CASE REPORT
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Tonsillar Hypertrophy in Goltz-Gorlin Syndrome: Case Report and Literature Review

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ABSTRACT

Goltz-Gorlin syndrome, also known as focal dermal hypoplasia or nevoid basal cell carcinoma syndrome, is a rare multisystemic disease caused by autosomal dominant mutations in the *PORCN* gene. The characterizing features are keratocystic odontogenic tumors in the jaw, multiple basal cell carcinomas, calcification of the falx cerebri, palmar or plantar pits, and skeletal abnormalities. This paper reports the case of a 3-year-old girl with Goltz-Gorlin syndrome, showing progressively increasing tonsillar hypertrophy with obstructive effect on the oropharynx. The lymphatic tissue was remarkably papillomatous in aspect. Pathologic examination after tonsillectomy showed hyperplastic, morphologically normal tonsillar tissue, without arguments for papilloma, active inflammation, or malignancy. This paper highlights the rare manifestations of ENT pathologies in GGS which demand attention early on and long-term follow-up.

Keywords: Goltz-Gorlin syndrome, focal dermal hypoplasia, nevoid basal cell carcinoma syndrome, tonsillar hypertrophy, obstructive sleep apnea syndrome

Case Presentation

A 4-month-old girl was referred to the medical genetics clinic of the Antwerp University Hospital (UZA). The perinatal history of the child was uneventful, but soon after birth some remarkable skin lesions and abnormalities in facial structure were noticed. The girl showed hypoplastic pinnae with attached earlobes, hypoplastic finger nails with grooved aspect, and two skintags on the fingers. In addition, the clinical eximantion revealed a midline lip notch, an anteriorly dislocated anus, and a hairy sacral region. She also presented syndactyly of the first-second and third-fourth ray of the right foot along with ectrodactyly of the third ray. Radiography showed multiple lucencies in the mandible, but no calcification of the falx cerebri or rib anomalies. Cardiac echocardiography revealed a pulmonary valve stenosis. Ophtalmological exam was normal. The girl displayed two of the major criteria for Goltz-Gorlin syndrome (GGS), namely keratocystic odontogenic tumors and palmar pits. Genetic investigation showed a pathologic variant of the *PORCN* gene (c.137-1 G>C) and the clinically suspected diagnosis of GGS was confirmed. The girl was referred to the ENT department at the age of 6 months to exclude papillomatous lesions in the upper airway. Clinical ENT examination including fiberendoscopy was unremarkable at first presentation and during the initial follow-up. Meanwhile, the child grew up with recurrent upper airway infections and failure-to-thrive. Since she had repeated episodes of acute otitis media at the right ear, a ventilation tube was inserted at the age of 2. While under general anesthesia, a direct laryngoscopy was performed allowing for a thorough examination of the upper airway. This examination showed lymphoid hyperplasia on the palatine tonsils reaching toward the tongue base. The mucosa of the tonsils was papilloma-like and compressed the epiglottis during inspiration. A papillomatous lesion at the posterior part of the uvula was noticed. The subglottic area and lower trachea were free of papilloma-like lesions. A polysomnography was requested to exclude obstructive sleep apnea syndrome. This examination showed a normal sleeparchitecture, absence of snoring and an obstructive apnea-hypopnea index of 0.5/h. During follow-up, at the age of 3 years, progressively increasing tonsillar hypertrophy with an obstructive effect on the oropharynx was noticed. An indication for adenotonsillectomy was established. Before the start of the procedure, a drug-induced sleep endoscopy was performed. This examination showed

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laterolateral compression of the oropharynx by the hypertrophic papillomatous tonsils (Figure 1). The papillomatous lesion at the posterior part of the uvula had disappeared. The tonsillar tissue was sent for pathologic evaluation (Figure 2). This showed hyperplastic, morphologically normal tonsillar tissue, typical of chronic inflammation. There were no arguments for papilloma, active inflammation, or malignancy. The postoperative evolution was slow but steady, with initially low intake. In the weeks after the surgery, the parents noticed an increased hypernasal speech and nasal regurgitation while drinking, but this was of temporary character. At 1 month postoperatively, the parents reported an improvement in food intake and adequate weight gain.

