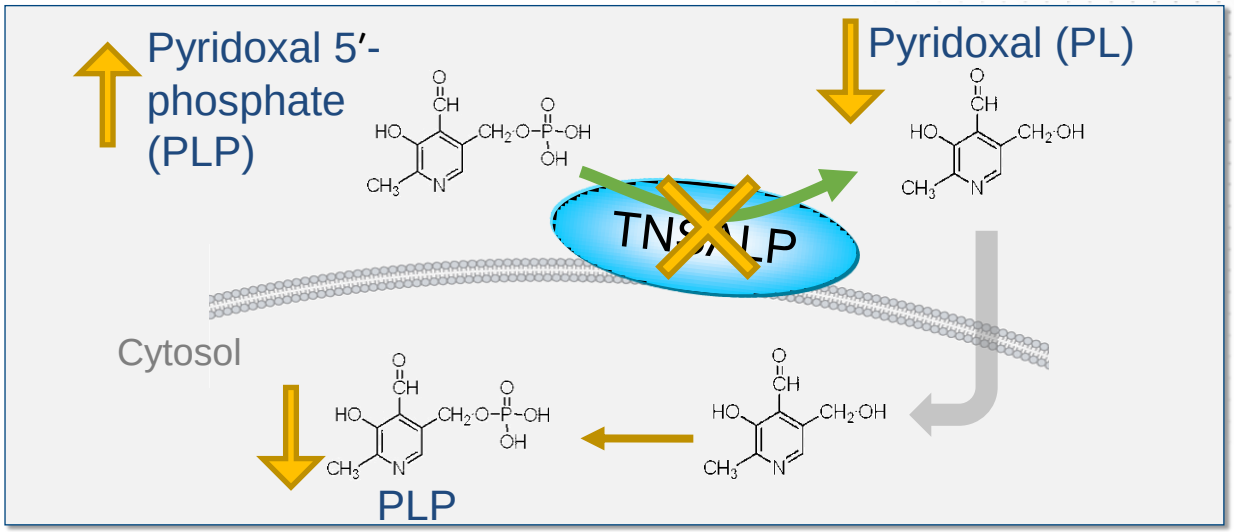
The role of TNSALP



- Pyridoxal 5′-phosphate (PLP) is the active form of vitamin B_6[1,2]
- In normal circumstances, TNSALP dephosphorylates PLP, producing pyridoxal (PL)[3,4]
  - PL crosses the cell membrane and is rephosphorylated into PLP
  - PLP is involved in neurotransmitter synthesis (eg, gamma aminobutyric acid [GABA], dopamine, serotonin, etc)
- PLP deficiency in the brain may result in fatal vitamin B_6–reponsive seizures[2,5]

References: **1.** Mornet et al, *GeneReviews,* 2007. **2.** Whyte, *The Metabolic and Molecular Bases of Inherited Disease*, 2001. **3.** Rockman-Greenberg, *Pediatr Endocrinol Rev,* 2013. **4.** Sebastián-Serrano et al, *Comput Struct Biotechnol J,* 2015. **5.** Whyte, *Principles of Bone Biology,* 2008.

