

Research paper

Chronic autoimmune thyroid disease in children and adolescents in the years 1999-2004 in Lower Silesia, Poland

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ABSTRACT

The aim of the study was to analyze data related to chronic autoimmune thyroid disease at diagnosis and at follow-up of children and adolescents in Lower Silesia in the years 1999-2004. Age, gender, incidence of thyroid disease in the family, clinical presentation, hormonal findings, levels of thyroid antibodies, results of ultrasonography, and fine needle aspiration biopsy (FNAB) were recorded. 100 children, 10 boys and 90 girls, were included in the analysis. The mean age at diagnosis was 12.3 ± 2.3 years and at last examination 14.9 ± 1.9 years. At diagnosis, increased levels of TSH without overt hypothyroidism was observed in 26 children. In 11 children hyperthyroidism was detected whereas 63 children were euthyroid. An increased level of thyroid peroxidase antibodies was observed in 65% of the children. Ultrasonography was characteristic for Hashimoto's thyroiditis in all patients. Fine needle biopsy was performed when there were diagnostic difficulties (35% children). Thus, in all the children the diagnosis of Hashimoto's thyroiditis was ascertained either by high antibody titer or FNAB. Associated diseases were observed in 33% of the children. Thyroid disease in the family was present in 25% of the children. There was a gradual decline in the number of new cases presented from 1999 to 2004. The reason for this decline remains speculative.

Key words: Hashimoto's thyroiditis, Autoimmune thyroid disease, Iodine prophylaxis

INTRODUCTION

In the past, the most frequent cause of thyroid

disease in children and adolescents was iodine deficiency. To date, in developed countries, thyroid autoimmunity, either lymphocytic thyroiditis or Grave's disease, constitute the most frequently encountered thyroid pathology. Chronic thyroiditis, also called chronic lymphocytic or autoimmune thyroiditis, was first reported by Hashimoto in 1912¹ and it may be clinically manifested as enlargement or atrophy of the thyroid gland.² The term Hashimoto's

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thyroiditis is still used for the goitrous form of the disease. In about 90% of patients with Hashimoto's thyroiditis, high levels of antibodies against thyroid peroxidase (anti-TPO) and thyroglobuline (ATg) are detected. Antibodies blocking or stimulating the TSH receptor have been found in about 10% of the cases (usually in the atrophic form of the disease). Factors which predispose to the development of chronic lymphocytic thyroiditis are genetic and environmental³. Among the environmental factors are high iodine consumption, viral infections and drugs. Many authors have observed an increase in the incidence of autoimmune diseases of the thyroid after introduction of iodine prophylaxis in endemic regions.⁴⁻⁷ Most likely, environmental factors trigger an autoimmune process in subjects with a genetic predisposition.⁸⁻¹⁰ In Poland, obligatory iodine prophylaxis was introduced in 1997. In subjects over 18 years a relative increase of the cytologic diagnosis of chronic lymphocytic thyroiditis has subsequently been observed.¹¹ Contrary to these data, Zimmerman et al¹² did not detect induction of thyroid autoimmunity in iodine deficient children in Northern Morocco 1 year after the introduction of iodized salt. It is well known that Hashimoto's thyroiditis is associated not only with other autoimmune diseases, like diabetes type 1, Addison's disease, myasthenia gravis, vitiligo, celiac disease, but also with genetic disorders like trisomy 21 or Turner's syndrome.

The aim of our study was to retrospectively analyze the mode of presentation and the follow-up of autoimmune thyroiditis in children and adolescents diagnosed in Lower Silesia in the years 1999-2004.

SUBJECTS AND METHODS

The study group included 100 children, 10 boys and 90 girls, who presented at the endocrine out patient department of the endocrine clinic of the University of Medicine Hospital in the years 1999-2004, and originated from Lower Silesia. The age at presentation was 12.3 ± 2.3 years and at last examination 14.9 ± 1.9 years. The following data were recorded: physical examination data, serum values of TSH, FT4, FT3, antithyroid antibodies (anti-TPO), as well as results of thyroid ultrasonography and fine needle aspiration biopsy (FNAB). TSH, FT3, FT4

and anti-TPO were determined by immunofluorescence. Normal values were: TSH; 0.4 to $4 \mu\text{U/ml}$, FT4; 0.8-1.9ng/dl, FT3; 1.5-4.1 pg/ml; anti-TPO 0-35 IU/ml. Ultrasonography was performed by using a high frequency 715MH3 linear RA transducer.