Discussion

Goltz-Gorlin syndrome (GGS) is an autosomal dominant disorder with a high level of penetrance and variable expression. A loss-of-function mutation in the *PORCN* gene causes abnormalities in tissues of ectodermal and mesodermal origin such as bones, skin, teeth, nails, ears, and eyes.[1] The most typical features are keratocystic odontogenic tumors in the jaw, multiple basocellular carcinomas (BCC), and skeletal abnormalities.[2] In addition to this triad, calcification of the falx cerebri, palmar and plantar pits, spine and rib anomalies, relative macrocephaly, facial milia, frontal bossing, ocular malformation, and cleft lip and/or palate are also found.[3] Since the syndrome can present with a myriad of symptom combinations, the diagnosis is often challenging and can be apparent only after decades of life. Kimonis et al.[4] developed several major and minor diagnostic criteria, on which the tentative diagnosis is now commonly made. The major criteria are basocellular carcinomas, keratocystic odontogenic tumors, palmar and/or plantar pits, and ectopic calcifications of the falx cerebri. A summary of the major and minor criteria of GGS is listed in Table 1. In patients with few apparent anomalies, the oral manifestations will most commonly lead to the clinical diagnosis of this condition. This can be explained by the appearance of keratocystic odontogenic tumors in 75-100% of patients with GGS and their very high recurrence rate.[5] Therefore, an important role is reserved for dentists, since routine radiographic exams can show odontogenic tumors in patients with otherwise mild expression of the syndrome. Firm proof of the diagnosis, however, has to be made by molecular genetic testing.

Otolaryngological manifestations of the syndrome are rare. We found only a few reports in literature, mainly case reports were on adults or teenagers with GGS. To the best of the authors' knowledge, we present the youngest patient with

Main Points

- Goltz-Gorlin syndrome can present with a myriad of clinical symptoms, ranging from mild to severe, and tentative diagnosis is based on several major and minor diagnostic criteria.
- ENT-related symptoms include tonsillar hypertrophy with obstructive sleep apnea syndrome, ossicular chain abnormalities, odontogenic keratocysts, and basocellular carcinoma in the head and neck region
- Early recognition and appropriate follow-up of ENT features contribute to improved patient care.

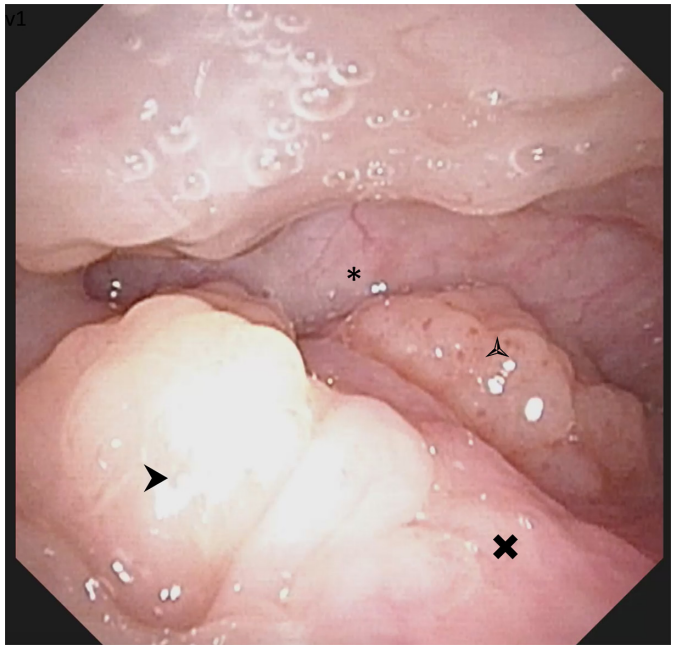

Figure 1. Clinical image during drug-induced sleep endoscopy before tonsillectomy. * = posterior pharyngeal wall, ✖ = soft palate, ➤ = papillomatous lesion on back side of the soft palate/uvula, ⅄ = left tonsil with papillomatous appearance.

