International Journal of Pediatric Otorhinolaryngology 77 (2013) 1606–1608

Contents lists available at SciVerse ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl

Case report

Vomer aplasia in a patient carrying a de novo mutation of the TP63 gene (3q27)

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ARTICLE INFO

Article history:
Received 11 April 2013
Received in revised form 26 June 2013
Accepted 30 June 2013
Available online 29 July 2013

Keywords:
Vomeral bone
Ossification
EEC
Clefting
P63 gene
Nasal septum

ABSTRACT

The congenital vomer defect (CVD) is a rare and still partially unknown condition. Only few cases have been reported in the international literature and the large majority of them appeared to be isolated. We report a case of CVD detected in a 7-year-old girl affected by ectodermal dysplasia clefting syndrome caused by a mutation of the *TP63* gene.

1. Introduction

Congenital defect of nasal septum is very uncommon and may comprise a broad spectrum of different types of malformations ranging from a minor alar cleft to a congenital vomeral defect (CVD) [1]. This latter is an extremely rare condition, characterized by a defect of the postero-inferior half of the nasal septum that was first described by Mohri and Amatsu [2] in 2000. Until now only a few cases of CVD have been reported [1–8] and the large majority of them appear to be isolated. Only Verim et al. [8], examining the patients' immediate relatives through laboratory test, endoscopic and radiological examinations, detected the hereditary nature of the vomer defect. Even if a gene profile analysis was not performed, the authors speculated that this condition could be a multifactorial hereditary disease.

In this report we present a case of congenital vomeral defect of the septum detected during nasal endoscopy in a 7-year-old girl affected by ectodermal dysplasia clefting (EEC) syndrome caused by a mutation of the *TP63* gene (3q27) encoding the p63 transcription factor that is essential for ectoderm and limb development. To the best of our knowledge, no previous studies reported the CVD among the orofacial abnormalities associated with EEC. Thus, this report may serve as a useful reminder to anyone caring for someone with this rare condition.

2. Case report

A 7-years-old girl followed by the Pediatric Department of our hospital because affected by EEC syndrome, was admitted to the Department of Otolaryngology Head and Neck surgery of our hospital with a complaint of nocturnal snoring associated with recurrent episodes of acute otitis media. The patient phenotype was characterized by dry, light skin, hyperpigmented and wrinkled in the periorbital region. Hair of the scalp were fine in texture and lighter in color and the lower eyelids of both sides showed sparse eyelashes. She had a few dental agenesis and conical teeth. Sweat glands and nails were normal. Syndactyly of the first and second finger of the right hand and ectrodactyly of the third and fourth toes of the left foot were present at birth and were surgically treated at the age of 4 years. Otolaryngological examination revealed a bifid uvula. Finger palpation of the palate, fiberoptic evaluation of palatal elevation and search for velo-pharyngeal insufficiency did not demonstrated any signs of submucous cleft palate. The anterior displacement of anus was also present at birth.

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http://dx.doi.org/10.1016/j.ijporl.2013.06.027

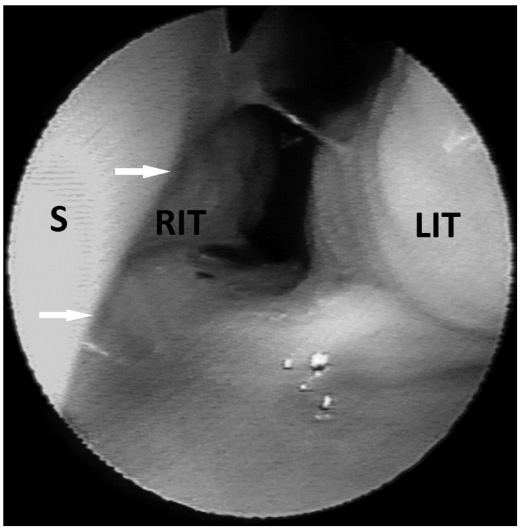

Fig. 1. Endoscopic view of the septal defect. S, septum; RIT, right inferior turbinate; LIT, left inferior turbinate. The white arrows indicate the posterior margin of the nasal septum.

