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ORIGINAL ARTICLE

The Administration of Steroids and its Impact on Caspase-3 Expression in Pediatric Adenoid Hypertrophy

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Abstract

Objective Adenoid hypertrophy is a prevalent pediatric condition, often necessitating surgical intervention. Intranasal steroid administration shows promise as a conservative treatment, particularly by inducing apoptosis in adenoidal cells, leading to a reduction in adenoid size and inflammation. This study aims to characterize the expression profile of caspase-3 as an apoptotic inducer protein in inflammatory and epithelial adenoid tissues and explore its association with steroid administration.

Methods We performed immunohistochemical staining for caspase-3 proteins in adenoid tissues obtained from 51 pediatric patients aged between 2.5 and 12 years (mean age: 6.09 ± 2.1 years) who underwent adenoid surgery. A retrospective analysis of clinical data was conducted, categorizing participants into steroid treatment receivers ($n = 25$) and non-receivers ($n = 26$). Subsequently, the lymphoid inflammatory tissue and epithelial tissue from the adenoid were compared in terms of caspase-3 protein expression, and associated clinical variables were assessed.

Results Immunohistochemical analysis revealed significant caspase-3 expression in inflammatory tissues. The expression levels were scored, and no significant correlation was observed between inflammation and epithelium based on caspase-3 expression (correlation coefficient = 0.143; $p > 0.05$). Furthermore, demographic and clinical characteristics did not show a statistically significant difference in caspase-3 expression levels.

Conclusion Caspase-3 expression was significant in inflammatory adenoid tissue, but it showed no association with nasal steroid administration.

Keywords Adenoid Hypertrophy · Pediatric · Caspase-3 · Immunohistochemical · Inflammation · Epithelium

Introduction

Adenoid hypertrophy (AH), a frequent surgical indication in pediatrics, arises from the enlargement of lymphoid tissue, specifically the pharyngeal tonsils. This condition is attributed to an augmented immunologic response during early life, often triggered by chronic or recurrent upper respiratory tract infections or allergies [1, 2]. Enlarged adenoids can obstruct the nasal airway, leading to various health issues such as mouth breathing, nasal diseases, growth deficiency, asthma, speech problems, cor pulmonale, otitis media with effusion, obstructive sleep apnea, eustachian tube dysfunction, and chronic adenoidal infection [1]. The prevalence of AH varies between approximately 34–70%, depending on the study population and diagnostic criteria. Child-specific studies indicate a prevalence of 17.6% [1, 3].

Adenoid hypertrophy is a complex condition involving various cellular mechanisms that are not fully understood.

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Nevertheless, several studies have identified potential proteins that may play a role. Interleukins, particularly IL-32, have demonstrated a potential effect on the progression of AH [4]. Downregulation of the anti-inflammatory protein TIPE2 may exacerbate AH in children [5]. Heat shock protein 70 (HSP70) may play a role in the pathogenesis of AH in children [6]. While apoptosis alone cannot fully explain the pathogenesis of AH and related disorders, some studies have indicated a potential role of the apoptosis-related protein, particularly Caspase-3, in the apoptotic processes contributing to AH [7].

Adenoidectomy is a conventional measure to treat AH and relevant symptoms. However, intranasal corticosteroids, commonly referred to as nasal steroids, serve as potent anti-inflammatory medications primarily targeting inflammation within the nasal passages [8]. Their efficacy primarily lies in suppressing the immune response and inhibiting inflammatory mediators like cytokines, chemokines, and other molecules contributing to inflammation [4]. Corticosteroids exhibit the ability to modulate the delicate balance between cell survival and apoptosis, thereby contributing to the resolution of inflammation. Additionally, these medications demonstrate anti-proliferative effects on specific cell types. This anti-proliferative action becomes particularly significant in the context of inflammatory tissue, where it aids in regulating the growth and survival of cells involved in the inflammatory response. The collective evidence points to Caspase-3 (caspase-3) as a pivotal protein influencing apoptosis, survival, and proliferation [8, 9]. While the overarching role of Caspase-3 is acknowledged, the precise mechanisms underlying its functions remain incompletely understood.

Therefore, this study aims to characterize the expression profile of caspase-3 in adenoid tissues. The investigation includes examining the association between caspase-3 expression and demographic and clinical risk factors, including gender, age, cesarean section history, premature birth, and breastfeeding practices. The study also seeks to ascertain whether caspase-3 in adenoid epithelial cells can serve as a key biomarker for assessing the effectiveness of nasal steroid administration.

Methods

Study Design and Recruitment of Participants

Archival sampling was conducted to retrospectively assess clinical data related to pediatric patients who underwent adenoidectomy procedures at a distinguished otolaryngology clinic between the years 2022 and 2023.

The clinical diagnosis of AH was primarily established through a comprehensive assessment involving medical history and physical examination. Patients commonly presented with persistent symptoms, such as nasal congestion, difficulty breathing through the nose, chronic mouth breathing, snoring, sleep disturbances, recurrent ear infections, chronic sinusitis, and speech or dental issues. The physical examination included nasal endoscopy for direct visualization of adenoid size and an oral examination to identify signs of mouth breathing, such as a dry mouth and dental abnormalities. The decision to proceed with adenoidectomy was typically based on the severity and persistence of symptoms, taking into account their impact on the individual's overall health and quality of life. Adenoidectomy was recommended for cases of nasal obstruction and sleep-disordered breathing attributed to enlarged adenoids.

Subjects who had available adenoid tissue samples were appropriately included in the designated dataset. Participants meeting the inclusion criteria were then conveniently assigned to either the group receiving nasal steroids for a minimum of two months or the non-receiver group.

Certain exclusionary criteria were thoughtfully implemented to uphold the internal validity and scientific rigor of the study. Patients without a confirmed diagnosis of AH, those without a history of adenoid surgery, or cases where adenoid tissue samples were unavailable were excluded. Additionally, individuals above the age of 12 and those with incomplete clinical data were excluded. Ultimately, the study sample comprised 51 subjects, with a mean age of 6.09 ± 2.1 years. The age range spanned from 2.5 to 12 years, and the gender distribution reflected a ratio of 23 females to 28 males, specifically representing a targeted age group of children. Subsequently, the study investigated the immunohistochemical staining characteristics of caspase-3 proteins in inflammatory and epithelial adenoid tissues from these 51 patients.

Data Collection

To systematically gather demographic and clinical data regarding the subjects, we utilized an internally developed comprehensive checklist. This instrument facilitated the collection of essential information, including age, gender, steroid administration, type of birth, gestation period, and breastfeeding period. The data were acquired retrospectively, ensuring a rigorous examination of the subjects' background.

Subsequently, inflammatory and epithelial tissues, extracted from the surgical intervention sites in accordance with standardized procedures by adept otolaryngosurgeons, underwent histopathological scrutiny. These tissue samples were appropriately embedded in paraffin for subsequent

analysis. Utilizing an immunohistochemical methodology, the expression of the caspase-3 genes was meticulously assessed. Microscopic examination following immune staining allowed for the classification of protein expression into discrete categories, denoted as 0, 1, 2, or 3, thereby enabling a precise evaluation of the observed enzyme levels.

Histopathological Examination

The histopathological analysis of adenoid inflammatory and epithelial tissues serves as a valuable means to obtain comprehensive insights into the cellular and architectural attributes of the opoptotic pathway in inflammatory tissue, thereby aiding in follow-up the steroid treatment. This meticulous examination encompasses the microscopic scrutiny of tissue specimens procured from inflammatory adenoid tissue and comparing with epithelial tissue, thereby enabling the identification of distinctive morphological characteristics and molecular modifications that contribute to informed therapeutic decisions and prognostic predictions.

The process commenced with the procurement of adenoid tissue during surgical resection procedures. These tissue samples were subsequently immersed in a 10% buffered formalin solution, which served the purpose of preserving their structural integrity and preventing decay. Subsequent to fixation, the tissue underwent a series of procedural steps aimed at preparing thin sections suitable for microscopic evaluation. This entailed embedding the tissue in paraffin wax, which facilitated the creation of 4 μm thin sections through the utilization of a microtome. The resultant sections were then placed onto glass slides and subjected to staining techniques with hematoxylin and eosin (HE) to facilitate the examination and analysis of tissue morphology and immunohistochemical (IHC) staining to visualize and detect the expression of the caspas3 gene.

