Multimodal Distribution versus Logarithmic Transformation of Thyroid Volumes in Adolescents: Detection of Subgroup with Subclinical Thyroid Disorders and Its Impact on the Assessment of the Upper Limit of Normal Thyroid Volumes

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Abstract. Our objective was to evaluate whether there is a multimodal distribution of thyroid volume (ThV) in iodine-replete adolescents and to examine the relation between excessive ThV and the presence of thyroid hypochonogenicity (HE), serum thyroperoxidase antibodies (anti-TPO) and TSH levels >4.5 mIU/l. ThV was measured by ultrasound in adolescents aged 13 yr (N = 1083) and 17 yr (N = 1089) from 22 schools in 6 districts of eastern Slovakia and expressed as ml and ml/m² body surface area. For each age group the multimodal distribution of ThV values was tested by computing their frequency at intervals of 0.5 ml/m² and plotting the cumulative frequency on a probability scale in which each segment with normal distribution should give a straight line. In all examined subjects the HE was evaluated by ultrasound; in 924 (42.5%) of those anti-TPO was estimated by radioimmunoassay and TSH by immuno-electrochemiluminescent assay. The medians of urinary iodine found in 55–164 spot urine samples from each of 6 districts (total number = 1003) were 126–142 µg/l, indicating an iodine-replete status. There was a trimodal distribution of ThV in each group, 80–85% in the lowest, 10–15% in the middle, and 5–7% in the upper segments. In the 10th ThV decile of the 17-yr group the frequency of HE (33/109 = 30.3%), anti-TPO (13/62 = 21.0%) and TSH (6/62 = 9.7%) was significantly higher than that in the 1st-9th decile (71/980 = 7.2%, P<0.001; 23/482 = 4.8%, P<0.001 and 5/482 = 1.0%, P=0.001, resp.). Similar differences were found in the 13-yr group (21/109 = 19.2% vs. 58/974 = 5.9%, P<0.001 for HE, 5/60 = 8.3% vs. 3/320 = 0.9%, P<0.001 for anti-TPO and 2/64 = 3.1% vs. 4/317 = 1.3% (not significant) for TSH >4.5 mIU/l. Thus in the 10% of subjects with the highest ThV, the frequency of HE and anti-TPO was 4–5 times higher than in the remaining 90%. Our data indicate that an epidemiological evaluation of a large population of adolescents can detect a group with early signs of thyroid dysfunction (e.g. excessive ThV, increased frequency of HE, anti-TPO and TSH >4.5 mIU/l), although such dysfunction may not be clinically apparent. This contrasts with numerous earlier reports which used a logarithmic transformation of the data in similar ThV sets, thus making the data appear homogeneous (unimodal) and with a normal distribution and obscuring the true multimodal distribution. This further prevents recognition of subjects with evidence of disordered thyroid status which thus become falsely included into a normal range.

Key words: Adolescents, Ultrasound, Normal thyroid volume, Multimodal distribution, Genetic factors


SEVERAL reports have attempted to define the average values and upper limits of thyroid volume (ThV) by ultrasound in adolescents from various countries [1–11]. A European collaborative study including 7599 children from 57 sites in 12 European countries [8] defined normal ThV using a cluster of 3265 adolescents from 23 sites located in The Netherlands, Slovakia, Austria and France in which the median urinary iodine was at least 100 µg/L. The median and 97 percentile level of ThV thus obtained for individual
age groups of 6 to 15 years were recommended by WHO as normal [9], the only criterion of thyroid normality being the median of urinary iodine values as found in a group of adolescents at the appropriate site. However, in the studies mentioned above the distribution of ThV was either considered normal in spite of being asymmetric or was normalized by logarithmic transformation, even in some recent studies [8, 10, 11]. According to our opinion, the latter approach deforms the genuine multimodal ThV distribution and thus prevents recognition of a cluster of subjects with excessive ThV.