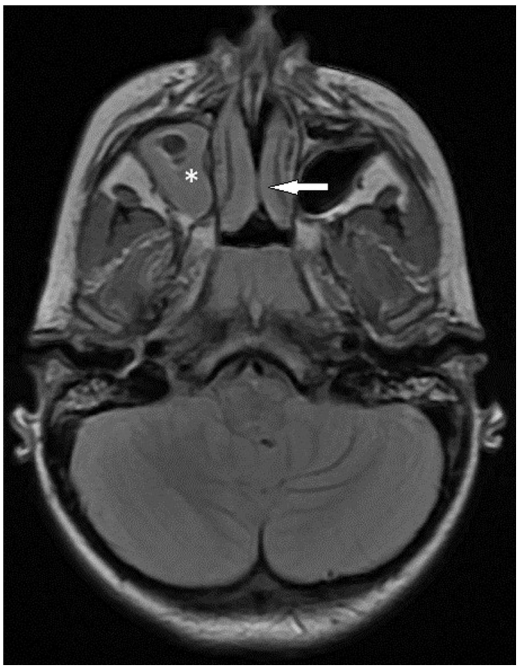

Fig. 2. Magnetic resonance of the maxillofacial region showed the aplasia of the vomeral bone (arrow) with a concurrent sinusitis (*).

The molecular study showed a de novo point mutation of the *TP63* gene leading to a substitution of the amino acid residue R204 localized in the DNA binding domain of the gene.

Diagnostic nasal endoscopy, performed in order to evaluate the presence of adenoid hypertrophy, demonstrated a wedge shaped defect in postero-inferior portion of the nasal septum (Fig. 1) that coincided with the location of the vomer. The septal defect was associated with hypertrophy of the adenoid tissue. The size of adenoid was small (<40%) according to the percentage of naso-pharyngeal space obstruction during nasal inspiration. Allergic skin testing with six common aeroallergens was negative. She had no history of nasal disease, maxillofacial trauma, nasal surgery or cauterization that could explain an acquired nasal defect. The patient also underwent Phoniatric assessment and acoustic speech analysis but no signs of velar insufficieny were found. Magnetic resonance of the maxillofacial region, performed in order to evaluate the septum defect, showed the aplasia of the vomeral bone with a concurrent sinusitis (Fig. 2). There were no other accompanying anomalies of the craniofacial region.

Table 1
Reported cases of CVD (from Yorgancilar et al. [4] modified). The concomitant disease and symptomatology have been reported as number of cases affected/total number of cases described in the single report.

Author	Sex		Age (mean)	Concomitant disease and symptomatology	Number Cases
	M	F			
Mohri and Amatsu [2]	4	2	38	Chronic otitis media	1/6
				Laryngeal polyp	1/6
				Acute otitis media	1/6
				Otitis media with effusion	1/6
				Pituitary adenoma	1/6
				Cholesteatoma	1/6
Dogru et al. [5]	1	1	30	Thalassemia	2/2
				Inferior concha hypertrophy	
Yilmaz and Altuntas [1]	1		19	Otitis media with effusion	1/1
				Inferior concha hypertrophy	
				Adenoid tissue hypertrophy	
				Septal deviation	
Lee [3]	1	1	36	Maxillary sinusitis	1/2
Kang et al. [7]	1		13	Chronic sinusitis	1/1
				Nasal polyp	
Herrero Calvo et al. [6]		1	34	Septum deviation	1/1
Yorgancilar et al. [4]	1		28	Retention cyst on the maxillary sinus	1/1
Verim et al. [8]	7	2	32	Septum deviation	6/9
				Inferior concha hypertrophy	6/9
				Retention cyst on the paranasal sinus	3/9
Schindler et al.		1	7	EEC	1/1
				Inferior concha hypertrophy	
				Adenoid tissue hypertrophy	
				Bifid uvula	
				Otitis media with effusion	
				Maxillary sinusitis	

Also the parents of the child underwent a diagnostic nasal endoscopy and their nasal septum appeared normal. As adenoid hypertrophy was not relavant, sleep apnea was not suspected and no treatment for snoring was planned.