Immunohistochemical Staining

Caspase-3 and p53 proteins were studied by immunohistochemical staining in the adenoid tissues of the patients. For immunohistochemistry, the formalin-fixed tissue sections dewaxed in xylene and rehydrated in ethanol sections were washed with distilled water for 3 min. The sections were peroxidase-incubated for 10 min using 3% hydrogen peroxide in methanol (v/v). Subsequently, the sections were washed with distilled water for 3 min and antigen retrieval was performed for 3 min using a 0.01 M citrate buffer, pH 6.0 in a domestic pressure cooker. Sections were placed in Tris-buffered saline (TBS) containing 0.15 M sodium chloride and 0.05 M Tris-HCL pH 7.6. Sections were incubated at room temperature for 10 min with superblock (SHP125; Scy Tek laboratories, West Logan, UT 84,321). The primary antibody was diluted through a diluting solution, based on the manufacturer company instructions. After sections were incubated with the primary antibody for anti-caspase-3 (E-AB-63,602, Elabscience Biotechnology Inc, USA) diluted 1:500, anti-p53 (M00001-4, Boster Biological Technology) diluted 1:200. The sections were incubated at room temperature with a biotinylated link antibody (SHP125; ScyTek Laboratories) followed by streptavidin/HRP complex (SHP125; ScyTek laboratories). After washing with TBS for 15 min, the sections were incubated at room temperature with biotinylated link antibody (SHP125; ScyTek Laboratories) then diaminobenzidine was used to visualize peroxidase activity in tissues. Nuclei were lightly counterstained with hematoxylin, and then the sections were dehydrated and mounted. Light microscopy and scoring of immunohistochemically stained sections were performed by a pathologist, who was unaware of the patients' clinical information. Scoring for each enzyme was: 0, negative (no staining); 1, weak staining; 2, moderate staining; 3, strong staining.

Statistical Analysis

IBM SPSS Version 25.0 (Armonk, NY: IBM Corp) was used performed statistical analysis. The numerical variables describing the patients' clinical and demographic characteristics were expressed as mean ± standard error of mean (SEM). The categorized variables were described as numbers of patients (n) and percentages (%) based on descriptive statistics. The Shapiro-Wilk test was performed to assess the normality profile and the Levene test was used to the homogeneity of variances. The Mann-Whitney U test was used to compare differences between two independent groups. Chi-square test was performed to determine the association between categorical data. The relationship between data was evaluated by Spearman's rank correlation test. A p-value lower than 0.05 was considered statistically significant.

Results

The study group comprised 51 children who underwent adenoid surgery. The demographic and clinical characteristics of the patients are presented in Table 1. The study included 23 females (45.1%) and 28 males (54.9%). Among them, 21 patients (41.2%) were five years old or younger, while 30 patients (58.8%) were older than five. Steroids were administered in 25 patients (49.0%), while 26 patients (51.0%) did not receive steroids. Cesarean section was the type of birth for 26 patients (51.0%), while 25 patients (49.0%) had vaginal births. The gestation period was less than 38 weeks

Table 1 Demographic and clinical characteristics of the patients

Variables	Category	Number (%)
Gender	Female	23 (45.1%)
	Male	28 (54.9%)
Age (years)	≤ 5	21 (41.2%)
	> 5	30 (58.8%)
Steroid usage	Yes	25 (49.0%)
	No	26 (51.0%)
Type of birth	Cesarean section	26 (51.0%)
	Vaginal birth	25 (49.0%)
Gestation period	< 38 weeks	12 (23.5%)
	≥ 38 weeks	39 (76.5%)
Breastfeeding period	< 12 months	26 (51.0%)
	≥ 12 months	25 (49.0%)

The results were expressed as number and percentage (%)

Table 2 Caspase-3 expression levels of the tissues

Level	Inflammation	Epithelium
0	27/51[a] (52.9%)	45/51[a] (88.2%)
1	24/51[a] (47.1%)	6/51[a] (11.8%)
Mean	0.47 ± 0.07 [b] (0–1)[c]	0.12 ± 0.05 [b] (0–1)[c]

Staining scores were determined according to the staining intensity of the tissues. 0: negative staining, 1: positive staining. a: Number of samples stained at specified level / Total number of samples (percent), b: Mean staining level ± SEM, c: The lowest staining level – The highest staining level

in 12 patients (23.5%), whereas it was 38 weeks or longer in 39 patients (76.5%). Regarding breastfeeding, 26 patients (51.0%) were breastfed for less than 12 months, while 25 patients (49.0%) were breastfed for 12 months or longer.