Genetics of HPP

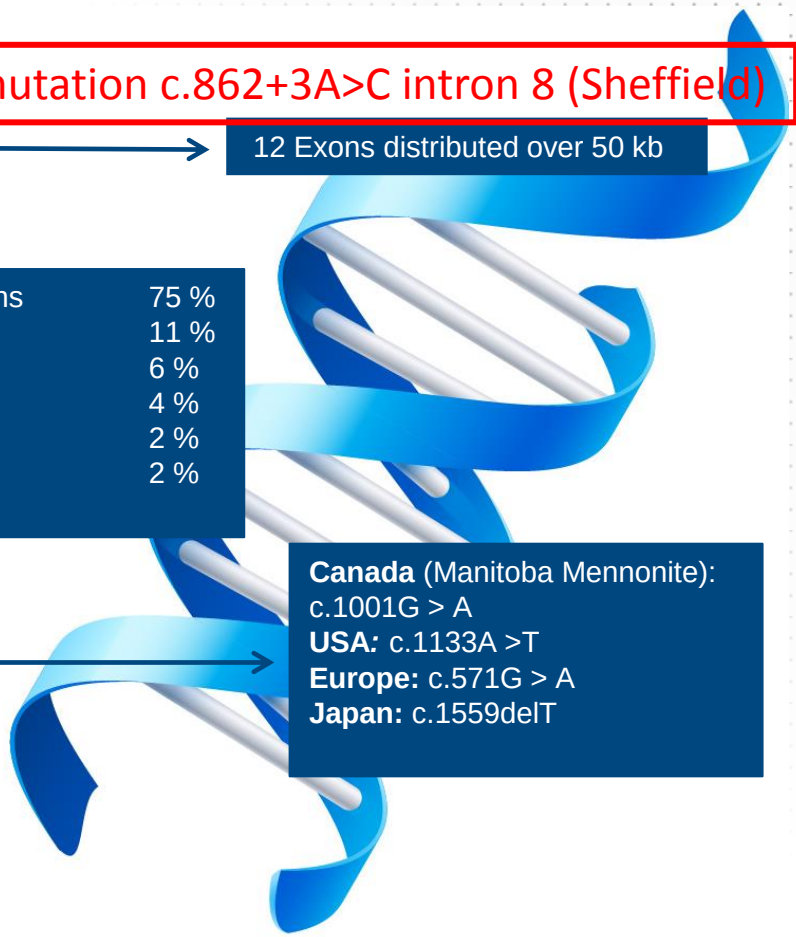
- The **Tissue Non Specific ALP** (**TNSALP**) gene is located on the short arm of chromosome 1 (1p36.1-34, 12 exons)[1]
- Over 300 different mutations have been described[2].
- The frequency of specific gene mutations is increased in some populations[3].

Splice site mutation c.862+3A>C intron 8 (Sheffield)

12 Exons distributed over 50 kb

Missense Mutations	75 %
Small deletions	11 %
Splicing	6 %
Nonsense	4 %
Small insertions	2 %
Other	2 %

Canada (Manitoba Mennonite): c.1001G > A
USA: c.1133A >T
Europe: c.571G > A
Japan: c.1559delT



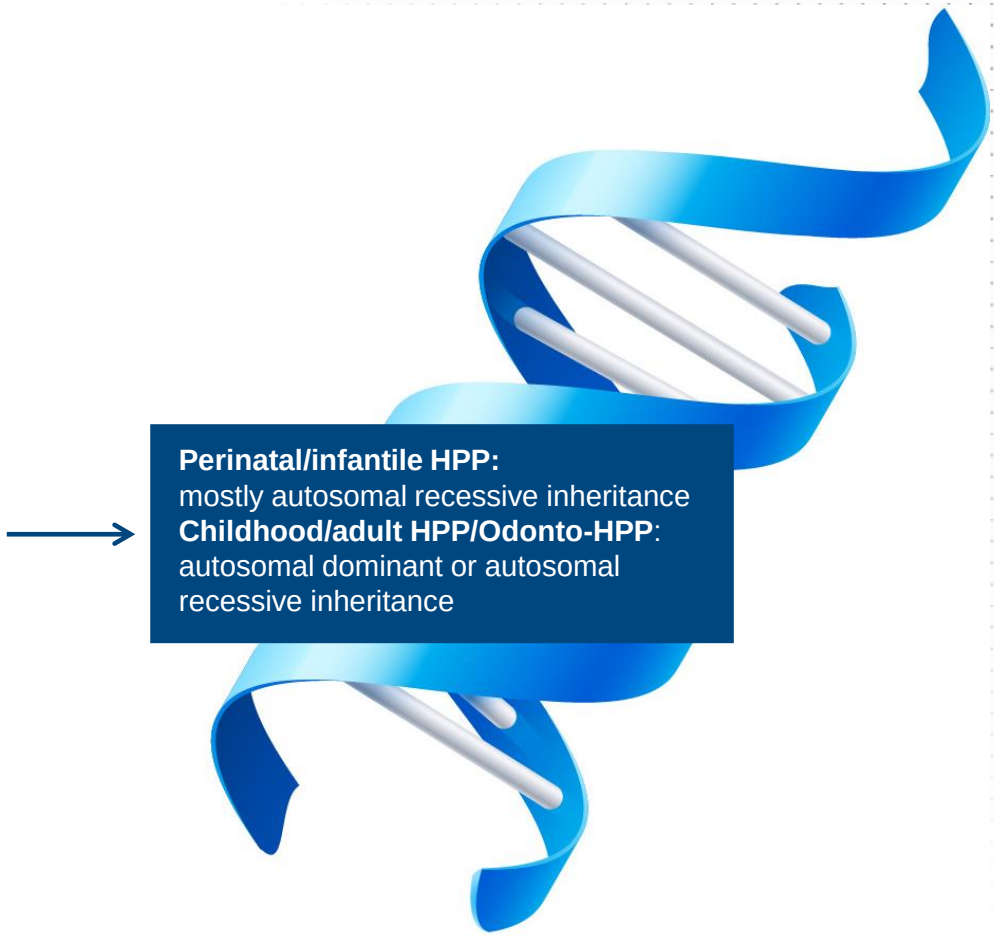
The Tissue Specific ALP gene is located on Chromosome 2 (2q37.1)[1].

