Preliminary fundamental aspects on the thyroid volume and function in the populatin of long term heavily polluted area in East Slovakia

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Preliminary fundamental aspects on the thyroid volume and function in the population of long-term heavily PCB polluted area in East Slovakia

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Introduction

Our previous examinations of employees of chemical factory formerly producing polychlorinated biphenyls (PCB) repeatedly showed increased thyroid volume as measured by ultrasound as well as increased frequency of thyroperoxidase, thyroglobulin and thyrotropin (TSH) receptor autoantibodies[1,2]. At the same time a considerable PCB pollution of soil, waters and food chain in large area surrounding that chemical factory was found[3,4]. The aim of present preliminary evaluation of data obtained within the EC project PCBRISK was to search for further interrelations between long-term organochlorine pollution and fundamental

markers of thyroid volume and function in large cohorts of population from three districts of East Slovakia.

Materials and Methods

Population: a total of 2046 adults, among them 834 males and 1212 females from three districts of East Slovakia was examined. There were 459 subjects <35 yrs and 1590 >35 yrs. From technical reasons some of somatic or laboratory data were not obtained from negligible number of subjects.

Thyroid volume (ThV), hypoechogenicity and nodules: ThV was measured by real time sonography using well known ellipsoid method with the aid of Sonoline (Siemens) apparatus and 7.5 mHz linear transducer. Thyroid hypoechogenicity was estimated by ultrasound in all thyroids. Such phenomenon is based on the decreased density of ultrasound waves reflected by decreased number of cell-colloid interfaces of thyroid tissue which being impaired mostly by autoimmune process in various extent. It was evaluated as positive or negative as based on the comparison of the density of echonormal thyroid image with that of normally low-echogenic surrounding muscles. Three dimensions of nodules were measured by ultrasound in anterior-posterior and lateral projection and were sorted according to the highest dimension.

Hormones, antibodies and urinary iodine: free thyroxine (FT4), total triiodothyronine (TT3), thyrotropin (TSH) and thyroperoxidase antibodies (anti-TPO) were measured with sensitive electrochemiluminiscent immunoassay using the apparatus Elecsys (Roche). Urinary iodine in a total of randomly selected 996 subjects from two districts was kindly estimated in the laboratories of Hitachi company by sensitive microcroplate method using mild ashing with ammonium persulfate followed by Sandell-Kolthoff colorimetric reaction[5].

Organochlorines (18 congeners of polychlorinated biphenyls [PCBs], hexachlorobenzene [HCB] and dichloro-p-chlorophenyl-ethene [DDE} were measured simulatenously by congener specific analysis using GC/ECD system as described in this volume by Kočan et al.[6]

Statistical evaluation: The differences between individual defined groups were evaluated by t-test and differences in the frequency of defined values with

binomial distribution by chi-square test. In addition, Spearman's rank correlation coefficient was used.

Results and Discussion

Thyroid volume, PCB and urinary iodine: ThV in all groups of subjects (e.g. either in pooled subjects of both sexes irrespectively of age or in groups specified by sex or age) was significantly correlated with PCB level ($r=0.208$; $p<0.001$. As shown in Tab. 1, in the 5th quintile of PCB levels ThV was significantly higher than that in the 1st-4th quintile with lower PCB levels Such differences are shown namely by the values of 75th and 90th percentile (Tab. 1). Increasing ThV values expressed as medians in all subjects related to deciles of increasing PCB level are shown in Fig. 1.Tab. 1 also shows that in the 5th quintile of PCB levels also the levels of selected persistent. organochlorine pollutants as HCB and DDE were increased which is particularly remarkable for DDE.

The average level of urinary iodine was 137 μg/L and medians for both districts were in the range between 101 and 150 μg/L which, according the criteria of WHO, is considered a sign of optimal and sufficient long-term iodine intake[7] which, for Slovakia, was also supported by previous European Study[8]. Thus, any interfering effect of different iodine intake on the increased ThV can be excluded and such differences could be ascribed mainly to the association of ThV with different concentrations of POP.

