Insulin-like growth factor alpha changes after tonsillectomy for obstructive and nonobstructive causes

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Objective
To assess the effect of tonsillectomy, weather performed for obstructive or nonobstructive causes, on the serum levels of insulin-like growth factor alpha (IGF-1).

Patients and methods
This prospective study was carried out on 60 children who underwent tonsillectomy or adenotonsillectomy at Zagazig University Hospitals. The children were divided into two groups: the first group included 30 children who underwent tonsillectomy because of obstructive symptoms and the second group included 30 children who underwent tonsillectomy because of recurrent tonsillitis with no manifestations of upper-airway obstruction. Preoperative and 3 months' postoperative blood levels of IGF-1 were estimated and the data were statistically analyzed.

Results
Six children from the first group (24 children) and four children from the second group (26 children) did not follow-up after surgery and were excluded from the study. Both study groups were matched for age and sex. In the first (obstructive) group, there was a statistically significant increase in the mean level of IGF-1 from 119.08109 ± 27.81797 preoperatively to 222.395 ± 6.62559 postoperatively and the difference was significant ($P < 0.0001$). However, in the second (infection) group, the mean IGF-1 values increased from 155.0715 ± 89.83015 preoperatively to 191.4075 ± 57.38667 postoperatively, and the difference was not significant ($P = 0.0883$).

Conclusion
Insufficient weight and height gain in children who had obstructive adenotonsillar hypertrophy could be attributed to low IGF-1, and this can be corrected after surgery. This is not the case in patients with chronic tonsillitis without upper-airway obstruction, and other factors may explain the retarded growth in these patients.

Study design
A prospective study.

Keywords:
growth, insulin, tonsillectomy

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Introduction

Adenotonsillar hypertrophy is usually associated with recurrent upper-airway obstruction in children. A reduced dietary intake and failure to gain weight are frequently reported by parents of children with a history of recurrent acute tonsillitis [1,2]. Also, it has been shown that sleep disordered breathing (SDB), which is characterized by snoring, mouth breathing and obstructive sleep apnea, is a risk factor for growth failure [3,4].

Although the exact cause of the poor growth is unknown, many reasons such as low caloric intake caused by poor appetite and dysphagia, high energy consumption due to difficult night breathing, nocturnal hypoxemia and nocturnal acidosis have been implicated [5,6]. Chronic inflammation may have an adverse influence on growth by inducing malnutrition or inflammatory mediators that inhibit the hypothalamic-pituitary growth axis [7]. Abnormal nocturnal growth hormone (GH) secretion and impaired GH action have also been suggested [8,9]. Nocturnal GH secretion is frequently reduced under clinical conditions involving sleep disorders [e.g. in children with obstructive sleep apnea syndrome (OSAS)], and surgical correction of OSAS may restore normal GH secretion [9]. SDB includes primary snoring, upper-airway resistant syndrome, obstructive hypoventilation and OSAS. Chronic upper-airway obstruction attributable to adenotonsillar hypertrophy is the most common cause of SDB in children [10]. Although the prevalence of OSAS in children has been reported to range from 1 to 3%, the prevalence of SDB in children may approach 11% [11].

The effects of GH on skeletal growth are mediated mainly by the stimulation of insulin-like growth factor

alpha (IGF-1) expression. IGF-1 constitutes a family of insulin-like peptide growth factors, the activity of which is modulated by insulin, nutrition and GH. GH stimulates the synthesis of IGF-1 in the liver and other target tissues [8]. IGF-1 is considered to be the main mediator of the growth-promoting actions of GH, reflecting the daily mean GH levels, and it has been reported to correlate well with the physiologic changes in GH secretion [12]. Insufficient weight and height gain have been well documented in children with recurrent tonsillitis and SDB, and 'catch-up' growth after adenotonsillectomy has been reported [5,13]. This study was conducted to assess the changes in IGF-1 after tonsillectomy, whether performed for obstructive or nonobstructive reasons.

Patients and methods

IGF-1 levels were measured preoperatively and 3 months postoperatively in the serum of 60 patients who underwent tonsillectomy or adenotonsillectomy at Zagazig University Hospitals during the period from January 2013 to December 2014. The study protocol was approved by the Institutional Review Board (IRB) at Zagazig University Hospitals. Informed consent was obtained from relatives of all the included study participants after explanation of the research purpose.