RESULTS

The results are presented as means and standard deviation (SD). All patients had normal growth, (Table 1) weight and puberty. Thyroid disease in the family was ascertained in 25% of the children. Mean age of the children at diagnosis of autoimmune thyroiditis was 12.3 ± 2.3 years. At diagnosis, 26 children (26%) had increased levels of TSH, without overt clinical hypothyroidism, 11% had symptoms of mild hyperthyroidism whereas 63% were euthyroid. In general, the patients were presented with the following signs or symptoms: thyroid enlargement, weakness, tachycardia, decrease or increase of body weight or dry skin. The mean level of TSH in the whole group at diagnosis was 15.18 ± 41.1 uIU/ml, the mean level of FT4 was $1.78 \text{ ng/dl} \pm 2.84$, the mean level of FT3 was $4.14 \text{ pg/ml} \pm 2.5$. Positive anti-TPO were found in 65% of the cases. The remaining did not have high titer and the diagnosis was made by FNAB. The mean level of antibodies (anti-TPO) was $622.15 \text{ IU/ml} \pm 579.9$. At last examination (aged 14.9 ± 1.9) mean level of TSH was $1.88 \text{ UI/ml} \pm 1.26$, FT4 $1.66 \text{ ng/dl} \pm 1.58$, FT3 $3.63 \text{ pg/ml} \pm 1.43$, anti-TPO $517.41 \text{ IU/ml} \pm 488$. The hormonal data and those of antithyroid antibodies are shown in Tables 2 and 3, separately for the 3 groups (euthyroid, hypothyroid and hyperthyroid). A characteristic ultrasonographic picture was observed in all patients: hypoechogenicity, with increased blood flow. The echo structure in general was heterogeneous. A fine needle biopsy was performed in 35% of children and in all of them the diagnosis of Hash-

Table 1. Certain anthropometric data of patients with chronic lymphocytic thyroiditis

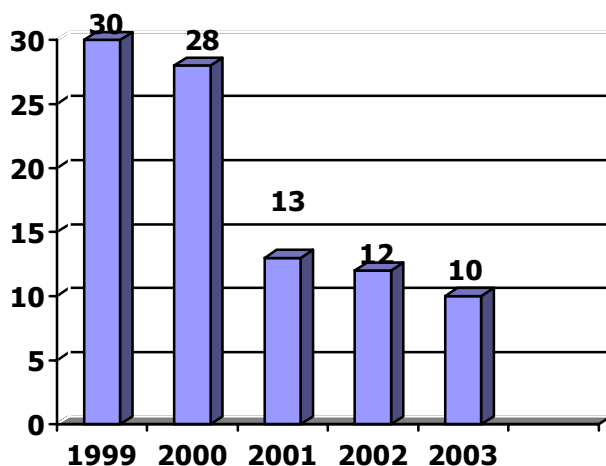
	age (years)	height (cm)	BMI (kg/m ²)
at diagnosis			
n = 100	12.3 ± 2.3	165 ± 9.6	20.5 ± 2.3
at last examination			
n = 100	14.9 ± 1.9	167 ± 9.5	20.3 ± 1.7

Table 2. Hormonal levels and anti-TPO titer at diagnosis (mean±SD)

Clinical condition	FT3 pg/ml N 1,5-4,1	FT4 ng/dl N 0,8-1,9	TSH mIU/ml N 0,4-4,0	ATPO uIU/ml N 0-35
Euthyroid n:63	4,1±1,1	1,7±0,9	2,41±1	135±53
Hyperthyroid n:11	4,9±1,5	2,9±1,9	0,25±0,6	667±302
Hypothyroid n:26	3,2±2	0,9±0,5	35,3±14,8	834±352

Table 3. Anti-TPO titer and thyroid hormones (mean±SD) at follow-up (aged 14.9 ± 1.9 years)

Clinical condition at presentation	TSH (μIU/ml)	FT4 (ng/dl)	FT3 (pg/ml)	anti-TPO (IU/ml)
Hypothyroid	2,7±1,5	1,2±0,5	3,3±2,3	679±340
Hyperthyroid	1,9±0,9	1,8±0,3	3,1±2,1	452±353
Euthyroid	2,5±1,7	1,2±0,5	2,7±1,7	120±34

**Figure.** The number of new cases of chronic autoimmune thyroiditis in the years 1999-2003.

imoto's was made. Malignancy was not detected in any of the cases. Additional diseases were observed in 33 children (33%); these were type 1 diabetes mellitus (14%), PCOS (5%), Turner syndrome (3%) and Down syndrome (3%). Thyroxine therapy was administered in the 26 patients with subclinical hypothyroidism.

