Successful treatment with enzyme replacement therapy in a girl with severe infantile Hypophosphatasia

Katrin Heldt[1], Dagmar l`Allemand[1]

[1]Children's Hospital of Eastern Switzerland, Dep. of Pediatric Endocrinology, Claudiusstr. 6, 9006 St. Gallen

Introduction

Infantile Hypophosphatasia (HPP)

- inborn error of metabolism, characterized by low serum alkaline phosphatase (ALP) activity
- caused by loss-of-function mutations within the ALPL-gene encoding the tissue nonspecific isoenzyme of ALP (TNSALP)
- TNSALP controls skeletal and dental mineralization by hydrolyzing inorganic pyrophosphate, a potent inhibitor of bone mineralization (Fig. 1)
- patients develop substantial skeletal disease, failure to thrive, and sometimes vitamin B6–dependent seizures before 6 months of age
- without treatment, HPP results in 50–100% mortality, typically from respiratory complications

Case Report

- ultrasound in the 12thw of pregnancy noticed a short femur (length < P.5)
- at the age of 6 w she presented with a lack of weight gain and growth arrest since birth, need of tube feeding due to vomiting and weakness
- oxygen supply since 2d because of respiratory insufficiency and episodes of apnea
- a single cerebral seizure terminated spontaneously

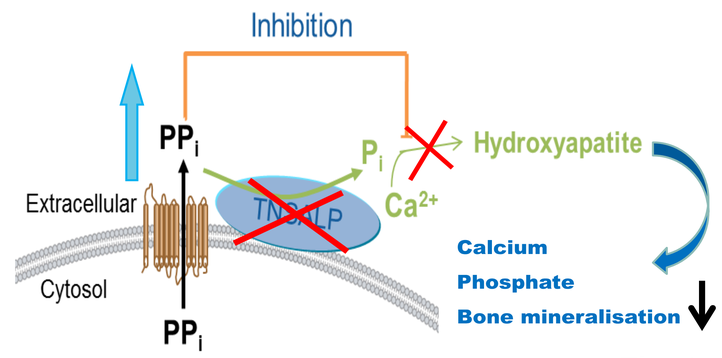


Fig. 1

- 3 month old girl with short stature, in a good clinical condition
- weight: 4.1 kg (P.<3, -2.98 SD), length: 52.8 cm (P.<3, -3.39 SD)
- rhizomelia of upper arms and femora (Fig. 2, 3c)
- broad nose bridge, high forehead, bulged fontanelle, distinct proptosis
- paradoxical breathing pattern with need of oxygen supply
- generalized muscular hypotonia with reduced physical activity
- radiographic findings include hypomineralization with cup-shaped distensions of the metaphysis and irregular zones of ossification (Fig. 3 a-c)
- laboratory examinations revealed a very low serum ALP activity and a high urinary excretion of phosphoethanolamine in urine
- exome sequencing: 2 heterozygous mutations in the ALPL gene

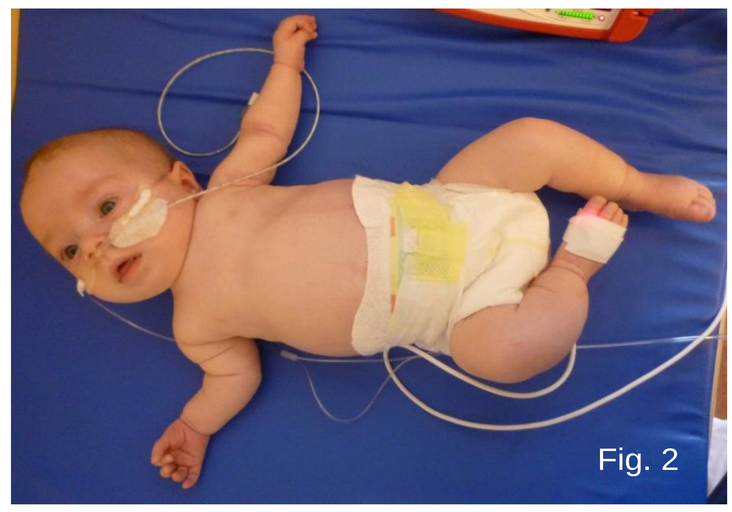


Fig. 2

Therapy

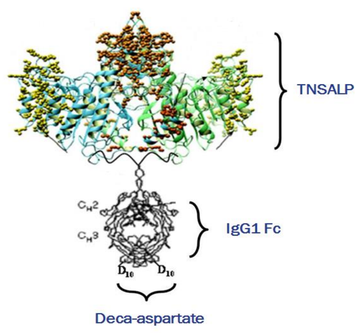
Human recombinant TNSALP (Asfotase alpha) 2 mg/kg s.c. every 2 d