Table 1. Association between thyroid volume in groups of all examined adults and also those divided according to sex or age from both areas and the levels of PCBs with additional presentation of mean levels of HCB and DDE

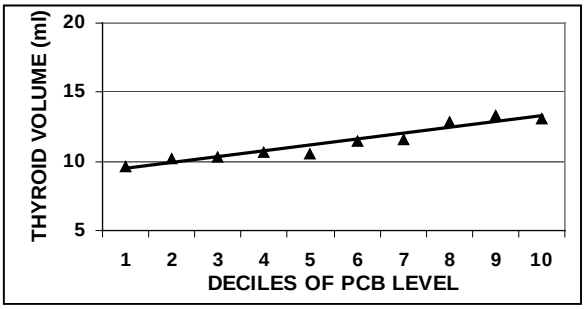
Group	Quint[1)]	No.	PCB[2)]		HCB[2)]	DDE[2)]	Thyroid volume (ml)			
			M[3)]	Range	M[3)]	M[3)]	Mean±SD[4)]	M[3)]	75 %	90 %
All adults	1-4	1640	906	148 - 2346	601	1527	9.55 ± 4.53	8.5	10.9	14.4
	5	407	3663	2349 - 101413	959	3222	11.15 ± 5.16	10.1	13.2	17.9
All males	1-4	611	1031	211- 2342	373	1430	10.52 ± 4.70	9.5	10.7	15.2
	5	223	3687	2349 - 77084	756	3223	12.26 ± 4.28	11.3	13.8	18.7

All females	1-4	1028	812	148 - 2331	730	1578	8.97 ± 4.33
8.1	10.3	13.7					
	5	184	3650	2377 – 101413	1305	3246	9.80 ± 5.18
8.8	11.7	14.1					
Adults <35	1-4	525	736	148 - 2324	196	852	8.73 ± 3.07
8.2	9.7	12.4					
	5	53	3423	2377- 9522	282	2098	9.62 ± 3.73
8.8	11.5 .	13.4					
Adults >35	1-4	1114	995	192 -2342	851	1922	9.94 ± 5.03
8.7	11.5	15.1					
	5	354	3687	2349 - 101413	1077	3512	11.39 ± 5.31
10.3	13.5	18.1					

[1)] - quintiles; [2)] – values are indicated in ng/g plasma lipids; [3)] – M = median; [4)] in all groups of population the differences between 1st-4th quintile vs. 5th quintile were significant ($p<0.001$)

As far as we are aware, the thyroid ultrasound volumetry has not yet been used for the evaluation of possible effects of POP on the thyroid, with the exception of our previous observations[1,2], although previously some authors reported goitre of undefined volume as evaluated by semiquantitative palpation either in the subjects affected by the Yucheng or Yusho accident[9].

Figure 1. Medians of thyroid volume in 2046 adults in deciles of increasing level



of polychlorinated biphenyls.

Nevertheless, in spite of these findings the mechanism resulting in such changes of ThV still remains to be elucidated. It should be underlined that, first, when doing field cross-section surveys in the area polluted by POP for nearly a half of century,

we are predominantly facing to sequels or outcomes of such long-term and possibly fluctuating effects of toxicants. In addition, we should expect to meet possibly not uniform, but rather varying individual sensitivity of subjects to toxic effects of POP which is possibly based on their hereditary background. From such circumstances several non-linear interrelations possibly result between the levels of POP on one side and markers of their toxic effects in blood or some somatic changes of individual organs (e.g. ThV) on the other. It should be also kept in mind that about 10 to 15 years ago namely the levels of PCBs in the population of some polluted areas were presumably still higher than these actually found.

Thyroid hypoechogenicity and nodules: Frequency of thyroid hypoechogenicity was also associated with POP levels, that in 4th-5th quintiles of PCB level being significantly ($p<0.001$) higher than that in 1st-3rd quintiles in all males (e.g. 43/401= 10,7 % vs. 16/433= 3.6 %) and all females (97/416= 23.3 % vs. 135/796= 16.9 %). Such findings are presumably also associated with those off anti-TPO frequency as presented bellow.