ENT manifestations. The most commonly reported symptoms are periorificial papillomatae and conductive hearing loss, possibly caused by Eustachian tube dysfunction or abnormalities in the ossicular chain. Knöbber et al.[6] described the first case of a 21-year-old female patient with GGS in which anomalies of the stapes and incus of one ear were described. Our patient presented with conductive hearing loss at the age of 2, but this was attributed to the recurrent otitis media. Otitis media is highly prevalent at this age and hearing thresholds normalized following ventilation tube placement. Three studies discuss basocellular carcinoma in GGS. In the case by Lobo et al. the patient presented with a BCC in the right external auditory canal, treated by a nearly circumferential excision up to the tympanic membrane.[7] Another patient with a BCC of the ear was discussed by Lasso et al. The tumor originated from the temporal region and involved the middle ear, the intrapetrous part of the facial nerve and the dura mater. Resection required extensive use of local and free

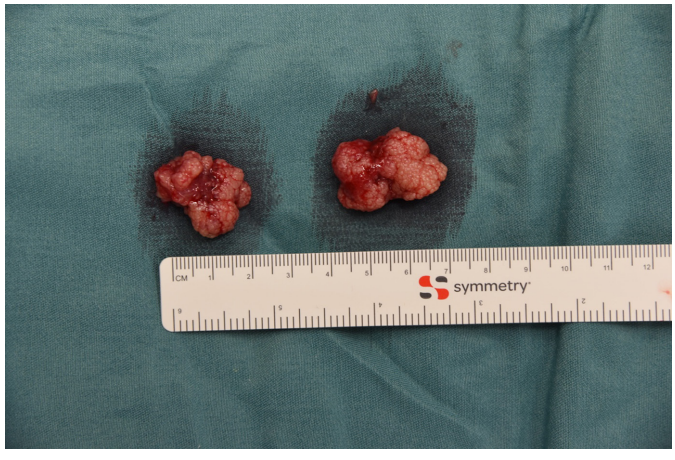

Figure 2. Tonsillar tissue after removal.

Table 1. Major and Minor Diagnostic Criteria of Goltz-Gorlin Syndrome

Major Criteria	Minor Criteria
Keratocystic odontogenic tumors	Macrocephaly
Multiple basal cell carcinomas (before the age of 30)	Cleft lip and/or palate
Calcification of falx cerebri	Vertebral and/or rib anomalies
Palmar or plantar pits	Polydactyly
First-degree relative with Goltz-Gorlin syndrome	Ovarian or cardiac fibromas
	Ocular anomalies
	Childhood medulloblastoma
	Lympho-mesenteric or pleural cysts

flaps.[8] A patient with a BCC of the left upper eyelid was presented by Tabuchi et al. Even after left orbital exenteration, a local recurrence several years later involved the ethmoid sinus. Treatment involving external ethmoidectomy, partial maxillectomy, and postoperative radiotherapy were successful.[9] Grundig et al.[10] reported a case of severe obstructive sleep apnea syndrome in a 16-year-old female patient with GGS. However, this obstructive pattern was caused by severe retrognathia, rather than by tonsillar hypertrophy. Mandibular advancement surgery cured the obstructive sleeping pattern. Papillomatous lesions of the larynx and hypopharynx were described by Gordjani et al[11] and Holzman et al. In the former article, obstructive lesions were found in a 14-year-old patient complaining of progressive dysphagia, hoarseness, and inspiratory stridor. A subtotal endoscopic laser resection of the lesion proved to be effective and histological examination also did not show morphological signs of human papilloma virus. The latter article described a case of a 13-year-old girl with GGS, who underwent an unrelated surgical procedure during which partial upper airway obstruction was noted. Direct laryngoscopy showed verrucous lesions in the hypopharynx and on the lingual surface of the epiglottis. Histologic examination showed lymphoid tissue with occasional expanded germinal centers.[12]

Early recognition of the syndrome is important because of the tendency to develop tumors, possibly with malignant potential.[13] Rigorous sun protection should be initiated at young age to avoid development of basocellular carcinomas. Moreover, in treating other tumors, radiotherapy should be avoided as much as possible since it can potentiate malignant changes in the nearby tissue.[14] A multidisciplinary approach is advocated for the diagnosis and treatment of patients with Goltz-Gorlin syndrome.[15] As the condition can exhibit both minor and major criteria (Table 1), it is important to address all anomalies to improve quality of life. Regarding the ENT manifestations of the disease, yearly clinical check-up is recommended.

Informed Consent: Informed consent was not required because the photographs do not allow for identification of the patient.

Peer-review: Externally peer-reviewed.

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