DISCUSSION

Environmental and genetic factors are both involved in the etiology of Hashimoto's thyroiditis (HT).^{10,13} In populations in whom iodine prophylaxis was introduced, an increase of autoimmune diseases of the thyroid was noted.³ The obligatory io-

dine prophylaxis consisting in iodination of kitchen salt (30±10 mg KI/kg salt) was introduced in Poland in 1997 and in the year 2002, Poland was accepted by WHO in the group of countries with sufficient iodine supply. The frequency of goiter has decreased in Poland to below 5% of the population.¹⁴ The studies performed in certain countries, currently with a good iodine supply, have shown an increase of autoimmune thyroiditis in children. In Greece in a study reported in 1999 it was shown that the predominant form of nontoxic goiter was autoimmune thyroiditis. In Poland, Bobeff and al found that in children from the Lodz macroregion the frequency of chronic thyroiditis increased from 3.7% in the years 1992-1996 to 11.2% in the years 1997-2001.¹⁵ Zimmerman and al have reported a transient increase in the prevalence of detectable antithyroid antibodies after introduction of iodized salt¹². In our own study we observed a decrease in the frequency of new cases of chronic lymphocytic thyroiditis from 1999 to May 2004 from 30% in the year 1999 to about 10% in 2003. This could be interpreted as a flare-up of HT shortly after the introduction of obligatory iodine prophylaxis and a tapering off subsequently. Alternatively, the decrease may represent a diversion of the patients to other centers. The majority of children were euthyroid (63%). Subclinical hypothyroidism was ascertained in 26% of the children, and a hyperthyroid state in 11%. It is of interest that the lowest titer of anti-TPO was detected in the euthyroid group and the highest in the hypothyroid. Hashimoto thyroiditis, as expected, was much

more frequent in girls, in agreement with other reports in the literature.^{16,17} In children with high TSH, the introduction of thyroxin therapy led to the normalization of TSH, without changes in anti-TPO titer over the 2 years of follow-up. Coexisting diseases were diagnosed in 33 children (33%), most often diabetes type 1, which is in agreement with the reports in the literature^{13,18-22}. Thyroid diseases in the family were ascertained in 25% of the children. Segni and et¹³ found a positive family history in 36% and Marinovic²⁰ in 23% of examined children.

In summary, in 65% of children with sonographic evidence of thyroiditis, a high titer of thyroperoxidase antibodies was detected. In the remaining 35% with low antibody titer, the diagnosis was ascertained by FNAB. The majority of the children (63%) were euthyroid at presentation (clinically and hormonally), and 11% were mildly hyperthyroid. There was a decline in the number of new cases of HT from 1999 to 2004, which could be incidental. Alternatively, it could be the result of a transient rise in the years 1999-2000 following obligatory salt iodination in Poland in 1997.

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Research paper

Improved somatic growth following adenoidectomy and tonsillectomy in young children. Possible pathogenetic mechanisms

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ABSTRACT

The effect of Adenotonsillectomy on somatic growth was studied prospectively in 57, randomly selected children (31 boys, 26 girls), aged 5.03 ± 1.32 (mean \pm 1SD) years. The indication for surgery was adenotonsillar hypertrophy with or without recurrent infections. Weight, height, triceps skinfold thickness, and Body Mass Index were measured prior to the operation and 6-13 months afterwards. Weight was significantly improved following T&A in all children. The improvement in height was significant only for children under 5 years. In an attempt to uncover the pathogenetic mechanisms, lactic acid, pyruvic acid, somatomedin-C (IGF-I), growth hormone (GH), insulin, glucose, pH, hemoglobin (H β), and white cell count (WBC) were also determined in the last 18 children, prior to and 6-8 months post operatively. For the comparison of pre and post operative values the paired t test was applied. Although the values of GH and IGF1 did not significantly increase post-op the IGF-1/GH ratio increased, possibly indicating improved IGF1 generation. There was also a rise in H β values and a lowering of WBC, probably reflecting the lower frequency of infections. All other metabolic indices did not change. In conclusion, linear growth post-Adenotonsillectomy improved in children aged <5 years and was associated with improved IGF-1/GH ratio, increased H β values and decreased in WBC.

