Clinical Evaluation of Adeno-Tonsillar Hyperplasia in Non-Syndromic Children and Adolescents during Growth Hormone Treatment

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Abstract

Objective: To evaluate the difference in size of pharyngeal and palatine tonsils in patients aged between 5 and 17 being treated with recombinant human Growth Hormone (rhGH).

Material and Methods: We conducted a prospective longitudinal observational study. Twelve patients in treatment with rhGH were evaluated by otorhinolaryngological physical examination, nasofibrolaryngoscopy and Obstructive Sleep Apnea (OSA)-18 questionnaire in two different time-points: when selected (T0) and after 6 months (T1).

Results: No significant associations were found regarding palatine and pharyngeal tonsil size with rhGH treatment. In relation to OSA-18 questionnaires, there was no statistically significant result in the absence of covariables for the general score as well as for the five domains that it comprises. When covariables were included in the analyses, controlled by the patient's age, we observed statistically significant increases in the general score and in the domains relating to sleep disorders, emotional suffering, diurnal problems and the caretaker's concerns.

Conclusion: In the present study, pharyngeal or palatine tonsils hyperplasia was infrequent during treatment with rhGH in the non-syndromic children and adolescents. However, the impacts on sleep and quality of life that may arise warrant careful monitoring during therapy.

Keywords: Adenoids; Pathology; Child; Human growth hormone; Adverse effects; Palatine tonsil; Pathology; Sleep apnea syndromes

Introduction

Recombinant human Growth Hormone (rhGH) is an important pharmacological agent for the stimulation of linear growth and the improvement of body composition in children with Growth Hormone Deficiency (GHD), Chronic Renal Insufficiency (CRI), Turner Syndrome (TS), Prader-Willi Syndrome (PWS), and other conditions [1-3]. More than three decades ago, it had been proved that treatment with rhGH is effective and with low risk [4-8]. There are, however, studies in the literature showing side effects that include benign intracranial hypertension, edema, worsening of scoliosis, gynecomastia, and hyperglycemia [1-3]. Adeno-tonsillar hyperplasia was reported by Gerard et al. [9] as another side effect derived from the use of rhGH, and also highlighted the presence of Obstructive Sleep Apnea (OSA) in children after the beginning of treatment [7].

Adeno-tonsillar hyperplasia is responsible for 70% to 75% of the cases of OSA in children [10,11]. OSA is a sleep respiratory disorder in which there is partial or complete obstruction of the upper airways, which interferes with normal sleep patterns and ventilation [11-15]. The estimated prevalence of OSA in children is 1% to 4% [13-15], with major adeno-tonsillar growth usually occurring between 2 and 8 years of age [10,16]. The most common clinical symptoms are nocturnal snoring, sleep fragmentation, excessive diurnal sleepiness, enuresis, behavioral alterations such as anxiety and a reduction in neurocognitive performance [13,15]. Non-treated OSA can lead to cardiovascular complications such as hypertension, arrhythmia, cerebral vascular accident, pulmonary hypertension and cardiac insufficiency [15].

In syndromic children such as those with PWS, the relationship between the use of rhGH and the development of adeno-tonsillar hypertrophy is well established [17,18], but there are no prospective studies in the literature with non-syndromic children. Therefore, with the increasing use of rhGH in non-syndromic children, it is important to prospectively study the development of adenotonsillar hypertrophy in patients treated with rhGH. We sought to evaluate the difference in size of pharyngeal and palatine tonsils over a 6-month period in patients aged between 5 and 17 years being treated with rhGH.

Material and Methods

We conducted a prospective longitudinal observational study approved by the Committee of Ethics and Research (CAEE: 01139218.9.0000.5479). We actively searched for children and adolescents who were under treatment with rhGH in the Pediatric Endocrinology Outpatient Clinic.

The patients included in the study were submitted to an evaluation in 2 different times: When selected (T0) and after 6 months (T1). If the child, at T0 or T1, presented an upper airway infection, we opted to perform the evaluation only when the respiratory disorder had completely resolved (a minimum interval of 15 days after the end of the symptoms).

