ENVIRONMENTAL EFFECT ON THYROID DISFUNCTION

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Abstract
The challenges of endocrinology, including those of endocrine disruption, force today's medical science to face the numerous environmental health risks. Disruption of the endocrine system, which in reality affects the unity of the psycho-neuroendocrine immune system, may play a role in the development of many diseases. In this work, one of the basic questions was whether the environmental loads can cause disease (transformation disorders and processes) in the thyroid gland. Our aim was to develop the novel diagnostic method or environment-related thyroid diseases. The endocrine disrupting compounds play an important role in inflammation and transformation of the thyroid gland. For this reason, upgrading any diagnostic method by adding environmental parameters is advised.

Introduction
The problem area of endocrine disruption in the introduction suggests that today's medical science, including the challenges of endocrinology [1] have to face numerous environmental health risks [2]. Disruption of the endocrine system, which actually affects the unity of the psycho-neuroendocrine immune system, may play a role in the development of many diseases. Thus, exploring the changing environmental conditions in the living spaces provided by society and the examining of the relationships among the health problems posed by those exposures can help us study the pathogens and pathomechanisms of certain systemic diseases.
In the last half century, endocrine disruptors (ED) have caused very serious dysfunctions in the endocrine glands, especially in the thyroid [3], which have led to severe functional variations. For diseases with thyroid proliferation [4] it is a major health and therapeutic question whether the benign and/or malignant thyroid diseases should be considered in conjunction with the pathogens.
Therefore, in this work, one of the basic questions was whether the environmental loads can cause disease (transformation disorders and processes) in the thyroid gland? In order to provide an answer, recognition of the disease, diagnostic typing and exploration of anamnesis relationships became necessary.
Our aim was to develop the novel diagnostic method for environment-related thyroid diseases.

Methods
The grown thyroid-gland was classified by European Thyroid Association (ETA) and American Thyroid Association (ATA) methods (Table 1).

Table 1 Risk classification systems for thyroid diseases (SPECT/CT based)

	1	2	3
ETA *2006 guidelines*	very low *the tumor is unifocal T1 (≤ 1 cm) N0M0 and there is no extension beyond the thyroid capsule*	low *the tumor is T1 (> 1 cm) N0M0, or T2N0M0, or multifocal T1N0M0*	high *the tumor is any T3; any T4; any T with N1 or M1*
ATA *2009 guidelines*	low risk *no local or distant metastases; no tumor invasion of local regional tissues; no aggressive histology or vascular invasion*	intermediate risk *microscopic invasion of the tumor into the perithyroidal tissue; cervical lymph node metastasis are present*;	high risk *macroscopic tumor invasion; incomplete tumor resection; distant metastasis; thyroglobulinemia*

By these classifications of thyroid diseases were not examined in the anamneses the effects of environmental (exposure to ED compounds) medic status*. In the endocrine regulation network, the linkage of TSH, aTG, anti-TPO factors were not studied. The guide of the Endocrine Society was used for taking the patients' medical history [5]. After the first medical examination, the patients (n=35) were diagnosed with thyroid dysfunction. In general, the laboratory test contains plasma hormone levels, hormone diurnal rhythm, U-hormones and their metabolites, stimulatory/inhibitory test and standard biochemistry in the examination method of endocrine disease.
In the present work, the diagnostic protocol was supplemented with environmental health issues in which we studied occupation, workplace, place of residence, number of electric devices inside and outside the home, plastic items and exposure to chemicals.

Determination of hormone and antibodies
Whereas the usual microsomal antibody tests employ unpurified microsomes as an antigen preparation, the anti-TPO tests use a purified peroxidase. The two procedures are of comparable performance in terms of clinical sensitivity, but better lot-to-lot consistency and higher clinical specificity can be expected from anti-TPO tests due to the higher quality of the antigen used. Recombinant antigen and polyclonal anti-TPO antibodies are used in the Elecsys Anti-TPO assay. Measuring range is 5.00-600 IU/mL (defined by the lower detection limit and the maximum of the master curve). Values below the lower detection limit are reported as < 5.00 IU/mL. Values above the measuring range are reported as > 600 IU/mL.

Immunoassay for the in vitro quantitative determination of antibodies to thyroglobulin in human serum and plasma. The anti-Tg determination is used as an aid in the detection of autoimmune thyroid diseases. The Elecsys Anti-Tg assay uses human antigen and monoclonal human anti-Tg antibodies. Measuring range is 10.0-4000 IU/mL (defined by the lower detection limit and the maximum of the master curve). Values below the lower detection limit are reported as< 10.0 IU/mL. Values above the measuring range are reported as> 4000 IU/mL.