In males, only 8/611 (e.g. 1.3 %) nodules were found in four lower quintiles, but 9/223 (e.g. 4.0 %; $p<0.01$) in the 5th quintile, four largest nodules of them (31-50 mm) being detected in 4th-5th quintile. In females the frequency of nodules was non-significantly higher, being 51/1028 (e.g. 4.9 %) in four lower quintiles and 15/184 (e.g. 8.1 %) in the fifth quintile, the largest nodule (31/50 mm) being found again in that upper quintile. These findings are presumably related to the proliferative processes in the thyroid tissue which could be associated with the increased levels of POP.

Thyroperoxidase antibodies: The frequency of positive anti-TPO showed sex and age changes dependent on the level of PCB. Thus, although in females the frequency was increasing slightly, being 73/309 (23.6 %) in the 1st quintile (PCB 148-627 ng/g) and 67/184 (36.4 %) in the 5th quintile (PCB 2342-101414 ng/g) ($p< 0.001$) , in males the respective difference was much higher, e.g. 10/101 (9.9 %) and 49/223 (21.9 % - $p< 0.001$).

Such changes in males were apparently not age but rather PCB dependent, since about the same values in 1st-3rd quintiles (PCB 148-1341 ng/g) were found in males aged 20-40 yrs (19/179 = 10.6 %) and also these aged 41-78 yrs (26/254 = 10,2 %), while in the 4th-5th quintiles with the highest PCB levels (e.g. 1341-101.413 ng/g) the respective values for males of both age groups were also about the same, but significantly higher ($p<0.001$), being 16/69 (23.1 %) and 82/332 (24.8 %), respectively. In contrast, in females similar but less pronounced PCB

dependent changes in the frequency of positive anti-TPO were found only in the group aged 20-40 yrs (e.g. 59/264 = 22.3 % in low PCB vs. 22/66 = 33.3 % in high PCB .quintiles; p=0.05), while the frequency in two upper quintiles was the same in both age groups, being 165/532 (31.0 %) and 122/350 (34.8 %), respectively. Since, as shown in Tab. 1, the levels off HCB and particularly of DDE were also considerably increased in the 5th quintile of PCB levels, their participation in the observed thyroid changes cannot be ruled out. However, it was not evaluated in this preliminary report.

Since the immunotoxic and immunomodulatory effects of POP have been repeatedly reported[10], it is assumed these played a certain role also in the above described changes. Of particular interest appears to be the more remarkable frequency of hypoechogenicity and positive anti-TPO in males which are considered signs of autoimmune thyroiditis.

Thyroid hormones and thyrotropin (TSH): the levels of both thyroid hormones measured (e.g. FT4 and TT3) were continuously increasing in each subsequent quintile of PCB levels and, if the values of all 2038 subjects were pooled, they were significantly correlated ($p<0.001$) with PCB levels (for FT4 $r=0.114$ and for TT3 $r=0.101$) and positive correlation between FT4 and TT3 was also found ($r=0,270$; $p<0.0001$). Finally, significant negative correlation was found between FT4 and TSH ($r=0.234$; $p<0.001$), while that between TT3 and TSH was slightly above the limit of significance ($r=0.060$; $p>0.07$) which, however, deserves to be kept in mind.

Since the displacement of T4 from specific plasma carrier proteins (e.g. transthyretin and thyroxine binding globulin or TBG) resulting in increased FT4 level in plasma and increasing FT4 flow to the target tissues belongs to well known effects of PCB in experimental animals[11], it may be assumed that one of the main long-term effects of PCB pollution was the perturbation of dynamic equilibrium between bound and free T4 in plasma

In conclusion, in this epidemiological study several significant changes in thyroid parameters were observed in the subjects with high organochlorine levels. It may be suggested that such changes may contribute to the development of clinically overt disorders namely in certain hereditary disposed individuals.

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