In a previous study performed in 1991–93 we observed about 9 percent of such excessive ThV among a large number (N = 4,254) of iodine-replete adolescents [7]. In that study, however, we did not obtain any blood samples. Subsequently we focused our attention on the etiology of the increased thyroid growth rate which was unlikely to result from individual iodine deficiency. In a seven-year longitudinal study, we found subgroups of about 20 percent rapidly growing thyroids in both of control adolescents and in those supplemented with small doses of iodide between 10 and 17 years of age [12]. Since the increased thyroid volume was independent of iodine supplementation, it was presumed to result from hereditary factors. This view was supported by our cross section study [13] showing significantly discordant ThV in several sibling pairs and triads subsequently born within 24 or 36 months, respectively. Since they were living in common households with their parents and attended the same school, they apparently had nearly the same life-long iodine intake. This is a more reliable criterion of iodine intake (i.e. the lifetime cumulated sum of iodine intake) than a single or even repeated estimates of urinary iodine. Because of considerable ThV difference between two siblings in about 9% of 251 sibling pairs (range of difference between two young siblings was 3.07–5.39 ml per squared meter of body surface area), it is very unlikely that this could result either from individual iodine deficiency or from some toxic environmental effect in only one of those siblings. In addition, there were 63.3% of sibling pairs with both thyroids small (average ThV 3.96 ml/m²) and 27.5% of these with both thyroids large (average ThV 5.85 ml/m²). Thus, also in this study we suggested that the increased ThV either in one sibling or in both siblings possibly resulted from hereditary factors [13].

The data of both previous studies [12, 13] thus suggested there was a heterogenous distribution of ThV independent of iodine intake. To evaluate this hypothesis, in a new prospective study we examined the interrelation between ThV in large groups of adolescents and the frequency of hypoechogenicity, positive thyroperoxidase antibodies, and increased TSH levels to determine the most appropriate technique of assessing normal thyroid volume in adolescents.

Materials and Methods

Subjects

Thyroid volume (ThV) was measured between 0830 and 1230 h by ultrasound in children aged 13 yr (N = 1083, 512 boys and 571 girls) and 17 yr (N = 1089, 447 boys and 642 girls) from 22 schools in 6 districts of East Slovakia, the areas with known industrial pollution being avoided. The study was performed in Spring period (April 15–June 30 2000). At the same time urinary and blood samples were obtained from those who had the consent of their parents. The study was performed from April 15 to June 30, 2000. The data on a total number of 71 children (32 boys and 71 girls aged 13 or 17 years) obtained by the same methods in the same period of 1998 and published in a previous report on siblings [13] were included also in this study.

Blood was obtained from cubital vein with a vacutainer Monovette (Sarstedt, Germany) and centrifuged in a refrigerated centrifuge. Serum and urine samples were then transported in a portable freezer to the laboratory and kept frozen at -20°C until assayed. About 80% of the pupils of the appropriate age were examined in each school after obtaining written informed consent of the parents and oral consent of children obtained immediately before examination. The survey was approved by the Ethical Committee, Faculty Hospital, Faculty of Medicine in Košice.

Thyroid volume

Thyroids were examined using a real-time instrument (Sonoline SI-400, Siemens, Germany) with a 7.5 MHz linear transducer. ThV for each lobe was calculated according to ellipsoid formula: width (cm) × length (cm) × thickness (cm) × correction factor 0.479 [14] and expressed as ml/m² of body surface.
body surface area was calculated by using the formula: (weight in kg$^{0.425} \times$ height in cm$^{0.725} \times 71.84 \times 10^{-4}$).

The measurements were made in each adolescent lying supine with the neck hyperextended by the same observer (M.T.) with long-term experience in field surveys and clinical ultrasound diagnostics [3, 4, 12, 13]. The intra-observer variation as estimated by 3 subsequent measurements of 50 ThV ranging between 3.0 and 20.5 ml (median 6.2 ml) was 3.9 ± 3.5% (mean ± S.D.). With a large number of measurements the ratio of plus and minus measurement errors approaches 1:1 and thus the final error in stratifying large numbers of ThV into classes (as used in this study) approaches zero. Therefore the effect of intraobserver variability on the final data was considered negligible.