The overall depiction of the images derived from the microscopic examination of the prepared tissue samples in the immunohistochemical analysis is presented in Fig. 1. The protein expression analyses conducted based on these visual data were scored according to the intensity of expression.

Immunohistochemical analysis was conducted on the tissues to evaluate Caspase-3 expression, and the results are presented in Table 2. Expressions were assessed in both inflammatory and epithelial tissues. Overall, 45.09% of the inflammatory tissues showed positive expression, significantly higher than the 11.8% observed in the epithelium ($p = 0.0001$).

Caspase-3 expression in the tissues was illustrated by categorizing them into inflammation and epithelium, as depicted in Fig. 2. No significant correlation was observed

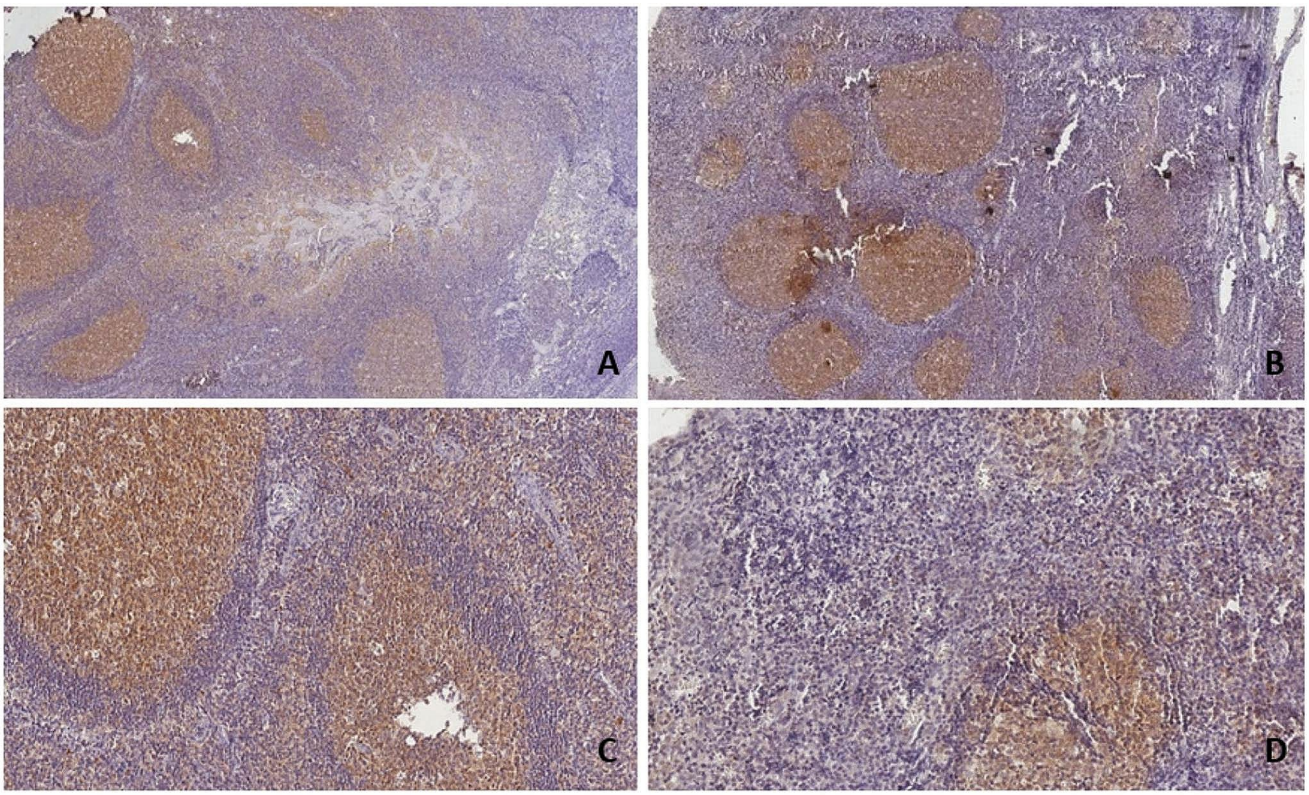


Fig. 1 General images of Caspase 3 enzyme expressions in the tissues were observed during the immunohistochemical analysis phase. **A**: Microscopic image of Caspase3 expression in a patient without steroid treatment (4x), **B**: Microscopic image of Caspase3 expression in a steroid-treated patient (4x), **C**: Microscopic image of Caspase3 expression in a patient without steroid treatment (20x), **D**: Microscopic image of Caspase3 expression in a steroid-treated patient (20x),

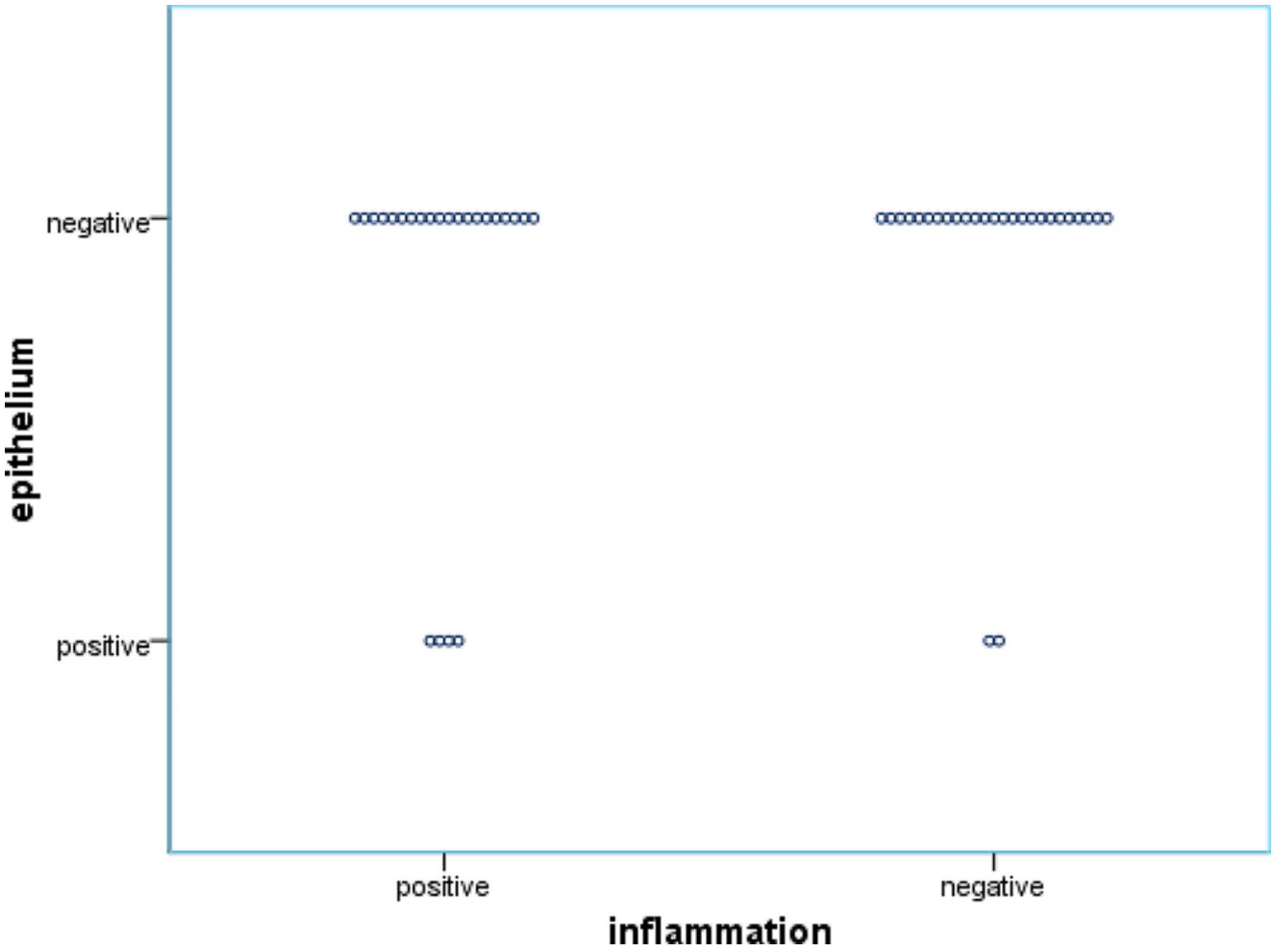


Fig. 2 Dot-plot graph of caspase-3 expression pattern

between inflammation and epithelium based on caspase-3 expression (correlation coefficient = 0.143; $p > 0.05$).