The inclusion criteria were children and adolescents between the ages of 5 and 17 years old, who were being treated with rhGH over a period of more than 6 months. The exclusion criteria were patients diagnosed with or under investigation for a genetic syndrome, patients submitted to previous adenoidectomy and/or tonsillectomy, rhGH treatment stopping before the end of a 6-month period after T0 interruption of treatment with rhGH until subsequent 6 months to T0, inadequate compliance with the rhGH treatment, and grade IV palatine or pharyngeal tonsils in T0.

We used nasofibrolaryngoscopy (EF-N XION Germany), to evaluate the size of the pharyngeal tonsils utilizing the CHO Classification [11,12] in which the degree of obstruction of the pharyngeal tonsil is divided in four degrees: I (Light): 0% to 25% rhinopharyngeal obstruction, II (moderate): 25% to 50%, III (moderate-severe): 50% to 75% or IV (severe): >75%. As for the palatine tonsils, we used the Brodsky Classification [11,12]: Grade I (tonsils occupying 25% of the space between the tonsillar pillars); Grade II (tonsils occupying 25% to 50% of the tonsillar pillars); Grade III (tonsils occupying 50% to 75% of the tonsillar pillars) and Grade IV (tonsils occupying more than 75% of the space between the tonsillar pillars). The exam was recorded and analyzed independently by 3 otolaryngologists. The evaluators did not know whether the children were at stage T0 or T1 when randomly analyzing the videos.

We measured the cervical circumference, weight and height of the children and adolescents and questioned their parents about symptoms of rhinitis, such as pruritus, repeated sneezing and runny nose. The adult accompanying the child was asked to complete the OSA-18 questionnaire (validated for use in Brazil), an evaluation tool for any sleep respiratory disorder and its impact upon the quality of life [19]. It comprises 18 items grouped in 5 domains (sleep disorders, physical suffering, emotional suffering, diurnal problems and caretaker's concerns) evaluated on a scale of 1 to 7. The total score may vary from 18 to 126 points, with the impact upon the quality of life characterized as light (≤ 59 points, mode moderate (60 to 79 points) or severe (≥ 80 points).

We used the Intraclass Correlation Coefficient (ICC) and the Fleiss Kappa Index to evaluate the agreement between the three investigators who analyzed the pharyngeal tonsils through nasofibrolaryngoscopy. When there was any divergency between the evaluators, we considered the most frequent values (modal) in the analysis. We conducted a chi-squared test to evaluate the growth of the palatine and pharyngeal tonsils, comparing the data from T0 and T1. The results of the OSA-18 questionnaire at T0 and T1 in relation to its total score, as well as for each of the 5 domains, were analyzed using the General Linear Model (GLM). This test was first conducted without the insertion of the covariables, and was then repeated with age, length of GH use, BMI and cervical circumference as covariables. Category measurements are shown as the frequency or percentage and numeric measures as mean ± standard deviation. All analyses were performed with SPSS software (v. 21) and the significance level set at 5% in all analyses.

Results

The initial sample consisted of 27 children/adolescents. During follow up, there were 15 losses due to cessation or inadequate use of rhGH, as well as loss of clinical follow-up, meaning that the final sample comprised 12 patients (Figure 1). The description of the sample and its descriptive characteristics can be found on Table 1. The individual data of the 12 included patients are presented in Table 2.

The agreement between the evaluators concerning the size of the pharyngeal tonsils assessed by the nasofibrolaryngoscopy exam was adequate. In T0, the ICC was of 0.899 (excellent agreement) and the Kappa was of 0.543 (moderate agreement). In T1, the ICC was 0.958 (excellent agreement) and the Kappa was 0.731 (substantial agreement).

There were no significant associations between the size of the tonsils and the treatment with rhGH in relation to palatine and pharyngeal tonsil growth, as well as with the pharyngeal tonsils (Table 3). In the comparison of the OSA-18 questionnaires between T0 and T1, there was no statistically significant result in the absence of covariables for the general score as well as for the five domains that it comprises. When covariables were included in the analyses,
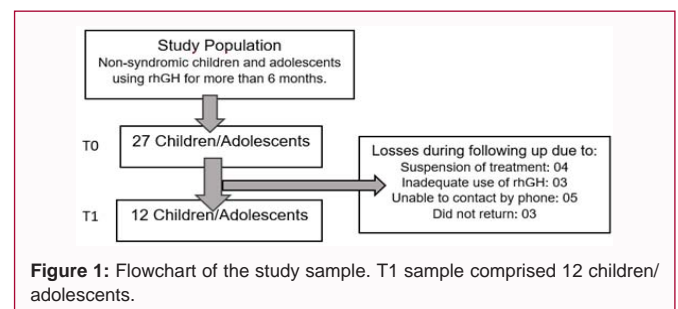
Figure 1: Flowchart of the study sample. T1 sample comprised 12 children/adolescents.

Table 1: Mean values for the continuous variables used in the study.

	CI (95%)	Mean ± SD
Age (years)	(6.0-15.0)	11.8 ± 3.0
Cervical Circumference (cm)	(18.0-68.0)	37.3 ± 15.9
Length of treatment (years)	(1.0-7.0)	3.5 ± 1.8
BMI (T0) (kg/m²)	(13.3-22.7)	18.3 ± 3.2
BMI (T1) (kg/m²)	(13.7-23.9)	18.1 ± 3.7

SD: Standard Deviation; BMI: Body Mass Index; CI: Confidence Interval

Table 2: Descriptive data for each patient.

	Age (years)	Gender	rhGH dosage (UI/kg/day)	LT (years)	BMI (kg/m^2)	Nasal Obstruction
1	15	M	0.1	7	17.6	No
2	7	M	0.1	2	13.8	No
3	11	M	0.1	3	15.3	No
4	14	M	0.1	5	19.2	Yes
5	14	M	0.1	3	22.7	Yes
6	13	M	0.1	4	22	Yes
7	6	M	0.1	2	21.3	Yes
8	10	F	0.1	6	16.4	No
9	11	F	0.1	1	16.7	No
10	13	M	0.1	4	19.2	No
11	14	F	0.1	2	21.4	No
12	9	M	0.1	3	13.3	No

LT: length of treatment; BMI: Body Mass Index; M: Male; F: Female

Table 3: Size of the pharyngeal and palatine tonsils at T0 and T1.

Patients	T0		T1	
	PT	PhT	PT	PhT
1	I	I	I	I
2	I	I	I	I
3	I	II	I	II
4	II	I	II	I
5	I	I	I	II
6	I	II	II	II
7	III	III	III	III
8	III	I	III	I
9	I	I	II	I
10	I	I	II	I
11	II	I	II	II
12	II	II	II	II

PT: Palatine Tonsils; PhT: Pharyngeal Tonsils

Table 4: Data from the OSA 18 questionnaires.

OSA 18 Domains	T0	T1
SD	6.8 ± 3.1	7.9 ± 3.1
PS	7.6 ± 3.4	8.0 ± 3.8
MS	7.2 ± 5.9	7.5 ± 6.5
DP	6.7 ± 4.0	7.2 ± 4.9
RP	5.6 ± 2.6	6.6 ± 4.6
Total	34.1 ± 11.6	37.2 ± 15.9

SD: Sleep Disorders; PS: Physical Suffering; MS: Mental Suffering; DP: Diurnal Problems; RP: Caretaker's Concerns

controlled by the patient's age, we observed statistically significant increases in the general score and in the domains relating to sleep disorders, emotional suffering, diurnal problems and the caretaker´s concerns. When controlled by the length of treatment with rhGH, we observed statistically significant increases in the general score and in the domain referring to sleep disorders. There was no influence of BMI and the cervical circumference on the results as covariables (Table 4).

Discussion

rhGH has been available as a treatment for more than 30 years [1,4,5,17], and several observational studies have shown its efficacy and short-term profile to be very favorable [4,6]. Among rhGH's side effects, a possible association with hypertrophy of the palatine tonsils has been suggested and, therefore, a routine inspection during physical examination has been recommended [7]. There are some studies identifying adeno-tonsillar hyperplasia and sleep apnea in children with PWS who have been treated with rhGH; however, there are no prospective studies in non-syndromic children relating to the palatine or pharyngeal tonsils with the use of rhGH. This was the main motivation for our study.