Keywords: Growth retardation, Adenotonsillectomy, Growth hormone, IGF1

INTRODUCTION

The major indications for adenotonsillectomy (T&A) have remained the same for many years and

include, recurrent pharyngotonsillitis and its complications, excisional biopsy, management of chronic ear disease, and chronic upper respiratory obstruction.¹⁻⁵ Currently, the most frequent indication for T&A is upper airway obstruction due to hypertrophy of the tonsils and adenoids.⁵ Chronic upper airway obstruction can lead to obstructive sleep apnea syndrome (OSAS) with chronic alveolar hypoventilation, cor pulmonale, cardiac failure⁶⁻¹⁵ sleep disorder

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ders,¹⁶⁻¹⁹ behavioral changes, learning disability, enuresis, and retarded growth.^{1,8,14,20-23} Published data on the influence of T&A on somatic growth refer to case reports,²⁴⁻²⁷ or include small number of patients,^{6-8,28} younger than 3 years, primarily affected by OSAS. In these studies, most of the children were underweighted pre-operatively (pre-op), and presented "catch-up" growth after T&A. Other trials^{29,23} looked retrospectively to the improvement of somatic growth. A small number of prospective studies, have been published in which, OSAS was mainly correlated to changes in growth post-op. Results concerning the influence of recurrent tonsillitis on somatic growth are controversial.^{20,30,31} There are reports^{28,8} which show that only tonsillectomy had a positive influence on somatic growth post-operatively (post-op), while others found that adenoidectomy is as effective as tonsillectomy or T&A. The pathogenetic mechanism involved have not been elucidated. In the present study the influence of T&A on height and weight was studied prospectively in children aged 5.03 ± 1.32 years, who were operated upon for various indications. An attempt was also made to look into pathogenetic mechanism responsible for the alteration in growth pattern, following T&A.

PATIENT SELECTION AND METHODS

Fifty seven children, 31 boys (54.3%) and 26 girls (45.6%) were studied. The age of the patients at entrance to the study was 5.03 ± 1.32 years. The children were randomly selected from the Ear-Nose-Throat clinic. The selection criteria were: substantial evidence to justify T&A, absence of any other concurrent disease that may affect growth and informed consent from the parents who accepted to participate in the study and the follow-up visits. Indications for T&A were: Adenotonsillar hypertrophy with or without recurrent infections. Five tonsillectomies (T), 21 T&A, and 31 adenoidectomies (A) were performed. Nineteen of the children experienced ear problems such as: recurrent acute otitis media, or otitis media with effusion. For these children myringotomy with or without ventilation tube insertion, was also performed.

The weight, height, and triceps skinfold thickness

were measured the day prior to surgery, between 9-10 am and the body mass index was estimated using the formula: weight (kg)/height (m).² The measurements were carried out by the same person, following an identical procedure, i.e. the children were weighted in their indoor clothing and without shoes, using a stable balance. The height was measured as length up to the age of five years (lying down) and as height (upright position) past the age of 5 yrs, using the Harpenden stadiometer. The triceps skinfold thickness was measured using the Holtain skinfold caliper. Six to thirteen months after operation, the children were once again measured following the same protocol. For the statistical analysis the paired t test was applied. For the auxologic data the standardized weight and height (z scores) and their percentiles were used while for the other parameters the actual values were used.

In the last 18 children of this series the following parameters were additionally determined: lactic acid (Monotest Boehringer), pyruvic acid (Combination test Boehringer), somatomedin-C/IGF-I (Radioimmunoassay-RIA, Nichol's reagents), growth hormone (RIA), glucose (glucose oxidase), insulin (RIA), pH (venous blood), haemoglobin (Hb), and white cell count (WCC) by routine methodology, prior to the operation and 6-8 months post operatively.

Parents were asked to report on changes in the activity, the appetite and frequency of infection of their children following the operation.

RESULTS

Weight (Table I)

The weight standardized value (z score) for the total group significantly increased following the operation (pre-op value 0.2481 ± 1.26 , post-op value 0.8793 ± 1.43 , $p=0.0001$) and the mean percentile value also increased from the 54th percentile, to the 68th ($p=0.0001$). No difference was observed in these changes between boys and girls.

There was also no difference in the changes observed whether the pre-op weight was above or below the 50th percentile.