**Thyroid echogenicity**

In the thyroid gland, the cell-colloid interface represents a dominant factor in sound reflection. In normal thyroids a large proportion of sound waves hits the cell-colloid interface at right angles and is reflected back to the transducer. The tissue thus appears echonormal and its echogenicity is higher than that of surrounding muscle. In contrast, in tissue with an increased number of damaged follicles only a small proportion of sound waves hits the decreased number of acoustic interfaces and the tissue thus appears as low-echogenic which means that the echogenicity is lower than that of surrounding muscles. Special attention was paid to the echo pattern in all subjects examined. Although the evaluation was subjective, it should be highly reliable because of the extensive and long-term personal experience of the observer. In the present study both homogeneous and inhomogeneous hypoechochogenicity were considered as the same category. The routine procedure was to evaluate the echo-pattern first and to determine the three dimensions of each lobe and obtain the volume only after this first step.

**Thyroid volume distribution**

The distribution of ThV was tested by plotting the distribution frequency on a probability scale [15]. Thus, for each age group the distribution frequency of ThV values was computed for intervals of 0.5 ml/m$^2$ body surface area and the cumulative frequency was plotted on probability scale for normal distribution (Fig. 1). With this technique each segment of normal distribution tends to appear as a straight line against the variate (ThV) as the abscissa. The multimodal distribution was checked by evaluating the number of segments which deviated from an overall linear trend [15]. The best linear fits for individual segments of each cumulative frequency were then obtained with a computer. The limits between the overlapping zones of the individual segments were chosen arbitrarily.

The multimodal distribution for 17-yr group shown in Fig. 1 was then expressed in Fig. 2 by using the arbitrary method of symmetrical extension and arbitrary limits between the individual segments. Thus, the left arm of the whole group distribution was considered identical with the left arm of the lower segment and was symmetrically extended to the right side. Further, the left arm of the middle segment was obtained by subtracting the values of the right arm of the lower segment from those of the whole group and was again symmetrically extended to the right side. The distribution of the upper segment was obtained in a similar manner. Thus, the sum of values for each segment in each range of ThV gives the value for the whole group at the appropriate ThV range.

**Urinary iodine**

Spot urine samples were obtained from 1003 subjects approximately between 10.00 and 12.00 hr (55–162 from each of 6 districts) and urinary iodine was estimated by the colorimetric ceric ion arsenious acid reaction applied after mild acid wet ash digestion of samples in a thermostock for 60 min at 115°C [16].

Since the approach of spot urine samples and expression of urinary iodine as a concentration was used, the data obtained could not be used for evaluation of individual intake of iodine. In such a case iodine concentration varies depending on how much liquid the subjects have been drinking and this variation will tend to even out among many subjects. For such reason at least 40 subjects were used to determine the mean concentration of urinary iodine and a median value between 100 and 150 μg iodine/L urine to indicate an optimal iodine intake in a given area as recommended by ICCIDD [17] and used in European Thyromobil Study [8].
Fig. 1. Multimodal distribution of thyroid volume in large groups of 13- and 17-yr-old adolescents as shown by cumulative frequency plotted on a probability scale.

Fig. 2. Comparison of the multimodal and logarithmically transformed distribution of thyroid volume in 17-yr-old adolescents. The figure also shows the values of "mean" and "±2SD" for all subjects as well as "low limit of 10th decile". It should be noted that the values shown between 11 and 18 ml/m² belong to the upper segment.
**Hormone and antibody assays**

Serum levels of anti-TPO were measured with commercial kits (DYNO-test anti-TPO, Brahms Diagnostica GmbH, Berlin) in 387/1085 (41.6%; 189 boys and 198 girls) 13-yr and 544/1089 (49.9%; 214 boys and 330 girls) 17-yr-old adolescents. All samples were assayed initially in the same single point assay. The 72 samples from that assay which were above zero standard were then analyzed in duplicate in a repeat assay. The intraassay variation was <3%. Although the level of anti-TPO in 98% of patients with autoimmune thyroiditis was >60 U/ml, a cut-off level of 70 U/ml was used.

Serum levels of TSH were measured with an electro-chemiluminescent method using an automatic analyzer Elecsys (Roche, Basel, Switzerland) in the same cases as anti-TPO (see above). Intraassay variation was less than 2%. For the evaluation of the frequency of increased TSH values a cut-off level of 4.5 mU/l was used.

**Statistical analysis**

The data obtained in individual age groups were stratified according to the thyroid volume (as expressed as ml per squared meter of body surface) and then distributed in deciles. Means and SD of thyroid volume (in terms of either ml or ml/m²) were computed for each decile and the differences were evaluated with the use of ANOVA followed by Bonferroni’s multiple range test. The individual measures used (e.g. hypoechoogenicity, positive anti-TPO level and increased TSH level) were evaluated for each decile either as showing two possible outcomes (e.g. either present or absent) thus corresponding to a binomial distribution. Yates’ chi-square test was used to evaluate the differences in their distribution between the upper and lower deciles.

**Results**

**Urinary iodine**

The median of all 1003 values was 136 µg/l and the individual medians of 55–164 samples from each of 6 districts were in the range of 126–142 µg/l, thus showing an optimal and equal iodine intake [8, 17] in all areas examined and supporting a countrywide optimal iodine intake resulting from 50-year well monitored mandatory consumption of iodized salt.

**Multimodal distribution of thyroid volume**

In both the 13- and 17-yr groups three straight lines were obtained by a probability scale plot, which, according to the principle indicated a trimodal distribution of ThV (Fig. 1). Since there are overlapping zones between the individual segments of ThV distribution, no definite sharp limits between them could be clearly defined by the method used. Thus, 80–85% of cases were allotted to the lower, 10–15% to the the middle and about 5% to the upper segments.

**Thyroid volume versus hypoechoogenicity, positive anti-TPO and increased TSH**

There was a highly significant (P<0.001) progressive increase between each successive decile in thyroid volume (ml and ml/m² in both the 13-year-old and 17-year-old groups (Tables 1 and 2).

In the 13-yr group (Table 1) the total frequency of hypoechoogenicity in the 1st to 9th decile was 58/975 (5.9%), while that for the 10th decile (21/109 = 19.3%) was significantly higher (P<0.001). A similar difference was found in the 17-yr group (Table 2), the respective values being 71/980 (7.2%) vs. 33/109 (30.3%; P<0.01). In both age groups the total frequency of hypoechoogenicity in girls was non-significantly higher than in boys, e.g. 53/672 (7.9%) vs. 26/512 (5.1%) in the 13-yr and 76/642 (11.8%) vs. 28/447 (6.2%) in the 17-yr group.

The frequency of positive anti-TPO in the 10th decile was significantly higher than that in the 1st to 9th decile in both the 13-yr (4/62 = 6.5% vs. 3/325 = 0.9%; P<0.002; Table 1) and 17-yr group (13/62 = 20.9% vs. 23/482 = 4.8%; P<0.001; Table 2). The total frequency of positive anti-TPO was significantly higher in girls than in boys in the 17-yr group (30/330 = 9.1% vs. 6/214 = 2.8%; P<0.001; Table 2), but the difference in the 13-yr group was not significant (7/198 = 3.5% vs. 1/189 = 0.5%; Table 1). The study was performed between April 15 and June 30, 2000. The data on a total number of 71 children (32 boys and 71 girls aged 13 or 17 years) obtained by the same methods in the same period of 1998 and published in a previous report on siblings [13] were in-
Table 1. Thyroid volume, hypoechoogenicity, anti-TPO and TSH in 13-yr group

<table>
<thead>
<tr>
<th>Dec(1)</th>
<th>No(2)</th>
<th>Thyroid ml</th>
<th>ml/m²</th>
<th>He(3)</th>
<th>Anti-TPO</th>
<th>TSH (mU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± S.E.</td>
<td>Mean ± S.E.</td>
<td>M(3)</td>
<td>Range</td>
<td>N(4)</td>
</tr>
<tr>
<td>1</td>
<td>109</td>
<td>3.90 ± 0.12</td>
<td>2.60 ± 0.04</td>
<td>2.63</td>
<td>1.36–3.07</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>108</td>
<td>4.94 ± 0.08</td>
<td>3.31 ± 0.01</td>
<td>3.26</td>
<td>3.07–3.56</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>108</td>
<td>5.42 ± 0.12</td>
<td>3.76 ± 0.01</td>
<td>3.71</td>
<td>3.56–3.97</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>108</td>
<td>6.05 ± 0.07</td>
<td>4.13 ± 0.01</td>
<td>4.50</td>
<td>4.29–4.29</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>108</td>
<td>6.48 ± 0.09</td>
<td>4.46 ± 0.01</td>
<td>4.43</td>
<td>4.29–4.63</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>108</td>
<td>7.16 ± 0.10</td>
<td>4.79 ± 0.01</td>
<td>4.75</td>
<td>4.63–4.96</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>108</td>
<td>7.71 ± 0.08</td>
<td>5.19 ± 0.01</td>
<td>5.12</td>
<td>4.96–5.49</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>108</td>
<td>8.63 ± 0.10</td>
<td>5.73 ± 0.02</td>
<td>5.66</td>
<td>5.49–6.03</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>108</td>
<td>9.68 ± 0.11</td>
<td>6.38 ± 0.02</td>
<td>6.28</td>
<td>6.03–6.82</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>109</td>
<td>12.55 ± 0.26</td>
<td>8.14 ± 0.13</td>
<td>7.53</td>
<td>6.84–12.47</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>1083</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>81</td>
</tr>
</tbody>
</table>

(1) Dec = decile; (2) N = number; (3) M = median; (4) HE = hypoechoogenicity; (2/3) = number of cases with TSH >4.5 mU/L.

Table 2. Thyroid volume, hypoechoogenicity, anti-TPO and TSH in 17-yr group

<table>
<thead>
<tr>
<th>Dec(1)</th>
<th>No(2)</th>
<th>Thyroid ml</th>
<th>ml/m²</th>
<th>He(3)</th>
<th>Anti-TPO</th>
<th>TSH (mU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± S.E.</td>
<td>Mean ± S.E.</td>
<td>M(3)</td>
<td>Range</td>
<td>N(4)</td>
</tr>
<tr>
<td>1</td>
<td>108</td>
<td>4.79 ± 0.08</td>
<td>3.02 ± 0.04</td>
<td>3.12</td>
<td>1.89–3.47</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>109</td>
<td>6.13 ± 0.06</td>
<td>3.74 ± 0.01</td>
<td>3.76</td>
<td>3.47–3.96</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>110</td>
<td>6.87 ± 0.07</td>
<td>4.16 ± 0.01</td>
<td>4.18</td>
<td>3.96–4.35</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>109</td>
<td>7.47 ± 0.07</td>
<td>4.50 ± 0.01</td>
<td>4.50</td>
<td>4.35–4.67</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>108</td>
<td>8.01 ± 0.08</td>
<td>4.84 ± 0.01</td>
<td>4.82</td>
<td>4.67–5.00</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>109</td>
<td>8.58 ± 0.08</td>
<td>5.17 ± 0.01</td>
<td>5.15</td>
<td>5.00–5.37</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>109</td>
<td>9.38 ± 0.10</td>
<td>5.58 ± 0.01</td>
<td>5.59</td>
<td>5.37–5.81</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>109</td>
<td>10.21 ± 0.10</td>
<td>6.06 ± 0.01</td>
<td>6.01</td>
<td>5.81–6.35</td>
<td>6</td>
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<tr>
<td>9</td>
<td>109</td>
<td>11.50 ± 0.18</td>
<td>6.78 ± 0.03</td>
<td>6.71</td>
<td>6.35–7.34</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>109</td>
<td>14.91 ± 0.32</td>
<td>8.97 ± 0.19</td>
<td>8.17</td>
<td>7.35–18.19</td>
<td>33</td>
</tr>
<tr>
<td>Total</td>
<td>1089</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>104</td>
</tr>
</tbody>
</table>

(1) Dec = decile; (2) N = number; (3) M = median; (4) HE = hypoechoogenicity; (2/3) = number of cases with TSH >4.5 mU/L.

ccluded also in this study.

