Clinical course in a girl with hTPO mutation R161I in exon 5: 18 years of follow up

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Background

Out of the several genetic defects responsible for thyroid dyshormonogenesis, mutations in TPO gene are the most common causes of inherited defects in congenital hypothyroidism (CH). To date, more than 60 mutations that affect the TPO activity to varying extents have been described. Prevalent mutations are in exons 8-11 (catalytic site, Fig. 1)[1,2,3].

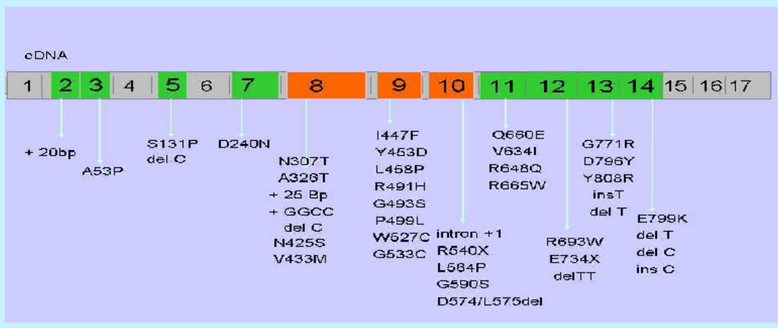

Fig. 1- Most common TPO gene mutations

Clinical case R.M.Y, born on 28.11.1996				
A newborn girl of Bulgarian origin, first uneventful pregnancy on term, S.C., Apgar 9, BW 3400 g, BL 52 cm, no thyroid diseases in the family. Congenital hypothyroidism was detected by the TSH screening (Tables 1, 2)				
Age	**NTSH** mU/l	**TSH** mU/l	**T4** nmol/l	**Tg** ng/ml
4d	297			
14d	681	1120	<25	547
2y3m	300	463	<25	211.6

Table 1- Screening, confirmation and reevaluation

Somnolent	No hypothermia
Difficult suckling	No goitre
Decreased activity	No bradycardia
Decreased muscle tonus	
Wide open anterior and posterior fontanelle	
Dry skin	
Obstipation	
Delayed bone age -32 gestation wks	

Table 2- Clinical presentation at day 14

Follow-up

Euthyroid state achieved at day 27, good parental adherence with the therapy during entire follow-up (frequent thyroid ultrasound, TSH, fT4, auxology, bone age). Normal physical growth and development according to the genetic potential (Fig. 2). Mental development: normal, high academic achievements. Twice (at 9 and 12 years) a significant thyroid enlargement along with TSH elevation (12-20 mU/l) and low-normal fT4 (9.6-12.4 pmol/l) was evident (Table 3). Bone age variations – 1 year ahead of the chronological during puberty.

Age decimals	**US** thyroid V ml	**TSH** mU/l	**fT4** pmol/L	**T4** nmol/L	**LT4** µg/kg/d
8,48	1.6	2.5	ND	138	3
9,64	11.1	12.4	14.6		2.6
10,4	7.3	0.47	22.8	187	2.6
11,48	7.4	2.6	21.1	131	
14,88	5.5	0.27	21.1	130	2.36
16,64	6.9	0.2	25.8	100	2.16

Table 3- Selected thyroid parameters

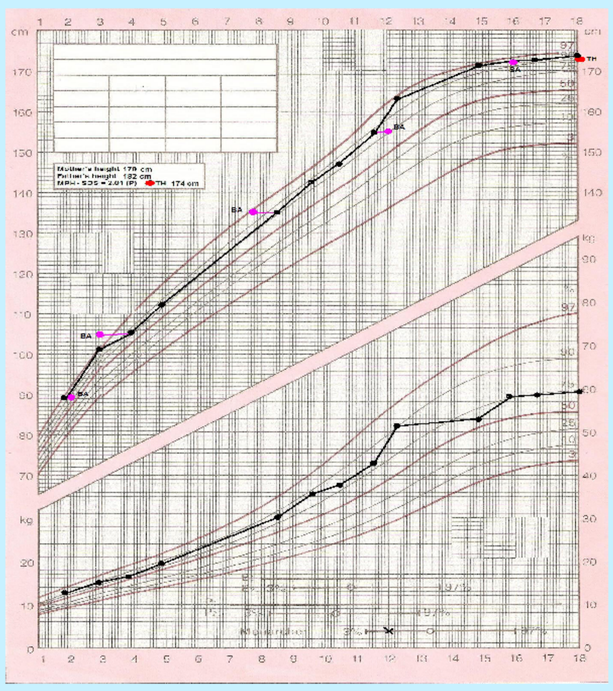

Fig. 2- Growth curve

Molecular genetic analysis

Candidate for hTPO molecular genetic studies based on permanent severe CH, orthotopic thyroid and high thyroglobulin levels. An uncommon homozygous mutation in exon 5, R161I was determined by dHPLC and sequencing after reevaluation (Fig. 3).

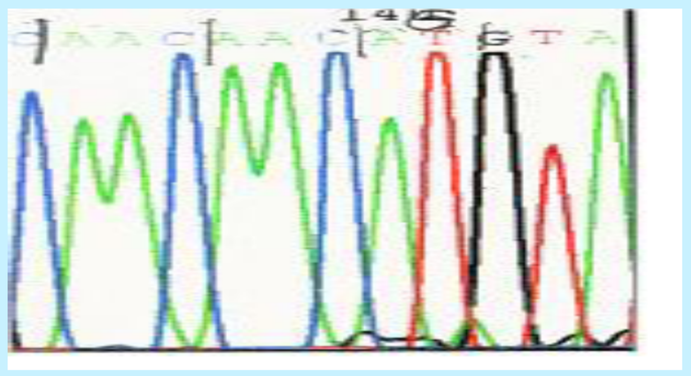

Fig.3- Substitution of AG-AT at nucleotide position 572 (R161I)

Conclusions

An earlier molecular genetic analysis would have prevented the reevaluation; in order to prevent thyroid enlargement a more frequent TSH monitoring is indicated, especially in puberty. The increased risk for thyroid cancer should be kept in mind.

References

1. Abramowicz M. J., Targovnik H. M., Varela V. et al. Identification of a mutation in the coding sequence of the human thyroid peroxidase gene causing congenital goiter. J. Clin. Invest. 1992, 90, 1200-1204 2. Bikker, H., Baas, F., De Vijlder J. et al. Molecular analysis of mutated thyroid peroxidase detected in patients with total iodide organification defects. J. Clin. Endocr. Metab. 1997, 82, 649-653 3. Bakker, B., Bikker, H., Vulsma, T. et al. Two decades of screening for congenital hypothyroidism in the Netherlands: TPO gene mutations in total iodide organification defects (an update). J. Clin. Endocr. Metab. 2000, 85, 3708-3712

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Thyroid

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