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

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Background: Iodotyrosine deiodinase (DEHAL1) is a thyroid enzyme that deiodinates mono- and diiodotyrosines (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), THI: 177.5 cm (-0.4 SD)
- Physical examination: Soft goiter, estimated volume, no palpable nodules

Initial laboratory results:
- TSH: 150 μIU/mL (n: 0.30-4.5)
- FT4: 0.2 ng/dL (n: 0.78 – 1.54)
- FT3: 2.4 ng/dL (n: 2.2-4.7)
- TPO-antibodies <25 kIU/L (<70)
- TRAK < 0.3 kIU/L (<1.5)
- 2 weeks after starting treatment:
  - Patient reported shrinking goitrus size within 2 weeks
  - Ultrasonography (US): Goiter volume: 31 ml (N: <5.34 ml) (right lobe 14 ml, left lobe 17 ml), echolucency irregular with highly increased perfusion (flow velocity max. 1 m/sec)

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 environment

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 8 months WITHOUT any intake of levotyroxine (10/2013)
- FT4 0.98 ng/dL (n: 0.9 – 1.6)
- FT3 4.8 pg/mL (n: 2.3-5)
- Increasing goiter within 2 weeks and severe hypothyroidism during reliable administration of levotyroxine 37.6 μg/dag for 8 months and coincidently reduced fish consumption:
- TSH 100 μIU/mL (n: 0.53-3.59)
- FT4 <0.4 ng/dL (n: 0.9 – 1.6)
- FT3 3.1 pg/mL (n: 2.3-5)
- thyroglobulin: 350 μg/l (n: 3.5 – 77.9)
- no clinical signs of hypothyroidism, no signs of compression (6/2014)

Genetics of the DEHAL1-Genes:
- Novel homozgyous mutation in DEHAL1: p.A575SfsX62 ; 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.A575SfsX62) of the protein, almost completely truncating the enzyme
- Heterozygosity in apparently asymptomatic parents
- Siblings of index patient are currently under phenotypic and genetic investigations

Further investigation:
- Mutation in the DEHAL1 gene (p.A575SfsX62) was confirmed in a second family and a third family. All families had no history of consanguinity.

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 precocious diagnosis of DEHAL1 defects. Their early determination for preclinical diagnosis deserves further investigation

Literature: