Research paper

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

Harilaos S. Vontetsianos[1], Spiros E. Davris[1], George D. Christopoulos[1], Catherine Dacou-Voutetakis[2]

[1]ENT Department and [2]Endocrine Unit, First Paediatric Department, Athens University, Children's Hospital "Agia Sophia" Athens, Greece

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±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 (Hβ), 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 Hβ values and a lowering of WBC, probably reflecting the lower frequency of infections. All other metabolic indices did not change. In conclusion, linear grow post-Adenotonsillectomy improved in children aged <5 years and was associated with improved IGF-1/GH ratio, increased Hβ 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 failure[6-15] sleep disor-

Address correspondence and requests for reprints to:
C. Dacou-Voutetakis, V. Ipirou 4, Papagos, 156 69, Professor of Pediatric Endocrinology, Athens University, Head Endocrine Unit

Received 07-09-04, Revised 12-11-04, Accepted 25-11-04

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 concent 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 form 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 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).

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

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±3.3mm and 11.4 ± 3.7mm, 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 (μU/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 (Hβ 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 sleep[32] but the highest GH[33] 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 generetion, increased somatomedin inhibitors, or changes in the responsiveness 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 al[36] attributed the growth improvement post T&A to the lowering of energy expenditure which they observed, during sleep, post-op.

Bar et al[37] 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 Hβ values were higher and the WBC was lower post T&A. Moreover, in another study IL-1beta and IL6 values were significantly lower post T&A.[42] An increase in Hβ 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 impairement in IGF1 generation possibly as a result of better nutrition and or decrease in the frequency of infections.

REFERENCES

1. Eliaschar I, Lavie P, Harperin E, Gordon C, Alroy G, 1980 Sleep apnea episode as indications for adenotonsillectomy. Arch Otolaryngol 106: 492-496.
2. Grundfast KM, Wittich DJ, 1982 Adenotonsillar hypertrophy and upper airway obstruction in evolutionary perspective. Laryngoscope 92: 650-56.
3. Konno A, Hoshino T, Togawa K, 1980 Influence of upper airway obstruction by enlarged tonsills and adenoids uppon recurrent infection of the lower airway in childhood. Laryngoscope 90: 1709-1716.
4. Potsic WP, 1990 Tonsillectomy and adenoidectomy. An update plus sleep apnea. Common Problems in Pediatric Otolaryngology 297-301.
5. Darrow DH, Siemens C, 2002 Indications for tonsillectomy and adenoidectomy. Laryngoscope 112: 6-10.
6. Brouillete RT, Fernbach SK, Hunt CE, 1982 Obstructive sleep apnea in infants and children. The Journal of Pediatrics 100: 31-40.
7. Guilleminault C, Eldridge FL, Simmons FB, Demert WC, 1976 Sleep apnea in eight children. Pediatrics 58: 23-30.
8. Lind MG, Lundell Bo PW, 1982 Tonillar hyperplasia in children. A cause of obstructive sleep apneas. CO_2 retention, and retarded growth. Arch Otolaryngol 108: 650-654.
9. Mangat D, Orr WC, Smith RO, 1977 Sleep apnea, hypersomnolence and upper airway obstruction secondary to adenotonsillar enlargement. Arch Otolaryngol 103: 383-386.
10. Potsic WP, 1989 Sleep apnea in children. The Otolaryngologic Clinics of North America – Ped Otolar 22: 537-544.
11. Reilly JS, 1988 Tonsillar and adenoid airway obstruction. Modes of treatment in children. International Anesthesiology Clinics 26: 54-57.
12. Singer LP, Saenger P, 1990 Complications of pediatric obstructive sleep apnea. Otolaryngologic Clinics of North America 23: 665-676.
13. Stool SE, Eavey RD, Stein NL, Sharrah WG, 1977 The "Ghubby Puffer" Syndrome. Clinical Pediatrics 16: 43-50.
14. Sukerman S, Healy GB, 1979 Sleep apnea syndrome associated with upper airway obstruction. Laryngoscope 89: 878-885.
15. Yonkers AJ, Spaur RC, 1987 Upper airway obstruction and the pharyngeal lymphoid tissue. Otolaryngologic Clinics of North America 20: 235-239.
16. Mandel EM, Reynolds III CE, 1981 Sleep disorders associated with upper airway obstruction in children. Pediatric Clinics of North America 28: 897-903.
17. Mark JD, Brooks JG, 1984 Sleep associated airway problems in children. Pediatric Clinics of North America 31: 907-918.
18. Potsic WP, Wetmore RF, 1990 Sleep disorders and airway obstruction in children. The Otolaryngologic Clinics of North America 23: 651-663.
19. Stradling JR, Thomas G, Warley ARH, Williams P, Freeland A, 1990 Effect of adenotonsillectomy on nocturnal hypozaemia, sleep disturbance, and symptoms in snoring children. The Lancet 335: 294-53.
20. Barr GS, Osborne J, 1988 Weight gain in children following tonsillectomy. The Journal of Laryngology and Otology 102: 595-597.
21. Bate TWP, Price DA, Holme CA, Mc Gucken RB, 1984 Short stature caused by obstructive apnea during sleep. Arch Dis Child 59: 78-80.
22. Hodges S, Wailoo MP, 1987 Tonsillar enlargement and failure to thrive. British Medical Journal 295: 541-542.
23. Williams EF 3rd, Woo P, Miller R, Kellman RM, 1991 The effects of adenotonsillectomy on growth in young children. Otolaryngol Head & Neck Surg 104: 509-516.
24. Van Someren VH, Hibber J, Stothers JK, Kyme MC, Morrison GAJ, 1989 Indentifying hypoxaemia in children admitted for adenotonsillectomy. Br Med J 298: 1076.
25. Everett AD, Koch WC, Saulsbury FT, 1987 Failure to