3. Discussion

The nasal septum consists of the septal cartilage anteriorly, the perpendicular plate of the ethmoid bone superiorly and the vomer postero-inferiorly. This latter is a wedge-shaped bone that connects the hard palate and the superior part of the nasal septum, forming the posteroinferior part of the septum [2]. The vomer develops via intramembranous ossification from direct ossification of mesodermal cells in three steps during the prenatal stage [8]. The earliest appearance of vomeral bone is at the 8th week of gestation when intramembranous ossification begins on the membrane that covers the cartilaginous nasal capsule. In this phase, two ossification centers are present and are located in the posteroinferior part of the nasal septum, between the nasopalatine nerves laterally and the nasal septal cartilage medially. In the second phase the two paired bones fuse caudally in the midline at the 17th gestational week taking a U shape as seen in the coronal plate. Finally, in weeks 19–23 of fetal life the bone structure assumes a Y shape as the bones fuses in the inferior part of the U-shaped structure [7,8].

Congenital defect of the vomeral bone is a rare condition and until now only few cases have been reported (Table 1). In order to clarify its etiology Mohri and Amatsu [2] proposed two theories: the first one is the ‘‘immature ossification center theory’’ which postulates the presence of an incomplete or immature ossification center. The other one is the ‘‘incomplete downward growth theory’’ which holds that the posterior extension and downward growth of the primary nasal septum are stunted even if the ossification centers are mature. Nonetheless, the etiology of the CVD is still a subject of debate. Dogru et al. [5] reported two cases of CVD with thalassemia trait in southern Turkey and suggested that these conditions were related. Verim et al. [8], examining the patients’ immediate relatives, speculated that this condition could be a multifactorial hereditary disease and proposed the ‘‘incomplete touch theory’’ in order to explain the genesis of CVD. According with this theory, the vomer defect is caused by an incomplete union of the ossification line of the septal cartilage with the surrounding tissues [9]. In fact, the vomerine ossification, begins before the ossification of the perpendicular plate, immediately after its contact with the ossification line adjacent to the cartilaginous septum. For this reason, any delay in the contact between the ossification line and the mesenchymal cells will interrupt the mineralization of the vomer [8]. Moreover, according to the clinical presentation of the studied case series, the authors speculated also that the vomer may develop independently from the fusion of the palatal shelves with the nasal septum [8]. None of the nine patients with CVD enrolled in the study were affected by imperfect palatopharyngeal closure or cleft palate and also in previous reports cleft palate was not present even if the clinical presentation differs. Yilmaz and Altuntas [1] reported the case of a 19-years-old man with CVD and bilateral otitis media, septal deviation, adenoid hypertrophy and hypertrophy of the posterior end of both inferior conchae. The authors speculated that the defect of the vomeral bone and conchal hypertrophy determined an abnormal airflow that, associated with compensatory adenoid hypertrophy, might have predisposed to ear disease.

Considering the literature data available it is possible to suppose that CVD could be a genetic disease. Our case represents the first report of a girl with a CVD carrying a gene mutation associated with orofacial malformations. It is possible that the vomer aplasia here described was isolated and not related to the EEC syndrome. However, it is also possible that the P63 gene could be implicated in the development of the vomer aplasia, as it is involved in the regulation of transcription of a wide range of genes it. Mutation of the *TP63* gene in mice, in fact, determines reduced cell proliferation in epithelium and mesenchyme with consequent disorganization and hypoplasia of the palatal epithelium that finally lead to palatal malformation. It is possible that also in humans the mutation of the *TP63* gene determines alterations in mesenchymal cells that, according to the ‘‘incomplete touch theory’’ [8], could lead to an incomplete union of the ossification line of the septal cartilage with the surrounding tissues causing the interruption of the mineralization of the vomer. However, the evidence that children with P63 mutations demonstrate a wide range of phenotypes [10] suggests that the variation in phenotype could be secondary to the complex interplay between the specific mutations of the *TP63* gene and the many modifying loci.

4. Conclusion

In conclusion the CVD may be present in patients affected by mutation of the *TP63* gene with bifid uvula even without submucous cleft palate. It is possible that the complex interplay between the specific mutations of this gene and the many modifying loci plays a role in the development of this rare condition. Further studies, including animal models and larger population of patients with ECC are needed to further explore this hypothesis.

Source of financial support or funding

None.

Financial disclosure

No financial disclosure.

Conflict of interest

None.

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