The children were divided into two groups. The first group included 30 patients who underwent adenotonsillectomy for obstructive sleep apnea, and they had clinical and radiological signs of adenoid hypertrophy. The second group consisted of 30 children who underwent tonsillectomy because of recurrent tonsillitis. This group of patients had neither a history of obstructive symptoms nor radiological evidence of adenoid hypertrophy that requires adenoidectomy. Children with known upper-airway abnormalities, underlying disease predisposing upper-airway obstruction, facial anomalies, asthma or perennial allergy and patients with chronic diseases such as diabetes mellitus or liver disease were not included in the study.

A preoperative anesthetic evaluation was performed, including routine blood and urinary tests along with chest radiography. Preoperative blood samples for measuring IGF-1 were taken during surgery. Adenotonsillectomy was performed for the first group and tonsillectomy was performed for the second group under general anesthesia, and patients were discharged on the same day of surgery.

The patients were seen 3 months postoperatively, and blood tests were repeated to detect postoperative IGF-1. As the preoperative blood samples were taken after 8 h of fasting, postoperative blood samples were also taken after 8 h of fasting to avoid the possible effects of fasting on serum IGF-1. Serum was extracted from the blood samples, centrifuged and stored frozen at -20°C to analyze the serum IGF-1.

All serum samples were studied by the same biochemist in one assay. Serum IGF-1 concentrations were measured by the chemiluminescent enzyme-linked immunosorbent assay method with commercially available kits from DRG (DRG Instruments Gmb H, Marburg, Germany).

Principles of the test

An IGF-1 enzyme-linked immunosorbent assay kit is a solid plasma-linked immunosorbent assay based on the principle of competitive binding. Patient's samples were acidified and neutralized before the assay procedure.

The microtiter walls were coated with a monoclonal antibody directed towards an antigenic site on the IGF1 molecule. The pretreated sample was incubated at room temperature with a conjugate (biotinylated IGF-1). The walls were washed, and then incubated with the enzyme complex (streptavidin–HRP complex). After addition of the substrate solution, the intensity of the color developed was reverse proportioned to the concentration of IGF-1 in the patient sample.

Preoperative IGF-1 levels were then compared with postoperative levels. The relationship between IGF-1 serum levels of patients was statistically investigated.

Statistical analysis

Data were processed using SPSS 14.0 statistical software for Windows (SPSS Inc., Chicago, Illinois, USA). The significance level was set at a *P* value less than 0.05.

Results

Six children from the first group (24 children) and four children from the second group (26 children) were lost to follow-up after surgery and they were excluded from the study. There were 11 male and 13 female patients in the first group, with their ages ranging from 3 to 6 years (mean of 4.455 ± 1.254 years). There were 12 male and 14 female patients in the second group, with their ages ranging from 4.5 to 10 years (mean 5.201 ± 2.11 years). There was no statistically significant difference in the age or the sex distribution between the two groups (Table 1). In the first (obstructive) group,

there was an increase in the mean level of IGF-1 from 112.08 ± 27.8 preoperatively to 222.395 ± 6.62559 postoperatively, and the difference was highly significant ($P < 0.0001$). In the second (infection) group, although the mean IGF-1 values increased from 155.07 ± 89.83 preoperatively to 191.4 ± 57.387 postoperatively, the difference was not significant ($P = 0.0895$) (Table 2). The mean preoperative IGF-1 levels in the obstructive group was significantly less than that in the infective group, whereas the mean postoperative IGF-1 level was found to be significantly higher in the obstructive group than in the infective group (Table 2).

Discussion

Failure to gain weight and height is frequently noted in children with tonsil and adenoid hypertrophy. The precise mechanisms of this are unknown. Impaired nocturnal GH secretion in accordance with the abnormal sleep patterns had been proposed as the cause of the growth delay in children with adenotonsillar hypertrophy [13–15]. IGFI is considered as the main mediator of GH action [14–17]. The purpose of this study was to assess the effect of surgery on IGF-1 levels in patients undergoing tonsillectomy for upper-airway obstruction or for chronic tonsillitis without airway obstruction.

The improvement in growth after surgical removal of the nasopharyngeal airway obstruction is a well-known phenomenon, possibly involving multiple factors such as increased GH secretion, increased caloric intake, decreased energy expenditure and an increase in serum IGF-1 and insulin-like growth factor binding protein-3 (IGFBP-3) levels [16,18,19]. Anabolic and growth-promoting effects of GH are mediated mainly by the stimulation of the expression of IGF1 in the liver and the peripheral tissues [8]. Most of the circulating IGF-1 is bound to a carrier protein called IGFBP-3. The synthesis of IGFBP-3 is also controlled by GH. Circulating concentrations of IGF-1 and IGFBP-3, which seem to correlate well with the physiological changes in GH secretion, are strongly related to diurnal GH secretion, thus reflecting mean daily GH levels [7,17].

