Altonaer Kinderkrankenhaus
Ein Unternehmen des UKE

GOITROUS HYPOTHYROIDISM OF PUBERTAL ONSET CAUSED BY A NOVEL MUTATION IN DEHAL1 GENE

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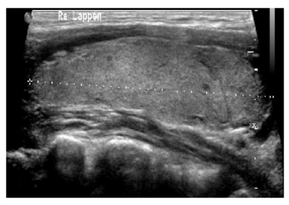
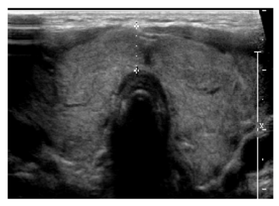
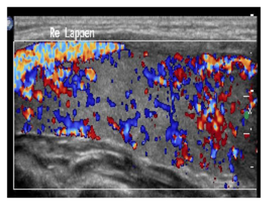
Background: Iodotyrosine deiodinase (DEHAL1) is a thyroidal enzyme that deiodinates mono- and diiodtyrosines (MIT, DIT) and recycles iodine, essential for synthesis of thyroid hormone. Iodotyrosine deiodinase deficiency leads to hypothyroidism, goiter and variable mental retardation. The age for clinical onset was reportedly very diverse, allegedly related to individual iodine nutrition.

Clinical case: (there is informed consent on showing clinical data and images):

- 11 year old boy, consulting primary care physician because of large goiter, developed within 3 weeks, no clinical signs of hypothyroidism, no other clinical symptoms
- Former History: Healthy, normal psychomotorical development
- Third child, offspring of consanguineous parents from Lebanon
- Body height: 146,4 cm (-0,3 SD), Body weight: 34,9 kg, BMI 16,3 kg/m² (-0,5 SD), THt: 177,5 cm (-0,4 SD)
- Physical examination: Soft goiter, estimated volume, no palpable nodules
- Initial laboratory results:
  - TSH>150 mU/l (n: 0,30-4,5) → *Treatment with levothyroxine75µg/day*
  - fT4 0,2 ng/dl (n: 0,78 – 1,54)
  - fT3 2,4 ng/l (n: 2,2-4,7)
  - TPO-antibodies <25 kU/l (<70)
  - TRAK < 0,3 IU/l (<1,5)
- 2 weeks after starting treatment:
- Patient reported shrinking goitrous size within these 2 weeks
- Ultrasonography (US): Goiter volume: 31 ml (N: <5,34 ml (1)) (right lobe 14 ml, left lobe 17 ml), echotexture irregular with highly increased perfusion (flow velocity max. 1 m/sec)

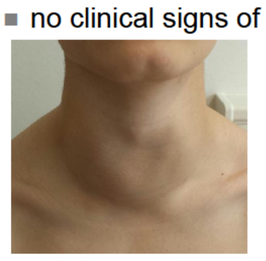
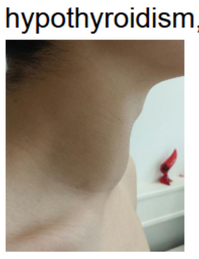
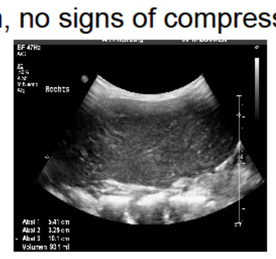
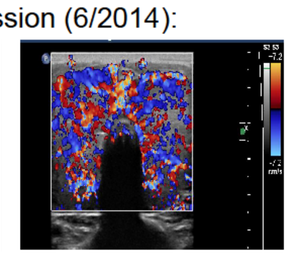




Further course:

- **Inconsistent results of clinical outcome in the context of therapy adherence: Normal thyroid hormone levels after non-compliance. Hypothyroidism and increasing goiter size under reliable good adherence to therapy.**
- **Bad adherence to therapy, but normal thyroid hormone levels and only mildly elevated goiter size after 3 and 5 months WITHOUT any intake of levothyroxine** (10/2013)
  - TSH 1,53 µIU/ml (n: 0,53-3,59)
  - fT4 0,98 ng/dl (n: 0,9 – 1,6)
  - fT3 4,8 pg/ml (n: 2,3-5)

  Ultrasonography: Goiter volume: 17ml, echotexture irregular, normal perfusion
- **Increasing goiter within 2 weeks and severe hypothyroidism during reliable administration of levothyroxine 37,5 µg/day for 6 months and coincidentally reduced fish consumption:**
  - TSH 100 µIU/ml (n: 0,53-3,59)
  - fT4 <0,4 ng/dl (n: 0,9 – 1,6)
  - fT3 1,1 pg/ml (n: 2,3-5)
  - Thyroglobulin: 8828 ng/ml (n: 3,5 – 77,0)
  - no clinical signs of hypothyroidism, no signs of compression (6/2014):

  Ultrasonography: Goiter volume: **150ml** (right lobe 93 ml, left lobe 60 ml) echotexture irregular, increased perfusion

- Last follow up (6/2015): **Levothyroxine 150 µg** daily :
  - TSH 0,52 µIU/ml (n: 0,53-3,59)
  - fT4 1,24 ng/dl (n: 0,9 – 1,6)
  - fT3 4,58 pg/ml (n: 2,3-5)