Table I. Pre, and post-op mean values for body Weight expressed in z scores and percentiles

All children	n	Pre-op	Post-op	p
Percentile	57	54.3	67.9	0.0001
z score	57	0.2481	0.8793	0.0001
Boys	n	Pre-op	Post-op	p
Percentile	31	51.1	67.2	0.0001
z score	31	0.079	0.7511	0.0002
Girls	n	Pre-op	Post-op	p
Percentile	26	58.3	68	0.0005
z score	26	0.4488	1.032	0.0001

The changes observed according to the type of operation were as follows: Significant increase for those who underwent T&A and A ($p < 0.001$ for both), but not, for those who underwent T ($p > 0.1$). In the latter group however, the sample was small (5 children).

Height (Table II)

The height standardized value (z score) for the total group was significantly increased post-op (pre-op value 0.4994 ± 0.9 , post-op value 0.6578 ± 1.01 , $p = 0.0002$) and the mean percentile also increased from the 65th to the 69,6th percentile ($p = 0.0001$). This difference emerged from the children under the age

Table II. Pre, and post-op mean values for Height expressed as z scores and percentiles

All children	n	Pre-op	Post-op	p
Percentile	57	65.1	69.6	0.0001
z score	57	0.4994	0.6578	0.0002
Boys	n	Pre-op	Post-op	p
Percentile	31	59.1	65.2	0.0008
z score	31	0.2379	0.44	0.0022
Girls	n	Pre-op	Post-op	p
Percentile	26	72.3	74.9	0.058
z score	26	0.8111	0.9173	0.0462
Children under five years	n	Pre-op	Post-op	p
Percentile	29	64.2	71.1	0.0002
z score	29	0.408	0.6667	0.0003
Children over five years	n	Pre-op	Post-op	p
Percentile	28	66.1	68.2	0.133
z score	28	0.5941	0.6485	0.2019

of five, while for the group of children over five (28 children), no significant changes in either standardized value, or percentile were observed ($p = 0.2019$, 0.133 respectively). Boys grew somewhat better than girls (Table II).

There was no difference in the changes observed whether the pre-op height was above or below the 50th percentile.

The changes observed according to the type of operation were as for the weight: Significant increase for those who underwent T&A and A ($p < 0.001$ for both), but not, for those who underwent T only ($p > 0.1$). In the latter however, as we mentioned before, the sample was small (5 children).

Skinfold thickness (SFT)

The SFT also increased significantly post-op (mean pre-op and post-op values 10.6 ± 3.3 mm and 11.4 ± 3.7 mm, respectively $p < 0.01$).

Body Mass Index (BMI) values increased from a pre-op value of 15.85 ± 1.7 to 16.7 ± 2.1 post-op ($p < 0.001$).

Hormonal and other hematologic parameters

Concerning the search for pathogenetic mechanisms the following changes between pre-op and post-op values were observed (Table III): IGF-I form 0.69 ± 0.31 to 0.91 ± 0.71 , growth hormone form 4.1 ± 4.5 to 2.1 ± 3.7 , lactic acid from 17.69 ± 5.04 to 20.07 ± 7.14 , pyruvic acid from 0.37 ± 0.18 to

Table III. Pre, and post-op mean values for the hormonal and other hematological parameters

Parameter	n	Pre-op	Post-op	p
IGF-I (IU/L)	18	0.69 ± 0.3	0.91 ± 0.7	> 0.1
G.H. (mg/ml)	18	4.1 ± 4.5	2.1 ± 3.7	> 0.1
IGF1/GH	18	0.56 ± 0.54	1.38 ± 1.53	$P < 0.025$
Lactic acid (mg/dl)	17	17.6 ± 5	20.0 ± 5	> 0.1
Pyruvic acid (m/dl)	17	0.37 ± 0.18	0.38 ± 0.2	> 0.1
Glucose (mg/dl)	18	91.2 ± 1.5	98.7 ± 17	> 0.1
Insulin (μ U/mg)	18	14.6 ± 12.7	18.3 ± 15.3	> 0.1
pH (venous)	16	7.33	7.33	> 0.1
Hb (gr/dl)	18	12.2 ± 0.8	12.6 ± 0.95	0.037
White cell count	18	11558	9036	0.005

0.38 ± 0.2 , glucose from 91.2 ± 15.6 to 98.7 ± 17.1 , insulin from 14.6 ± 12.7 to 18.3 ± 15.03 and pH didn't change (7.33). The above changes were not statistically significant. The ratio IGF1/GH increased from a pre-op value of 0.56 ± 0.54 to 1.38 ± 1.53 post-op ($p < 0.025$).