The serum TSH level was also analyzed in the same subjects as with anti-TPO measurements (N = 931; Tables 1 and 2). There was no value <0.2 mU/L and the total frequency of values >4.5 mU/L in the pooled age groups was very low (15/931 = 1.6%), being 6/381 (1.6%) in the 13-yr group and 9/544 (1.7%) in the 17-yr group. The only significant difference was in the 17-yr group between the 10th decile (6/62 = 9.7%) and 1st to 9th decile (3/482 = 0.6%; P<0.001; Table 2). The girls/boys ratio of the values >4.5 mU/L was 10/5 (2/1).

There was no difference between the average of pooled TSH levels for individual deciles (Tables 1 and 2). Among 15 subjects of both age groups with increased TSH, the range of TSH levels in 10 of them was 4.7–7.2 mU/L, while the remaining four had the levels of 8.3, 8.7, 10.9 and 26.6 mU/L. Among 36 subjects of both age groups with positive anti-TPO but a normal TSH level (<4.5 mU/L), there were 12 with high normal values (2.5–4.4 mU/L, median 3.4), nine of them belonging to those with high ThV (e.g. 8th to 10th decile).

Thus, in the 10% of subjects with the highest ThV
the frequency of hypoechogenicity, anti-TPO and increased TSH level was about 3–8 times higher than in the remaining 90 percent. These data indicate that at age 17 about 10% percent of the children had excessive thyroid volume, which itself may be considered a sign of thyroid disorder. About 30% of those children had hypoechogenicity and about 10% had positive anti-TPO, which may be considered as signs of subclinical autoimmune thyroiditis. This view results from the observations that in the general population of normal children, thyroid hypoechogenicity and positive anti-TPO are most likely due to an autoimmune disorder, since other disorders which could cause this ultrasound phenomenon in adults are extremely rare in adolescents. In the 17-yr olds the frequency of hypoechogenicity (104/1089 = 9.6%), positive anti-TPO (36/544 = 6.6%) and increased TSH (9/544 = 1.7%) was higher than that in the 13-yr olds, e.g. 79/1084 (7.3%; P<0.05) for hypoechogenicity, 7/387 (1.8%; P<0.001) for anti-TPO and 5/387 (1.3%; not significant) for increased TSH (>4.5 mU/L).

Fig. 2 shows the comparison of multimodal distribution of ThV as found in 17-yr group with that obtained after the logarithmic transformation, which changes the genuine asymmetric distribution into a symmetric and seemingly unimodal pattern thus giving the false impression that all thyroids included are normal. It is also shown that the 10th decile represents a considerable part of that false normal distribution. It should be noted that the low limit of mathematically defined 10th decile is close to the low limit of arbitrarily obtained upper segment. The findings of significantly higher thyroid volume as well as of higher frequency of HE, positive anti-TPO and increased TSH level in the 10th decile compared to pooled 1st-9th deciles (Table 2) support the view that the cases clustered in the 10th decile differ considerably from those clustered in lower deciles. Thus, it appears that although the logarithmic transformation is statistically justified, for adolescent thyroids it appears biologically false since it does not reveal the true multimodal biological status of the thyroids, demonstrated above (Figs. 1 and 2).

