Long-term Follow-up of Patients with Congenital Hypothyroidism due to Thyroid Peroxidase (*TPO)* Mutations

Leraz Tobias[1], Tal Almagor[2,3], Ghadir Elias-Assad[2,3], Shlomo Almashanu[4], Osnat Admoni[2,3],Morad Khayat[5], Yardena Tenenbaum-Rakover[2,3]

[1]Pediatric Department B, Ha'Emek Medical Center, Afula, Israel; [2]Pediatric Endocrine Institute, Ha'Emek Medical Center, Afula, Israel; [3]The Rappaport Faculty of Medicine, Technion, Haifa, Israel; *[4]The National Newborn Screening Program, Ministry of Health, Tel-HaShomer, Israel*; *[5]Genetic Laboratory, Ha'Emek Medical Center, Afula, Israel*

Background:

Hereditary inborn errors of thyroid hormone synthesis account for 10-15% of congenital hypothyroidism (CH). Thyroid peroxidase (TPO) deficiency is the most common enzymatic defect with a frequency of 50-90%. Little is known about the clinical outcome of patients with *TPO* mutation.

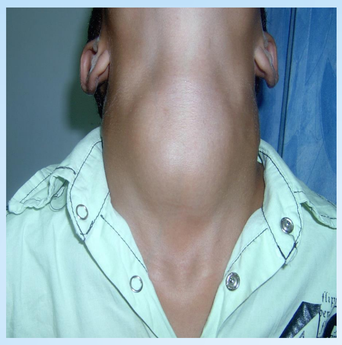
Objective:

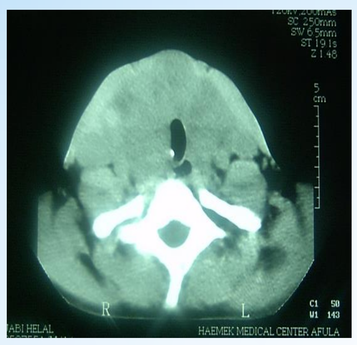
We aimed to characterize the long term clinical outcome in patients with TPO deficiency and to assess the association between development of multi nodular goiter (MNG) and adherence to therapy.

Results:

Clinical findings at presentation		No. of patients (%)
Symptoms and signs at presentation	Jaundice Macroglossia Umbilical hernia Course facial features Hypotonia Large fontanel Goiter Hypothermia Asymptomatic	12 (36) 9 (27) 9 (27) 8 (24) 6 (18) 4 (12) 4 (12) 2 (6) 4 (12)
Follow up at 1 year	Delayed milestones	10 (30)

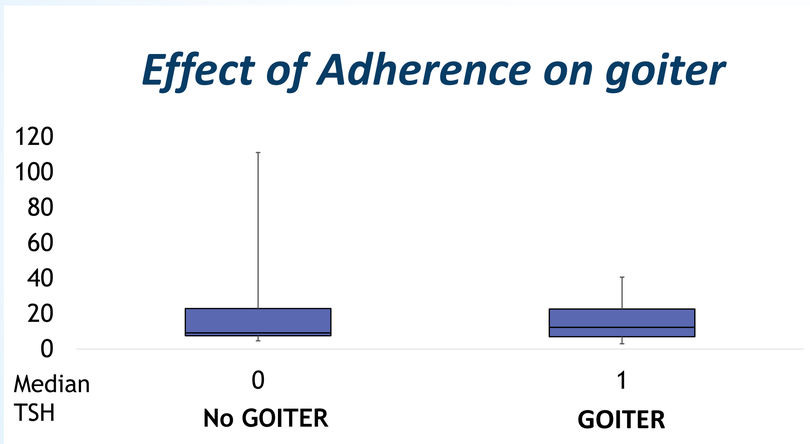
Goiter development





- ***21 (61%) patients developed goiter***
- ***Mean age of goiter development 8 years (range 0.9-22)***
- ***8 (24%) patients underwent thyroidectomy***

Effect of Adherence on goiter



Outcome of thyroidectomy			
Age (y)	**Fine needle aspiration**	**Pathology**	**Post surgery complications**
34	Not done	Hyperplastic nodular gland	No
15	Follicular cystic lesion with cellular atypia (Bethesda 3)	Follicular adenoma	No
16	Multiple follicular cells with enlarged nucleus - suspected follicular tumor (Bethesda 4)	Hyperplastic nodular gland	Hypoparathyroidism Nephrolithiasis
25	Not done	Minimally invasive follicular carcinoma of left lobe	No
15	Follicular hyperplasia (Bethesda 2)	Hyperplastic nodular gland	Hypoparathyroidism Nephrolithiasis
19	Not done	Hyperplastic nodular gland	No
15	Follicular cells with some metaplastic changes (Bethesda 3)	Not available	Hypoparathyroidism
12	Lymphoid hyperplasia (Bethesda 2)	Hyperplastic nodular gland	No

Molecular findings			
Exon	**Mutation**	**Protein**	**No of patients**
8	c.875C>T/c.875C>T	Ser292Phe	2
9	c.1478G>A /c.1478G>A	Gly493Ser	2
10	c.1618C>T/c.1618C>T	Arg540stop	17
	c.1618C>T/c.1478G>A		4
Total			29
Note done			4

Summary and Conclusions:

- This cohort is the largest, long-term follow up of patients with *TPO* mutations
- No association between non-adherence and development of MNG was found
- Our results indicate that elevated TSH alone cannot explain the high rate of goiter development in patients with *TPO* mutations
- *TPO* itself may have a role in suppression of thyroid growth
- The high rate of MNG development with time and the risk for thyroid carcinoma indicates the need for lifelong follow-up in these patients