Despite the large number of studies discussing the level of IGF-1 in patients undergoing adeotonsillectomy, most of these studies included patients in one group, with no differentiation between those undergoing surgery for mere upper-airway obstruction and those undergoing surgery for recurrent infection or both [14,20]. Our study categorized the patients into the upper-airway obstruction group and the infection-only group. Although it is impossible to rule out infection from the first group, the effect of upper-airway obstruction on IGF1 was ruled out from the second group. Our results showed that postoperative IGF-I levels at 3 months were significantly higher than its preoperative levels in patients who underwent adenotonsillectomy for obstructive reasons. These findings are consistent with studies by Nieminen *et al.* [14] Yilmaz *et al.* [16] and Gümüssoy *et al.* [20]. We also found an increase in the postoperative levels of IGF1 in patients with chronic tonsillitis with no obstructive symptoms, but the increase was not significant compared with the preoperative levels. This in contrast to the study by Kiris *et al.* [7], who found a significant increase in IGF-1 in eight patients undergoing tonsillectomy for chronic tonsillitis.

We did not evaluate height and weight changes because the study period of 3 months was not enough to assess a significant change in the height and the weight of the operated children. However, other investigators found a significant increase in the height and the weight of children after adenoidectomy and adenotonsillectomy [7]. They concluded that adenotonsillectomy, separately or together, may influence the GH-IGF-1 axis by increasing IGF-1 levels, leading to acceleration in growth, not only in patients with adenotonsillar

Table 1 Age and sex of the obstructive and the infective groups

Patients	*N* (%)		*P* value
	Obstructive (24)	Infective (26)	
Sex			
Male	11 (45.8)	12 (46)	0.1393[a] (*t* = 1.5035)
Female	13 (54.2)	14 (54)	
Age	4.455 ± 1.254	5.201 ± 2.11	0.1393[b] (*t* = 1.5035)

[a]Fisher exact test. [b]Chi square test.

Table 2 Preoperative and postoperative IGF-1 levels in the obstructive and the infective groups

	Preoperative IGF-1 level		Postoperative IGF-1 level		*T*-test	*P* value	Significance
	Mean	SD	Mean	SD			
Obstructive group (24 patients)	112.08	27.8	222.395	6.62559	−18.8985	<0.0001	Highly significant
Infective group (26 patients)	155.07	89.83	191.4	57.387	−1.7379	0.0895	Nonsignificant
T-test	−2.32		−2.73				
P value	0.026		0.01				
Significance	Significant		Significant				

IGF-1, insulin-like growth factor alpha.

hypertrophy, but also in patients with recurrent adenotonsillitis [17]. Apart from the improvement in GH secretion and function, other factors contribute to the improved growth observed after tonsillectomy and/or adenotonsillectomy. Ahlqvist *et al.* [21] postulated that increased postoperative weight may involve a reversal of a preoperative catabolic state to a postoperative anabolic state mediated by a reduction in catecholamine secretion. Barr and Osborne [22] showed that 83% of parents reported an increase in children's appetites after tonsillectomy or adenotonsillectomy. Camilleri *et al.* [23] has suggested that the postoperative weight gain may be in response to the surgeons' instruction to eat well during the recovery period. Aydogan and colleagues reported an overall 55.2% increase in the appetite in the postoperative period after tonsillectomy. They also detected a significant increase in weight in the group with increased appetite. They attributed the accelerated weight gain after tonsillectomy to an increased nutritional intake secondary to a reduction in the number of episodes of tonsillitis [13]. In a recent study, Topal *et al.* [24] investigated tonsillectomy as a risk factor for childhood obesity, and they found no significant effect of tonsillectomy in developing overweight in secondary-school-aged children.

Our results indicate that IGF-1 increases after tonsillectomy or adenotosillectomy. However, this increase is significant in case of surgeries performed for obstructive reasons and nonsignificant in case of surgeries performed for chronic recurrent infection without airway obstruction. Hence, in the absence of upper-airway obstruction, tonsillectomy should be performed for recurrent infection and not for weight gain or retarded growth. However, retarded growth can be an indication for tonsillectomy and/or adenotonsillectomy in cases of upper-airway obstruction, due to adenotonsillar hypertrophy, even without evidence of recurrent infection.

Conclusion

Insufficient weight and height gain in children who had obstructive adenotonsillar hypertrophy could be attributed to low IGF-1, and this can be corrected after surgery. This is not the case in patients with chronic tonsillitis without upper-airway obstruction, and other factors can explain the retarded growth in these patients.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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