Discussion

The evaluation of these observations was based on the present and previous evidence that the dietary intake of iodine in the whole population of Slovakia is the same and sufficient. This results from the mandatory consumption of iodized salt since the early fifties with restrictions against importation of any other salt, as described in more detail elsewhere [12]. The efficacy of such long-term iodine prophylaxis is supported by the analyses of urinary iodine performed in this or our previous field surveys [3, 4, 7, 12], including those conducted in Slovakia under the European Thyromobil Study by Delange et al. [8] and, in addition, by the small ThV observed in the large majority of adolescents in the same studies. These data strongly support the view that the either sporadic or individual iodine deficiency in Slovakia is highly unlikely. It should be mentioned, however, that the iodine concentration in spot urine samples, as used in this and several recent studies [8, 10, 11] is considerably influenced by the actual concentration of urine. From such reason the values are not suitable for any studies of interrelation between urinary iodine and thyroid status in terms of individual subjects, but is being used only for the evaluation of iodine intake in certain area provided that at least 40 spot urine samples were taken from that area as recommended by International Council for Control of Iodine Deficiency Disorders [17].

The present findings show that, in spite of an apparently uniform and sufficient iodine intake, a multimodal distribution of ThV was found in the adolescent population. In all age groups, the lower segment contains about 80% of the children, corresponding to 75% with slowly growing thyroids in a previous longitudinal 7-year follow-up [12] and 72% of small thyroids found in sibling pairs [13]. In the adolescents with a low thyroid volume in this segment, there was a low frequency of impaired thyroid echostucture and positive thyroperoxidase antibodies. In contrast, a significantly higher frequency of such signs was found in subjects in the upper segment, also similar to the previous observation in sibling pairs [13]. Low thyroid echogenicity indicates a solid tissue structure which is more frequent in autoimmune thyroiditis and its value in the diagnosis of such disease has been repeatedly emphasized [17, 18]. An increased level of thyroperoxidase antibodies is also a marker of autoimmune thyroiditis.

Our data indicate that the distribution of ThV in iodine-replete adolescents is heterogenous, in contrast to numerous reports in which attention was apparently not focused on such possibility and the distribution of ThV was either considered homogenous in spite of
being asymmetric [1–5] or was masked by obtaining a normal distribution after logarithmic transformation [8, 10, 11]. As shown in this study, such transformation should be considered a systemic error since its use, although mathematically correct, is not biologically appropriate and obscures the true heterogeneous distribution. The logarithmic transformation apparently prevents recognition of the distinct subgroup of subjects with evidence of disordered thyroid status (e.g. high TSH, hypoechogenicity, positive anti-TPO and a few cases of increased TSH) which, due to this systemic error, become falsely included into a normal range. Similar cases with a normal or increased TSH, a normal serum TSH, and a positive anti-TPO have been classified as autoimmune thyroiditis type 1 [20].

A field survey such as ours cannot provide the data needed to explain the molecular nature of the thyroid disorders observed in this subgroup of adolescents. However, based on these and mainly on our previous data [11, 12] the participation of genetic influences is highly probable. This is particularly suggested by the remarkably discordant thyroid volumes in sibling pairs and triads in which any environmental influences or individual iodine deficiency may be excluded [12]. Further studies should be directed to determining the intrinsic molecular mechanism responsible for excessive thyroid growth related at least partly to the development of autoimmune process.

The data of this study also suggest that perhaps there should be a revision of the defined upper limit of normal range of adolescent thyroid volume which perhaps should exclude several subjects with large thyroids and evidence of subclinical thyroid disorders as predominantly clustered in the 10th decile of thyroid volumes and which apparently should not be considered normal. It appears that even in several recent extensive field surveys [8, 10, 11] the attention has not been paid to such questions and the thyroids of all children and adolescents from the areas with normal urinary iodine were considered normal as based on normal urinary iodine only without any examinations of some ultrasound or laboratory signs of thyroid disorders.

Acknowledgements

The authors wish to thank the late Prof. Monte A. Greer (Oregon Health and Science University, Portland, Oregon, USA) for critical reading the manuscript and correcting the English, the late Prof. John R. Goldsmith (Ben Gurion University, Beer Sheva, Israel) for statistical consultation, and Ms. Irena Rigová, Alica Mitková and Silvia Kuklová for technical assistance. This work was partly supported by Merck Pharma (Slovakia), by the Slovak Committee for UNICEF, and by grant No. 2/4131/97 from VEGA (Bratislava, Slovakia).

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