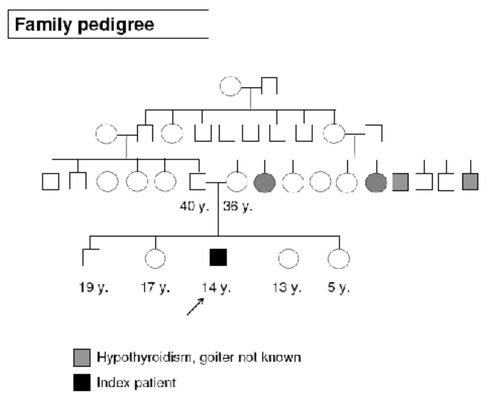
  Ultrasonography: Goiter volume: **41 ml** (right lobe 22 ml, left lobe 19 ml)

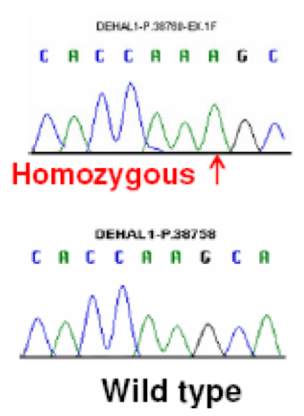
Distinctive characteristics of the clinical course suggested iodine deficiency caused by iodotyrosine deiodinase deficiency:

- ***Long lasting euthyroid hormone levels during therapy pause***
- ***Increasing goiter size and development of severe hypothyroidism during reliable administration of medication and after reducing fish consumption in the family***
- ***Increase and reduction of goiter size in short time period***
- ***Elevated fT3/fT4 ratio, typical finding in iodine deficiency, against the background of iodine sufficient enviroment***

Genetic investigations of the DEHAL1-Gene:

- **Novel homozygous mutation in DEHAL1: p.A57SfsX62 ;** consisting of the insertion of one nucleotide in exon 1 (c.168-169insA)
- This pathogenic deletion causes a frameshift leading to an early stop-codon at amino acid 62 (p.A57SfsX62) of the protein, almost completely truncating the enzyme
- Heterozygosity in apparently asymptomatic parents
- Siblings of index patient are currently under phenotipic and genetic investigations





Iodotyrosine deiodinase deficiency (ITDD)/ Dehalogenase deficiency:

- Iodotyrosine deiodinase enzyme (DEHAL1) deiodinates MIT and DIT and returns most of iodide to the intrathyroidal iodine pool (recycling)
- ITDD leads to in increase of MIT and DIT in the thyroid, the plasma and urine resulting in iodine depletion (See figure 1)

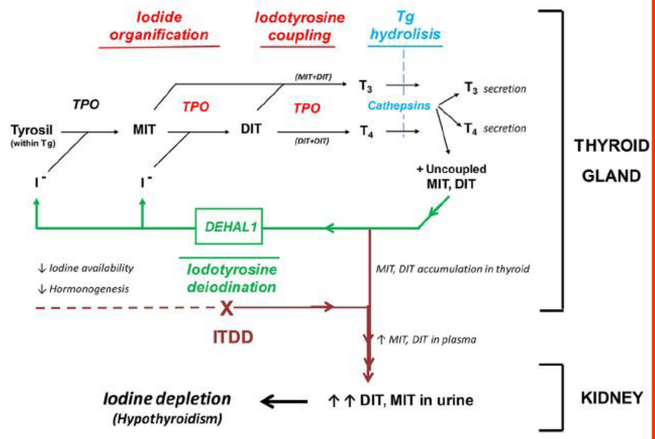


Figure 1: Iglesias, A., 2014 (2)

Genetics and clinical appearance of ITDD:

- The DEHAL1 gene (Chromosome 6p24, 6 Exons) was first cloned by Moreno 2002 using SAGE (3)
- Only few clinical cases with proven DEHAL1 mutations are reported so far in the literature. The age of clinical appearance is variable. Four patients of three unrelated families with hypothyroidism due to DEHAL1 mutations were reported (4): One girl presented hypothyroidism at 18 months, 2 siblings in infancy and one boy at the age of 8 years. Another boy with DEHAL1 mutation identified through genome-wide approach appeared with goiter and hypothyroidism at the age of 15;9 years (5)
- Autosomal recessive inheritance is suggested, there are also suggestions of dominant inheritance in some families (Afink, G. et al., JCEM 2008; Codaccioni, JL. et al., Acta Endorinol 1978)

Conclusion:

- Full *DEHAL1* defects may remain asymptomatic for many years after birth in iodine-sufficient environments
- Clinical presentation may start at puberty with rapid development in goiter and hypothyroidism
- Iodine intake has influence on the course of hypothyroidism and goiter size
- Goiter size is very sensitive to correction of hypothyroidism
- The novel mutation is the most amino-terminally located mutation so far in DEHAL1, and completely deletes the functional nitroreductase domain of the enzyme
- Neonatal screening program does not detect patients with ITDD and children are at risk of mental retardation because of delayed diagnosis of hypothyroidism
- MIT and DIT in urine are possible biomarkers for preclinical diagnosis of *DEHAL1* defects. Their early determination for preclinical diagnosis deserves further investigation

Literature:
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