References: 1. Greenberg CR. et al. *AM J Hum Genet*. 1990. 46(2):286-92. **2.** Mornet E et al. www.sesep.uvsq.fr/03_hypo_mutations.php. 2014.
3. Mornet E. Orphanet *J Rare Dis*. 2007. 2:40

Genetics of HPP

- The variability of the disease can be high in siblings, even if the same mutation is present[1].

- In HPP the mutations can be from autosomal dominant or recessive inheritance[1].



References: 1. Whyte, M. In Thakker R, Whyte M, Eisman J, Igarashi T (Eds.), Genetics of Bone Biology and Skeletal Disease. New York, NY: Elsevier. 2013. Chap 22.

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

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

- Hypotonia
- **Non-progressive proximal myopathy**
- **Muscle pain**
- **Immobility**
- Delayed or missed motor milestones
- PERSISTENT GAIT IMPAIRMENT

NEUROLOGIC[1,2,10,12]

- Seizures
- Increased intracranial pressure

RESPIRATORY[1,10,12-14]

- Respiratory failure
- Respiratory insufficiency requiring support

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)

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Muscular and rheumatologic manifestations have lasting impacts on patients' lives.[1-7]

Muscular and rheumatologic consequences may include[1-10]

- Muscle and joint pain
- Muscle weakness
- Waddling gait
- Joint stiffness and swelling
- Delayed or missed motor milestones
- Calcium pyrophosphate dihydrate (CPPD) deposition, which may lead to chondrocalcinosis or pseudogout

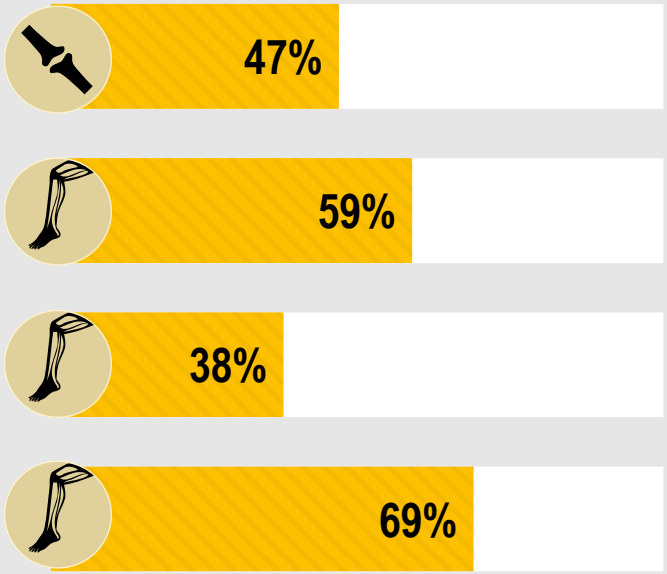
In a natural history study of patients ≤5 years of age[11,a] AND 6-12 years:

