P1-145

THE INVESTIGATION OF GENETIC ETIOLOGY IN FAMILIAL CASES WITH CONGENITAL HYPOTHYROIDISM

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Background: Congenital hypothyroidism (CH) is the most common neonatal endocrinological disorder in the world. CH can be transient or permanent. The most common cause of permanent CH is the developmental disorders of the thyroid gland, dysgenesis and constitutes approximately 85% of all permanent CHs. The following genes are associated with thyroid dysgenesis; *TSHR, TSHB, NKX2-1, NKX2-5, FOXE1, HHEX* or *PAX-8* genes, although most cases of thyroid dysgenesis are sporadic. Thyroid dyshormogenesis, which is caused by defects in thyroid hormone biosynthesis, accounts for approximately 15% of permanent CH and is associated with the following genes: *DUOX2, DUOXA2, TG, SLC5A5, TPO, SLC26A4* and *IYD*.

Aim: The aim of this study was to determine the genetic and etiological factors of CH.

Subjects and Methods: 49 patients (female; n = 24), from 24 families were included in the study. The data, collected retrospectively, consisted of medical history, physical examination, clinical findings, thyroid hormone levels and etiological tests. Gene panel consisting of 19 genes (*PAX8,* NKX2-1, NKX2-5, *FOXE1, TSHR, SLC5A5, SLC26A4, TG, TPO, DUOX2, DUOXA2, IYD, SLC26A7, DUOX1, ZNF607, SLC6A4, GLIS3, TSHB, THRA*) that may cause CH was performed in Medipol University Genetic Department. Each patient was screened for these mutations and disease causing mutations were investigated by Sanger sequence analysis. Pathogenicity of the novel nonsynonymous mutations were analysed *via in silico* prediction programs. The SPSS for Windows 22.0 was used for statistical analysis.

Results: Sixteen families had consanguineous marriages and 12 families had a history of hypothyroidism. Twenty patients were diagnosed with neonatal screening programme and 2 patients with hyperbilirubinemia, 5 patients were diagnosed during hospitalization in neonatal intensive care unit and 22 patients were diagnosed during the routine control. The mean age at presentation (mean±SD) was 1.3±2.1 years (median: 0.2; range 0.03-8.8). The mean TSH level at presentation was 152.3 ± 207.9 mIU/ml (median: 51.8; range 4.2-820), and the level of fT4 was 8.8±5.9 pmol/L (median: 9.4; range 0.04-19.7). All patients underwent ultrasonography and one patient had thyroid agenesis. In the etiological evaluation; scintigraphy was performed to 23 patients from 17 families. Thyroid agenesis and thyroid hyperplasia were detected in two patients. Perchlorate discharge test was performed in 21 patients from 16 families and two of them could not be evaluated due to errors in processing. Four patients had normal results, 9 patients (family, n=9) had partial dyshormogenesis and 6 patients had complete dyshormogenesis (family, n = 6). Iodine capture test was also performed to these patients which was high in 2 patients and low in one patient. Five of the patients from 5 families were evaluated as transient congenital hypothyroidism.

Table 1. Clinical and laboratory findings of patients

Family No	Patient	Additional findings and therapy	At presentation			Etiological tests				Genetic analysis
			Age (years)	TSH (mIU/ml) (N:0.4-4.35)	fT4 (pmol/L) (N:11.8-21.6)	Thyroid US	Thyroid scintigraphy	Perchlorate discharge test	Iodine uptake	
I	**Patient 1**	Familial short stature, GH treatment	2.1	9.5	10.7	N	N		N	*TSHR* c.1349G>A
	Patient 2	Familial short stature	1.5	7	17.3	N	N	29%	N	
II	**Patient 1**	Precocious puberty, GnRHa treatment	5.9			N				*TPO* gene-R540*
	Patient 2	PDA	0.17	40.4	12.7	N				
	Patient 3		0.13	600	6.2	N	Thyroid hyperplasia	13%	N	
III	**Patient 1**	obesity	1.69	200	3.4	N	N	53.8%	N	*TPO* gene c.1477G>A
	Patient 2	-	0.08	60	10	N				
IV	**Patient 1**	-	0.08	500	5.15	N	N	17%	N	*SLC26A7* gene c.280G>A (novel)
	Patient 2	-	0.17			N				

TSH thyroid stimulating hormone, *fT4* free thyroxine, *GH* growth hormone, *PDA* patent ductus arteriosus, *US:* Ultrasonography

Genetic analysis revealed that four families with consanguineous marriages (4/24, 16.7%) had mutations in 3 different genes. Family I was followed because of dyshormogenesis, had a homozygous c.1349G>A (p.R450H) mutation in the *TSHR* gene. One of these siblings had familial short stature and was receiving growth hormone (GH) treatment because of GH deficiency. Second family was followed because of dyshormogenesis, had a homozygous c.1477G>A (p.G493S) mutation in the *TPO* gene. Third family with partial dyshormogenesis had a homozygous missense p.R540* mutation in the *TPO* gene, which causes stop codon. One of these siblings had a history of heart failure due to PDA, the other sibling had a history of GnRH analogue therapy because of central precocious puberty, and the third sibling had a history of total thyroidectomy. Family IV was followed because of partial dyshormogenesis and had a homozygous novel c.280G>A (p.G94R) mutation in the *SLC26A7* gene.

Conclusions:

- In our study, the overall mutation rate was 16.7%. Genetic etiologies may differ in cases of dyshormonogenesis.
- A novel mutation was shown in the *SLC26A7* gene in a family with partial dyshormogenesis.
- Genetic analysis can be used to clarify the etiology, to be informed about prognosis and to provide genetic counseling especially in familial cases.
- It has been suggested that a greater number of related genes should be screened for the recognition of genetic causes that may cause of CH.

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