thrive due to obstructive sleep apnea. Clinical Pediatrics 26: 90-92.
26. Sciffmann R, Faber J, Eidelman AI, 1985 Obstructive hypertrophic adenoids and tonsils as a cause of infatile failure to thrive: reversed by tonsillectomy and adenoidectomy. Int J Pediatr Otorhinolaryngol 9: 183-187.
27. Shaw NJ, Bowler I, Dear PRF, 1987 Tonsillar enlargement and failure to thrive. British Medical Journal 295: 1065.
28. Leiberman A, Tal A, Brama I, Sofer S, 1988 Obstructive sleep apnea in young infants. Int J Pediatr Otorhinolaryngol 16: 39-44.
29. Berkowitz RG, Zalzal GH, 1990 Tonsillectomy in children under 3 years of age. Arch Otolaryngol Head Neck Surg 116: 685-686.
30. Grace A, Veitch D, Ryan R, Barnes N, Coles T, 1988 Recurrent tonsillitis and growth in children. Int J Pediatr Otorhinolaryngol 16: 91-93.
31. Mills RP, Hibbert J, 1983 The effects of recurrent tonsillitis on growth and cervical lymphadenopathy in children. Int J Pediatr Otorhinolaryngol 6: 77-82.
32. Finkelstein JW, Roffwarg HP, Boyar RM, Kream J, Hellman L, 1972 Age-related change in the twenty-four-hour spontaneous secretion of growth hormone. J Clin Endocrinol Metab 35: 665-670.
33. Underwood LE, Azumi K, Voina SJ, Van Wyk JJ, 1971 Growth hormone levels during sleep in normal and growth hormone deficient children. Pediatrics 48: 946-954.
34. Phillips LS, Unterman TG, 1984 Somatomedin activity in disorders of nutrition and metabolism. Clin Endocrinol Metab 13: 145-189.
35. Zadic Z, Chalew SA, Raiti S, Kowarski AA, 1985 Do short children secret insufficient growth hormone? Pediatrics 76: 355-360.
36. Marcus CL, Carroll JL, Koerner CB, Hamer A, Lutz J, Loughlin GM, 1994 Determinants of growth in children with the obstructive sleep apnea syndrome. J Pediatr 125: 556-562.
37. Bar A, Tarasiuk A, Segev Y, Phillip M, Tal A, 1999 The effect of adenotonsillectomy on serum insulin-like growth factor-I and growth in children with obstructive sleep apnea syndrome. J Pediatr 135: 76-80.
38. Selimoglu E, Selimoglu MA, Orbak Z, 2003 Does adenotonsillectomy improve growth in children with obstructive adenotonsillar hypertrophy? J Int Med Res 31: 84-87.
39. Yilmaz MD, Hosal AS, Oguz H, Yordam N, Kaya S, 2002 The effects of tonsillectomy and adenoidectomy on serum IGF-I and IGFBP3 levels in children. Laryngoscope 112: 922-925.
40. Nieminen P, Lopponen T, Tolonen U, Lanning P, Knip M, Lopponen H, 2002 Growth and biochemical markers of growth in children with snoring and obstructive sleep apnea. Pediatrics 109: 55.
41. Tsatsoulis A, Siamopoulou A, Petsoukis C, Challa A, Bairaktari E, Seferiadis K, 1999 Study of growth hormone secretion and action in growth retarded children with juvenile chronic arthritis (JCA). Growth Horm IGF Res 9: 143-149.
42. Unal M, Ozturk C, Gorur K, 2002 Effect of tonsillectomy on serum concentrations of interleukins and TNF-alpha in patients with chronic tonsillitis. ORL J Otorhinolaryngol Relat Spec 64: 254-256.
43. Elverland HH, Aasand G, Miljeteig H, Ulvik RJ, 2004 Effects on tonsillectomy and adenoidectomy on hemoglobin and iron metabolism. Int J Pediatr Otorhinolaryngol 68: 419-423.