



# Glucocorticoid Receptor Expression in Torus Tubarius Hypertrophy Tissue Causing Secretory Otitis Media in Children

Zhi-Pan Teng, Qi Li\*, Xiao-Fei Shen\*

Department of Otorhinolaryngology, Children's Hospital of Nanjing Medical University, 72 Guangzhou Road, Nanjing, Jiangsu Province 210008, China

## ABSTRACT

**Background:** Torus Tubarius Hypertrophy (TTH) after adenoidectomy causing nasal obstruction, recurrent snoring, sleep apnea, or mouth breathing has been reported more and more recently, partial resection of TTH conducted by a low-temperature plasma technique is a safe and effective therapy and some benefit from intranasal steroid therapy. However, the expression of Glucocorticoid Receptor (GCR) in TTH tissue is currently unknown and no paper reported secretory otitis media caused by TTH.

**Objectives:** To assess the expression patterns of the human GCR in TTH tissue in children and report secretory otitis media caused by TTH.

**Methods:** 5 children from Jan to Jun 2024 were included in this study. All children underwent partial resection of TTH and TTH tissues were collected for immunofluorescence.

**Results:** GCR- $\alpha$  and GCR- $\beta$  were both expressed in TTH tissues in 5 children, the expression of GCR- $\alpha$  was significantly higher than GCR- $\beta$ . Since it has been reported that the high expression of GCR- $\alpha$  is correlated to glucocorticoid therapy sensitivity, the glucocorticoid therapy may be curative to TTH in children.

**Conclusion:** TTH after adenoidectomy were reported more often in recently, partial resection of TTH operation conducted by a low-temperature plasma technique under general anesthesia is a safe and effective therapy, intranasal corticosteroids could be an alternative solution of TTH. However, the function of GCR in children with TTH still requires further investigation.

**Keywords:** Torus Tubarius Hypertrophy (TTH); Glucocorticoid Receptor (GCR); Children; Glucocorticoid therapy; Adenoidectomy; Corticosteroids; Anesthesia

## INTRODUCTION

Adenoidectomy conducted by a low-temperature plasma technique is one of the most curative operations in children with adenoid hypertrophy causing sleep-disordered breathing symptoms (nasal obstruction, snoring, sleep apnea, or mouth breathing) [1,2]. TTH after adenoidectomy is reported more often in recently, partial resection of TTH conducted by a low-temperature plasma technique is a curative therapy for TTH, whereas some benefit from intranasal steroid therapy [3-5]. However, the expression of GCR in TTH is currently unknown.

This study is to assess the expression patterns of the human GCR in TTH in children with adenoidectomy and reported TTH could cause secretory otitis media in children.

## MATERIALS AND METHODS

### Tissue preparation

This study was approved by the Ethics Committee of Children's Hospital of Nanjing Medical University. Informed consents were

**Correspondence to:** Qi Li, Department of Otorhinolaryngology, Children's Hospital of Nanjing Medical University, 72 Guangzhou Road, Nanjing, Jiangsu Province 210008, China, E-mail: liqi71520@hotmail.com

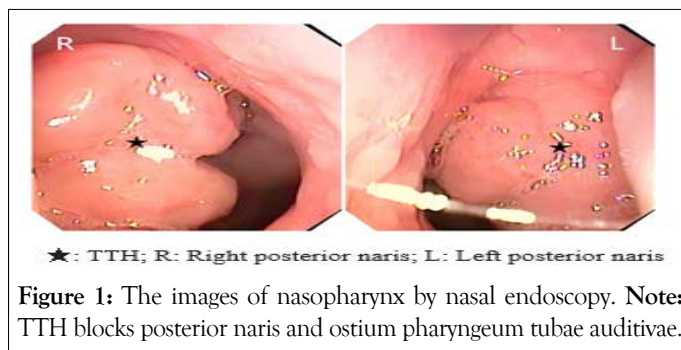
Xiao-Fei Shen, Department of Otorhinolaryngology, Children's Hospital of Nanjing Medical University, 72 Guangzhou Road, Nanjing, Jiangsu Province 210008, China, E-mail: flyfly1205@126.com