The expression levels of caspase-3 were analyzed based on the demographic and clinical characteristics of the patients, and the results are presented in Table 3. Caspase-3 expression was higher in males than females in both inflammatory and epithelial cells. Higher caspase-3 expression in both inflammatory and epithelial cells was observed in patients treated with steroids compared to those not treated. In inflammatory cells, caspase-3 expression was higher in patients born by cesarean section than vaginal birth, with a similar pattern noted in epithelial cells. Additionally, caspase-3 expression in inflammatory cells was higher in patients with a gestational age of fewer than 38 weeks. Expression of caspase-3 in inflammatory cells was greater in patients with a breastfeeding period of less than 12 months, while a similar pattern was found in the epithelium. However, no statistically significant difference was found in any group ($p > 0.05$).

Discussion

Caspase-3 is a critical mediator of programmed cell death, known as apoptosis, and functions as a significant marker of this process. It plays a key role in the cleavage of various essential cellular proteins, ultimately inducing characteristic morphological changes in apoptotic cells [9].

Caspase-3 expression levels in inflammatory adenoid tissue have been explored in a limited number of studies. In adenoid cystic carcinoma (ACC) of the salivary glands, immunohistochemical analysis revealed cytoplasmic expression of caspase-3 in tumor cells with varying staining intensities. Notably, no correlation was observed between caspase-3 expression and clinicopathological parameters of adenoid cystic carcinoma [10]. Although specific expression levels of caspase-3 in adenoid tissues are not explicitly detailed in the literature, it is implicated in the regulation of cell death and inflammation across various contexts. Moreover, the documented ability of steroids to induce apoptosis in adenoid cells suggests an anticipated

Table 3 The expression levels of caspase-3 based on the demographical and clinical characteristics

Variable	Inflammatıon	epıthelIUM
Gender		
Female	0.43 ± 0.11 [a] (0–1)[b]	0.09 ± 0.06 [a] (0–1)[b]
Male	0.50 ± 0.10 [a] (0–1)[b]	0.14 ± 0.07 [a] (0–1)[b]
p-value	*0.646*	*0.542*
age		
≤ 5	0.43 ± 0.11 [a] (0–1)[b]	0.14 ± 0.08 [a] (0–1)[b]
> 5	0.50 ± 0.09 [a] (0–1)[b]	0.10 ± 0.06 [a] (0–1)[b]
p-value	*0.618*	*0.643*
Steroid usage		
Yes	0.56 ± 0.10 [a] (0–1)[b]	0.16 ± 0.07 [a] (0–1)[b]
No	0.38 ± 0.10 [a] (0–1)[b]	0.08 ± 0.05 [a] (0–1)[b]
p-value	*0.214*	*0.362*
Type of birth		
Cesarean section	0.54 ± 0.10 [a] (0–1)[b]	0.12 ± 0.06 [a] (0–1)[b]
Vaginal birth	0.40 ± 0.10[a] (0–1)[b]	0.12 ± 0.07 [a] (0–1)[b]
p-value	*0.327*	*0.960*
Gestation period		
< 38 weeks	0.58 ± 0.15 [a] (0–1)[b]	0.08 ± 0.08 [a] (0–1)[b]
≥ 38 weeks	0.44 ± 0.08 [a] (0–1)[b]	0.13 ± 0.05 [a] (0–1)[b]
p-value	*0.376*	*0.676*
Breastfeeding period		
< 12 months	0.54 ± 0.10 [a] (0–1)[b]	0.12 ± 0.06 [a] (0–1)[b]
≥ 12 months	0.40 ± 0.10[a] (0–1)[b]	0.12 ± 0.07 [a] (0–1)[b]
p-value	*0.327*	*0.960*

Staining scores were determined according to the staining intensity of the tissues. 0: negative staining, 1: positive staining. a: Mean ± SEM, b: The minimum-the maximum

significant differentiation in caspase-3 expression in inflammatory lymphoid tissue. The evidence in the current study also demonstrates a differentiation in caspase-3 expression levels in inflammatory lymphoid tissues. This suggests that caspase-3, with its role in regulating inflammation, may also play a role in the pathogenesis of AH.