calcium, pyridoxine, paracetamol

physiotherapy

oxygen-support

enteral nutrition through nasogastric tube



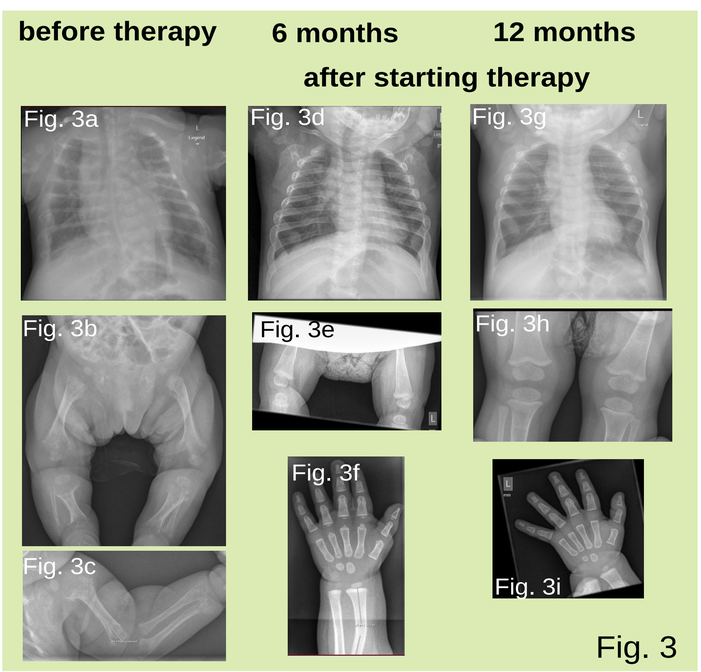


Fig. 3

- improvement in muscular hypotonia, neurological problems and skeletal mineralization (Fig. 3 d-i)
- respiratory function, growth and weight normalised

Key points

- rare disease (prevalence Europe: 1:300.000), may be life threatening
- specific symptoms in severe cases, but unspecific symptoms especially in milder forms (Fig. 4)
- easy to diagnose:
  - low (or below the limit of quantitation) blood ALP levels are the cardinal sign
  - abnormally elevated urinary phosphoethanolamine
  - genetics providing by company
- sufficient and easy to apply therapy for severe forms, actually no evidence for ERT in milder forms
- moderate annual therapy costs
- side effects are moderate and rare, and mostly limited to site injections reactions

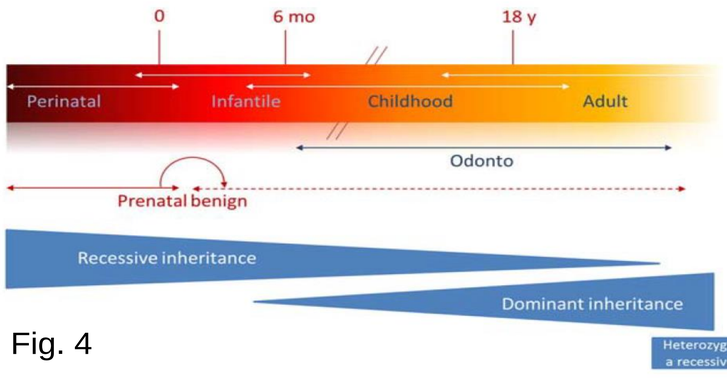


Fig. 4

Literatur:
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Claudiusstrasse 6 | CH-9006 St. Gallen | kispisg.ch

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Bone, growth plate and mineral metabolism

Katrin Heldt

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