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obtained from the guardians of participants. From Jan to Jun 2024, 5 children with TTH identified by nasal endoscopy at our institution, TTH caused recurred obstructive sleep apnea in 2 cases, secretory otitis media in 1 cases and both in 2 children (Figure 1). All 5 cases underwent partial resection of TTH performed by a low-temperature plasma technique under general anesthesia, 3 children underwent auripuncture or grommet insertion and TTH tissues were collected and fixed in 4% formalin, then stored at 4°C for processing.



**Figure 1:** The images of nasopharynx by nasal endoscopy. **Note:** TTH blocks posterior naris and ostium pharyngeum tubae auditivae.

### Immunofluorescence

The following sections detail the key steps of the immunofluorescence protocol applied to TTH tissue samples:

**Frozen section fixation:** Frozen section is baked at 37°C for 10-20 min and fixed in fixed solution for 30 min, washed in Phosphate Buffered Saline (PBS) (pH 7.4) on decolorizing shaking table for 3 times, 5 min each time.

**Antigen repair:** During the repair process, the buffer should be prevented from excessive evaporation. After repair, cool naturally. The slide was placed in PBS (pH 7.4) and washed by shaking on the decolorizing shaker for 3 times, 5 min each time.

**Sealing with serum in a circle:** After the section is slightly dried, add blocking solution and seal it for 30 min.

**Add the mixed reagents of the first and second primary antibodies:** The mixed configurations of the two different sources of primary antibodies are added to the prepared primary

antibodies and the slices are placed flat in a wet box at 4°C and incubated overnight.

**Plus secondary antibody:** Add the corresponding secondary antibody and incubate at room temperature for 50 min away from light.

**DAPI restaining nuclei:** Add 4,6-Diamidino-2-Phenylindole (DAPI) dye solution and incubate at room temperature away from light for 10 min.

**Quenched tissue autofluorescence:** Add quenching agent B solution for 5 min and rinse with water for 10 min.

**Sealing tablets:** anti-fluorescence quenching sealing tablets.

**Image acquisition:** DAPI excitation wavelength 330-380 nm, emission wavelength 420 nm; The excitation wavelength of 488 is 465-495 nm and the emission wavelength is 515-555 nm. The excitation wavelength of CY3 is 510-560 nm and the emission wavelength is 590 nm. The excitation wavelength of CY5 is 608-648 nm and the emission wavelength is 672-712 nm.

### Software

The software of Aipathwell by Servicebio was used to analyse the results of immunofluorescence.

## RESULTS

### Demographics

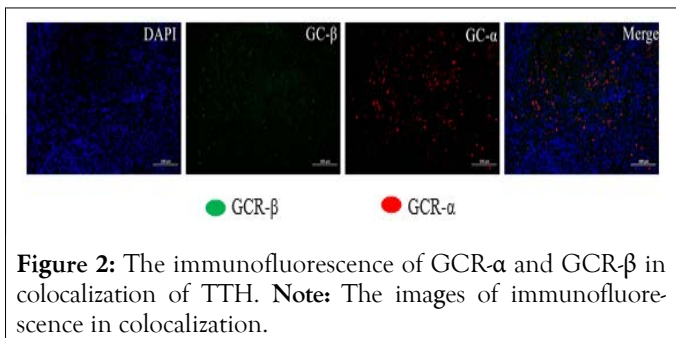
Of the 5 patients with TTH, 4 boys and 1 girl. The age of TTH ranged from 64-138 months and the age of first operation ranged from 28-78 months, only 1 child was diagnosed with Allergic Rhinitis (AR), 3 children underwent adenoidectomy and 2 underwent adenoidectomy along with tonsillectomy.