We evaluated the pharyngeal tonsils using a nasofibroscopy examination because it is more sensitive than Cavum Radiography (CR) [20,21]. Although CR is an objective exam, it offers a bidimensional and static reproduction of a dynamic and complex anatomical region and, therefore, relies to a great extent on subjective evaluation. In addition, the evaluation of the pharyngeal tonsil through CR is difficult due to the presence of soft tissues such as muscle and the mucous membrane in the posterior wall of the nasopharynx [20]. A study with 60 children with complaints of nasal obstruction but normal CR found that one-third of the children had pharyngeal tonsil hyperplasia, indicating the low sensitivity of CR [20]. Other difficulties with CR evaluations include bad positioning and patient movement-a small head rotation, which is particularly common in children, may produce a huge image alteration [20,22]. Therefore, CR is recommended for use as an initial exam but nasofibrolaryngoscopy is considered the gold-standard diagnostic tool in determining the size of the pharyngeal tonsil [21,22], with a sensitivity of 92% and a specificity of 71% [21]. We used CHO's Classification for the determination of the pharyngeal tonsil size as it provides four-degrees of differentiation, contrasting with other classifications [11,12], which usually only provide three. As even small alterations in size are important in the present study, we opted to use this classification.

In our study, rhGH dosage was 0.1 U/kg/day for the non-syndromic children and adolescents and it was not considered a variable in our results. A study in the USA assessing the safety of rhGH found that a dose of 0.37 mg/kg/week (equivalent to 0.10 U/kg/day) used in the treatment of children with idiopathic short stature had a safety profile equal or superior to that seen in other rhGH treated conditions and was not associated with any predictable side

effects [6]. The predictable side effects considered were intracranial hypertension, scoliosis, pancreatitis and hyperglycemia [6] and did not include adeno-tonsillar hyperplasia.

The OSA-18 questionnaire was chosen to evaluate the presence of sleep disorders and their impact on quality of life due to its proven test-retest reliability and internal consistency, and because it is considered to be a validated questionnaire [19]. The fact that the questionnaire was sometimes completed by the caretaker and not the patient was a study limitation because some children and adolescents did not sleep in the same room as the caretaker, compromising data consistency.

Although the majority of the patients did not present a sufficient score to indicate a moderate or high impact on quality of life at either T0 or T1, there was an increase in the general score of the questionnaire over the six-month period of the study in 8 patients (66.67%), suggesting that a slight worsening in the quality of life may have taken place. Although we cannot attribute this directly and exclusively to the use of rhGH, it should not necessarily be ignored; however, the drug's possible side effects were not the main object of our study. Besides, a statistically significant increase was seen in the overall score for the sleep disturbances and emotional suffering subscales of the OSA18 when controlling for covariates such as age and time under rhGH treatment. It may be considered as one effect of GH replacement on sleep microstructure, mainly in N3, however the findings should be verified in a larger trial [23].

In our study, we did not find any significant associations between the sizes of pharyngeal or palatine tonsils and rhGH treatment when patients were evaluated as a group, although individual cases where tonsil growth occurred during the analyzed period were identified, suggesting that further studies are warranted on the subject. Indeed, additional studies should be conducted examining the relationship between GH replacement and sleep microstructure.

In respect of the study's limitations, we should mention the relatively short follow up period and the small number of patients who completed the evaluation due to the high number of individuals who left the study. In addition, the inclusion of patients who were naïve to rhGH would have allowed us to evaluate whether the treatment impact is predominantly during the initial period, with a stable but increased tonsillar volume during the later phases of the treatment. The addition of a control group of children not receiving rhGH matched by age would have been helpful and is recommended in future studies.

Our results suggest that treatment with rhGH can be considered safe and beneficial for the pediatric non-syndromic population. However, the fact that this treatment can play a role in sleep and quality of life warrants careful monitoring during therapy in this population as in syndromic populations such as those with PWS.

Acknowledgment

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