Allergy and adenoid hypertrophy commonly coexist as conditions. Risk factors for allergies, including cesarean section, premature birth, and inadequate breast milk, may indirectly contribute to AH. The association of these relevant risk factors with the expression level of caspase-3, a marker of apoptosis, emphasizes the intricate relationship between these factors and AH. In evaluating steroid therapy, it becomes essential to recognize and address these factors for a comprehensive understanding of the patient's condition and to optimize the effectiveness of the treatment approach [11–14].

The literature suggests that steroid treatment, particularly intranasal steroids, may be effective in managing AH and its associated symptoms. A study reported a significant improvement in nasal obstruction symptoms in children with AH treated with nasal steroids [15]. Another study demonstrated the efficacy of intranasal steroids (mometasone furoate) over six weeks in alleviating pediatric chronic nasal obstruction caused by AH [16]. In a controlled clinical trial, the use of intranasal steroids (fluticasone propionate) post-adenoidectomy was found to prevent the recurrence of AH and related symptoms [17]. Furthermore, a study investigating short-term oral corticosteroid treatment in pediatric sleep-disordered breathing and AH suggested its potential efficacy in addressing AH due to its inflammatory-related background [2].

Intranasal steroid administration affects adenoid cells in general. Therefore, the hypothesis that caspase-3 expression levels in epithelial cells, which are easier to reach, may provide insight into the effectiveness of steroid treatment has been considered. Despite solid evidence of inducing caspase-3 expression in inflammatory tissues, the idea of follow-up through epithelial cells is not supported by the results, as no correlation of caspase-3 expression was found between inflammatory and epithelial tissues. Regarding the expression of caspase-3 in the epithelium tissue of the adenoid, the literature does not provide specific information. On the other hand, there is evidence that caspase-3 expression may not be correlated with the apoptotic index [18].

This study has several limitations, with the most notable being the relatively small sample size, potentially limiting the generalizability of the results to a broader population. It is crucial to recognize that our investigation represents an initial exploration into this area, and the smaller sample size was chosen to balance feasibility and resource constraints. A significant limitation is that the study does not provide information on the exact expression levels of caspase-3 in adenoid tissues, which would be valuable in understanding the potential impact of caspase-3 on inflammation and cell death.

Despite these limitations, the study offers valuable insights into the expression of caspase-3 in adenoid tissue samples and its correlation with various demographic and clinical parameters. Further research is warranted to comprehensively understand the intricate relationship between caspase-3 expression and clinicopathological parameters in the context of AH.

Conclusion

Caspase-3 was significantly expressed in inflammatory adenoid tissue. However, this expression was not associated with nasal steroid administration or demographic and clinical risk factors, including age, gender, cesarean section, gestational age, and breastfeeding practices. Therefore, the study suggests that caspase-3 expression may not be a reliable biomarker for assessing the success of steroid treatment in pediatric adenoid hypertrophy.

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Author Contributions EA, SO, YH, PK: Conceptualization, Methodology, Formal analysis. SYS: Data management. OD, GŞ: Graphical design. AAH, SO: Writing, Reviewing and Editing. All authors have read and approved the manuscript.

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Data Availability The authors confirm that all data supporting the finding of the study are available within the article, and the raw data supporting the findings were generated and available at the corresponding author on request.

Declarations

Ethics Approval and Consent to Participate Ethics committee approval was received for this study from the IRB Health Sciences University Ankara Atatürk Sanatorium Training and Research Hospital (No: 2012-KAEK-15/2254). The participant received detailed explanations about the study, and written informed consents were obtained. The study was designed and conducted according to relevant ethical regulations and was performed with respect to the Declaration of Helsinki and its later amendments.

Consent for Publication Not applicable.

Competing Interests The authors have no conflict of interest to declare.

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