### Immunofluorescence

DAPI channel nuclei are blue, channel 488 positive is green, CY3 positive is red and CY5 positive is pink. GCR-α is red and GCR-β is green. The colocalization red or green mean density were summarized in Table 1 and the images of TTH immunofluorescence were shown in Figure 2.

**Table 1:** Summary of results of the colocalization red or green mean density.

Items	First operation age (months)	Sex	Allergic Rhinitis (AR)	Colocalization red mean density	Colocalization green mean density
1	70	M	N	0.6802	0.0752
2	49	F	N	0.6458	0.0749
3	28	M	N	0.6926	0.1119
4	60	M	N	0.539	0.0912
5	78	M	Y	0.5061	0.1048



## DISCUSSION

The torus tubarius is the projecting posterior lip of the pharyngeal opening of the Eustachian tube, which forms the lateral border of nasopharynx [6]. Kim et al., first reported TTH after adenoidectomy in children [4]. Yang et al., and Teng et al., shared experiences of surgical treatment of TTH [3,5]. They all believed that TTH was more likely to happen in male children and in patients who took adenoidectomy before 5 years old [3-5]. All of them reported TTH causing sleep-disordered breathing symptoms, TTH could block the ostium pharyngeum tubae auditivae causing conductive hearing loss, we were first time to report secretory otitis media caused by TTH. Yang et al., and Teng et al., also introduced intranasal steroid therapy for TTH, but both could not give reasonable evidences [3,5].

Under normal physiological conditions, GCR is primarily localized in the cytoplasm and exists as GCR- $\alpha$  isoform and the GCR- $\beta$  isoform. Glucocorticoids exert their biological effects primarily through binding to GCR- $\alpha$  [7,8]. GCR- $\beta$  does not bind glucocorticoids and mainly interacts with DNA. However, recent studies have shown that GCR- $\beta$  has antagonistic effects on GCR- $\alpha$  [9]. GCR expression is important for glucocorticoids to exert their effects. Many clinical studies have indicated that the density of GCR- $\alpha$  and its affinity for glucocorticoids is positively correlated with glucocorticoid therapy efficacy [8,10]. Previous studies have shown that the expression level of GCR- $\alpha$  in adenoid tissues of Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS) children was significantly higher than that in non-OSAHS children [11,12]. And some articles found that intranasal steroid therapy would reduce the adenoid mass to improve the symptoms of obstructive sleep apnea [13-17]. In our study, the expression of GCR- $\alpha$  in TTH was significant high than GCR- $\beta$ , the ratio of GCR- $\alpha$  and GCR- $\beta$  was 5:1 to 9:1, high expression of GCR- $\alpha$  was a potential evidence for glucocorticoid therapy for TTH.

## CONCLUSION

GCR- $\alpha$  and GCR- $\beta$  were both expressed in TTH tissues in children and the high expression level of GCR- $\alpha$  may be an important factor affecting the sensitivity of TTH to glucocorticoid therapy in children. The limitation of the study is we could not obtain torus tubarius tissues from normal children for obvious ethical reasons, therefore we could not compare GCR expression levels between TTH tissue and normal torus tubarius tissue. Thus, randomized controlled trials of intranasal

steroids should be conducted in children with symptomatic snoring caused by TTH to delineate better the role and optimal duration of this therapeutic modality.

## FUNDING

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## ETHICS STATEMENT

This study was approved by the Ethics Committee of Children's Hospital of Nanjing Medical University. Informed consents were obtained from the guardians of participants

## AUTHORS CONTRIBUTIONS

Zhi-Pan Teng contributed to the acquisition and interpretation of data and drafted the manuscript.

Qi Li contributed to the design of the study, performed statistical analyses and critically revised the manuscript.

Xiao-Fei Shen contributed to the study design, provided critical feedback on the manuscript and supervision of the study.

## CONFLICT OF INTEREST

There is no potential conflict of interests of this manuscript.

## DATA AVAILABILITY STATEMENT

The data are available from the corresponding author on reasonable request.

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