A significant difference was found between pre-op and post-op values of hemoglobin (pre-op 12.2 ± 0.87 and post-op 12.6 ± 0.95 , $p = 0.037$) and white cell count (WBC) (11558.3 ± 3295.5 pre-op, and 9036.6 ± 2812.3 post-op, $p = 0.005$).

According to the parent's opinion the majority of the children had a better appetite and activity 6-13 months after the operation and, reportedly, less frequent infections post-op.

DISCUSSION

In this prospective study, somatic growth, as reflected in height, weight, BMI and skinfold thickness, were significantly increased after T&A in the total group. The improvement in height (z score) was highly significant only in children under five years, irrespective of the indication for surgery, and the pre-op z score. The underlying mechanisms for this improvement are not known. In the present study, parameters related to impaired oxygenation (lactic acid), growth (IGF1, GH) and infection (H β and WBC) were evaluated in an attempt to clarify the pathogenetic mechanisms involved.

Growth hormone (GH) is released in pulsatile fashion during a 24 hours period, mainly during sleep³² but the highest GH³³ values are associated with the onset of slow wave sleep (SWS). It has been shown that sleep disturbances and specifically a decrease in the amount of SWS occur in children with adenotonsillar hypertrophy. This effect is expected to decrease sleep associated GH secretion. The effect of GH on skeletal growth appear to be mediated through the somatomedins. The somatomedins or IGF factors are a family of insulin like peptide growth factors modulated by insulin and nutrition as well as by GH. Deficient growth in the presence of adequate GH secretion could occur because of decreased somatomedin generation, increased somatomedin inhibitors, or changes in the responsive-

ness of the target organ. In children who do not have GH deficiency, the presence of low somatomedin levels would suggest nutritional insufficiency, chronic illness or genetically impaired IGF1 generation.³⁴

Based on the above data we measured values of GH, IGF-1 and other parameters, possibly related to impaired growth. The values of GH IGF1, insulin and glucose did not statistically change post-op, whereas the IGF1/GH ratio significantly increased. With regard to GH, only single values in the morning were measured. A 24-hour integrated concentration of GH or provocative testing would have been more informative than basal values^{33,35} since it is quite possible that GH secretion pattern during sleep could be decreased pre-op. For obvious reasons, however, such an experimental design could not be materialized.

Other investigators have also attempted to interpret the increase in growth post T&A. Thus, Marcus et al³⁶ attributed the growth improvement post T&A to the lowering of energy expenditure which they observed, during sleep, post-op.

Bar et al³⁷ found that IGF1 values but not IGFBP3 increased post T&A in association with prolongation of slow wave sleep period. They infer that GH was increased post-op, but actual values of GH were not determined.

In another study, higher values of IGF1 and IGFBP3 were found.³⁸ Based on these findings, the authors speculated that the GH values had improved. Two other studies also found higher IGF1 and IGFBP3 values post T&A.^{39,40}

In our study, besides IGF1, GH values were also determined in 18 subjects, under basal conditions. Contrary to expectations, the basal GH values tended to be higher pre-op although not statistically significant. As mentioned previously, basal GH values do not adequately reflect sleep associated or 24 hour GH secretion. Nevertheless, the data are not in favor of lower GH values pre-op. It is quite interesting and provocative that the IGF1 to GH ratio was higher post-op suggesting an improvement in IGF1 generation by GH. This phenomenon is not unexpected, as it may be encountered in other situations of growth inhibition in which inflammatory respons-

es predominate. In such cases, GH may be normal, whereas IGF1 levels are low.⁴¹ Supporting evidence for such a phenomenon is derived from the information that infections were less frequent, the H β values were higher and the WBC was lower post T&A. Moreover, in another study IL-1 β and IL6 values were significantly lower post T&A.⁴² An increase in H β values post T&A was also detected by Elverland et al.⁴³

In conclusion, body weight improved in all children post-op. Height was improved only in children under the age of five. For the latter observation two explanations can be offered. The “catch-up” growth in children over five had already occurred, because the organism itself managed to overcome the pathological condition (escape phenomenon) or “catch-up” growth is not possible if the abnoxious factors are not removed early in life. Growth was improved post-op, irrespective of the pre-op percentile for weight and height. Gender was not an important factor. A significant difference in the IGF1/GH ratio was detected post-op possibly indicating improved IGF1 generation. Among the possible pathogenetic mechanisms involved, as emerged from our study, was an impairment in IGF1 generation possibly as a result of better nutrition and or decrease in the frequency of infections.

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