- **89% (24/27) had developmental delays**
  - **42% (10/24) had delayed walking**
  - **(>15 months of age)**

[a]Data from a noninterventional, retrospective chart review study designed to understand the natural history of 48 patients with perinatal- and infantile-onset ≤5 years of age.[11]

References: **1.** Rockman-Greenberg, *Pediatr Endocrinol Rev,* 2013. **2.** Chuck et al, *Ann Rheum Dis,* 1989. **3.** Seshia et al, *Arch Dis Child,* 1990. **4.** Berkseth et al, *Bone,* 2013. **5.** Balasubramaniam et al, *J Inherit Metab Dis,* 2010. **6.** Beck et al, *Rheumatol Int,* 2011. **7.** Data on file, Alexion Pharmaceuticals. **8.** Whyte et al, Endocrine Society's 97th Annual Meeting and Expo website, 2015. **9.** Weber et al, *Osteoporos Int,* 2015. **10.** Whyte, *Ann N Y Acad Sci,* 2010. **11.** Whyte et al, Poster presented at: 2014 Pediatric Academic Societies and Asian Society for Pediatric Research Joint Meeting, 2014.

Muscular/rheumatologic consequences can leave patient with significant disabilities.[1,2]



47% (15/32) of pediatric patients had joint pain and muscle weakness that limit daily activities[a,1,2]

59% (19/32) of pediatric patients had gait disturbance[a,3]

38% (22/59) of pediatric patients reported that they currently use a wheelchair[b,4]

69% (25/36) of adults reported that their walking has worsened since being diagnosed with HPP[c,5]

[a]Data from a noninterventional, retrospective chart review study designed to understand the natural history of 48 patients with perinatal- and infantile-onset ≤5 years of age[3]
[b]HIPS/HOST combined data from an Internet questionnaire and telephone survey that queried demographics, HPP-related illness history, disease progression, and health-related quality of life. One hundred eighty-four patients participated (59 children, 125 adults) [4]
[c]HOST was a telephone survey that queried demographics, HPP-related illness history, disease progression, and health-related quality of life. Fifty-one patients participated.[4]

References: **1.** Rockman-Greenberg, *Pediatr Endocrinol Rev,* 2013. **2.** Chuck et al, *Ann Rheum Dis,* 1989. **3.** Seshia et al, *Arch Dis Child,* 1990. **4.** Berkseth et al, *Bone,* 2013. **5.** Balasubramaniam et al, *J Inherit Metab Dis,* 2010. **6.** Beck et al, *Rheumatol Int,* 2011. **7.** Data on file, Alexion Pharmaceuticals. **8.** Whyte et al, Endocrine Society's 97th Annual Meeting and Expo website, 2015. **9.** Weber et al, *Osteoporos Int,* 2015. **10.** Whyte, *Ann N Y Acad Sci,* 2010. **11.** Whyte et al, Poster presented at: 2014 Pediatric Academic Societies and Asian Society for Pediatric Research Joint Meeting, 2014.

Literature

"only patients affected by the severe form of congenital hypophosphatasia present with neonatal seizures and epileptic encephalopathy with abnormal neurotransmitter metabolism"

=bad prognosis

Collmann et al, Childs Nerv Syst, 2009; Balasubramaniam et al, JIMD, 2010; Belachew et al JIMD Reports 2013

conclusions

- We present an adult female affected by hypophosphatasia and presenting clinically by a myopathy and therapy-resistant convulsions.