The Elecsys TSH assay employs monoclonal antibodies specifically directed against human TSH. The antibodies labeled with ruthenium complex consist of a chimeric construct from human and mouse-specific components. As a result, interfering effects due to HAMA (human anti-mouse antibodies) are largely eliminated. Measuring range is 0.005-100 µIU/mL (defined by the lower detection limit and the maximum of the master curve). The functional sensitivity

is 0.014 µIU/mL. Values below the lower detection limit are reported as < 0.005 µIU/mL. Values above the measuring range are reported as > 100 µIU/mL (or up to 1000 µIU/mL for 10-fold diluted samples).
TSH, Anti-TPO and anti-TG were measured from serum using electrochemiluminescence immunoassay (ECLIA) on Modular E170 analyzer (Roche, Mannheim, Germany) [6, 7].

Results

Table 2 Parameters and classification (ATA, ETA) of thyroid cancer patients

	code	age	ATA	ETA	TSH (mIU/l)	aTG (IU/ml	aTPO (IU/ml)
control					0,27-4,29	<115	<34
1	**AE**	29	1	2	4.67	**3298**	**>600**
2	**BA**	18	2	3	1,59	**1125**	**242**
3	BB	18	2	3	2,32	24,51	10,35
4	CSB	44	1	2	1,8	-	12,44
5	**CP**	66	2	3	2,44	**855**	-
6	DA	60	1	2	3,14	20,29	-
7	DI	64	1	2	2,46	34,1	-
8	DM	36	2	3	2,94	56,3	-
9	FI	38	1	2	3,32		23,59
10	HE	52	1	2	5,15	45,46	-
11	HL	76	1	2	1,30	21,55	8,24
12	HB	29	2	3	2,61	15,53	7,31
13	JA	23	1	2	0,85	<10,10	-
14	**KS**	43	2	3	3,28	**704**	-
15	**KG**	54	2	3	0,96	**238**	-
16	**KAN**	18	1	2	1,35	**304,40**	-
17	KI	59	1	2	0,72	28,72	-
18	MZS	50	1	2	1,38	46,16	-
19	**MA**	42	2	3	1,81	**367,80**	-
20	NN	32	1	2	1,11	-	17,87
21	NBA	22	1	2	0,97	18	-
22	**RV**	55	2	3	1,36	**458,3**	**78,39**
23	**SA**	35	2	3	11,13	**-**	**282**
24	SR	39	2	3	2,24	10,20	-
25	SZJ	61	2	3	0,45	-	8,65
26	SZI	77	1	2	0,68	10,47	-
27	SZT	27	1	2	1,52	22,48	-
28	TKM	40	1	2	1,44	38,4	-
29	TFP	48	1	2	1,05	19,71	-
30	TI	54	1	2	1,42	12,94	-
31	TT	21	1	2	0,80	-	10,76
32	TGYL	84	1	2	2,44	13,44	-
33	**VSG**	38	2	3	6,24	-	>**600**
34	VM	59	1	2	3,2	13,72	-
35	ZK	64	2	3	1,46	34,81	-

Table 3 Increased inflammatory parameters (aTG, aTP) in thyroid cancer

	code	age	TSH (mIU/l)	aTG (IU/ml)	aTPO (IU/ml)	TSH/aTG x 10^{-6}	TSH/aTPO x 10^{-6}	environmental factors
control			0,27-4,29	<115	<34	<4.29/115	<4.29/34	
median						*0,0353475*	*0,057794*	
1	AE	29	4.67	3298	>600	**0,00141***	**< 0,007789***	9
2	BA	18	1,59	1125	242	**0,00141***	**0,00657***	8
5	CP	66	2,44	855	-	**0,002853***	-	8
14	KS	43	3,28	704	-	**0,004659***	-	8
15	KG	54	0,96	238	-	**0,004033***	-	9
16	KAN	18	1,35	304,40	-	**0,004434***	-	6
19	MA	42	1,81	367,80	-	**0,004921***	-	8
22	RV	55	1,36	458,3	78,39	**0,002967***	**0,017349***	7
23	SA	35	11,13	-	282	-	**0,039468***	8
33	VSG	38	6,24	-	>600	-	**< 0,0104***	6

TSH: thyroid-stimulating hormone; aTG: antithyroglobulin antibody; aTPO: thyroperoxidase antibody
**p<0.01 relation to the median*

Inflammatory parameters and factors derived from TSH data were always lower than the calculated median of control. At the same time, these results can be correlated with environmental health issues.

Conclusions

It is common for endocrine disrupting compounds to play an important role in inflammation at low doses, therefore it seems worthwhile to determine the inflammatory factors (aTG, aTPO) in addition to TSH in the case of thyroid dysfunction. It could be also important to find out the patients' environmental exposition of endocrine disrupting compounds when taking anamnesis.

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