Original Article

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Sinonasal Anatomical Variations and Primary Acquired Nasolacrimal Duct Obstruction: A Single Centre, Case-Control Investigation

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Abstract

Objective: Primary acquired nasolacrimal duct obstruction (PANDO) is an idiopathic narrowing of the nasolacrimal duct caused by chronic inflammation and consecutive stenosis of the tissue. In the current investigation we aimed to study the etiopathogenic role of sinonasal anatomical abnormalities and paranasal inflammatory pathologies in PANDO.

Material and Methods: CT findings of 459 patients who had been diagnosed with unilateral PANDO in the period between April 2009 and March 2017 were compared with that of a control group, comprising 200 subjects without nasolacrimal duct obstruction who had referred to the ear nose throat (ENT) clinic with the complaint of vertigo and headache. A radiologist masked to the clinical situation of participants, examined the CT findings retrospectively.

Results: The prevalence of deviated nasal septum was found to be strongly associated with PANDO incidence (55.3% on PANDO side of patients vs. 28.3% among controls; $p < 0.001$). Significant increases, albeit of smaller magnitude, were also observed in the relative frequency of Agger nasi cells and maxillary sinusitis on PANDO side of cases (14.6% and 27.0%, respectively) compared to controls (9.5% and 20.6%, respectively) ($p = 0.023$ and $p = 0.038$, respectively). Unilateral PANDO was also found to be robustly associated with ipsilateral deviated nasal septum ($p < 0.001$). The odds of septal deviation occurrence were 3.037 times (95% Confidence Interval (CI), 2.303-3.990; $p < 0.001$) more on the PANDO than non-PANDO side of the studied cases.

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Discussion: Ipsilaterally deviated nasal septum appears to have a role in the development of unilateral primary acquired obstructive disease of the lacrimal drainage system. The incidence of PANDO might also be affected with Agger nasi cells and maxillary sinusitis. Multicenter studies are essential to further elucidate the interaction between type, severity, extent, and dimensions of different pathologies with nasolacrimal duct obstruction.

Keywords: Sinonasal abnormalities, Nasolacrimal duct, Anatomic variations, Computed tomography, Deviated nasal septum

Introduction

Primary acquired nasolacrimal duct obstruction (PANDO) is a syndrome caused by chronic inflammation and consecutive stenosis of tear duct which predominantly affects adult female patients and presents with excessive tearing or epiphora. While PANDO is considered to be mostly idiopathic in character, a plethora of competing theories have been suggested regarding its etiology over the years [1]. Nasal diseases, conjunctival infections, menstrual and hormonal fluctuation, sinusitis, eye make-up, female gender, smoking, history of dacryocystitis, and topical chloramid exposure are among the presumed predisposing factors for PANDO [2-5]. In addition, due to the proximity of paranasal sinuses and nasolacrimal duct, it has long been believed that abnormalities in sinonasal cavities might play a role in the production of nasolacrimal duct obstruction (NLDO) [6-7]. However, controversial data exist regarding the association of lacrimal drainage system disease with paranasal pathologies [6, 8-15].

In the current investigation, we retrospectively reviewed the sinonasal pathologies diagnosed by computed tomography (CT) in patients with unilateral PANDO. The prevalence of anatomical, inflammatory, and infectious abnormalities observed in the obstructed side of the PANDO patients were then compared with that of the contralateral (unobstructed) side of the

cases as well as with that of the healthy sides of a control group to establish the relationship between sinonasal anomalies and nasolacrimal disease.

Subjects and Methods

The current investigation was approved by the Ethics Committees of the Urmia University of Medical Sciences. Only those subjects who had signed the informed consent at the time of medical evaluation were included in the present research. Medical records and CT findings of 459 patients and 200 control subjects older than 18 years old, were reviewed retrospectively. All cases and controls were referred in the period between April 2009 and March 2017 to the ear nose throat (ENT) clinic of Imam Hospital affiliated with Urmia University hospital, a principal referral center in Northwest Iran. Subjects in the patient group were referred to the clinic by ophthalmologists and all had epiphora in one side with no apparent cause. The diagnosis of PANDO was achieved for all patients by classical symptomatic presentation along with conventional probing, syringing test and confirmed by DCG with contrast. Only patients with unilateral PANDO were included in the present investigation. 200 control individuals who had attended our ENT clinic because of headache and/or vertigo were enrolled as an independent control group. They all had undergone head CT scan and none of them had a history or evidence of PANDO, epiphora, or dacryocystitis. According to the medical records of the control group, causes of headache and/or vertigo were as follows: migrainous disorders (n=87, 43.5%), multiple sclerosis (n=16, 8.0%), benign paroxysmal positional vertigo (n=14, 7.0%), metabolic disorders (n=14, 7.0%), glaucoma (n=7, 3.5%), vestibular neuritis (n=4, 2.0%), vasculitic disorders (n=4, 2.0%), neurodegenerative disorders (n=3, 1.5%), and unclear etiology (n=51, 25.5%). Patients with a history of infiltrative or tumoral lesions, previous nasal and/or lacrimal surgery, sinonasal disease or fracture, and trauma around the eye that might damage the lacrimal drainage apparatus were excluded from the control group. Individuals with

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incompletely recorded medical files in terms of required information were excluded as well. Sociodemographic (*e.g.*, age, gender) and clinical characteristics (*e.g.*, details of any previous sino-nasal disease, symptoms and duration of PANDO) of the studied patients were extracted from medical files.

The older (between years 2009-2014) CT scans were conducted using a multichannel Toshiba scanner (Asteion 4, Otawara, Japan) with 3 mm section thickness in the coronal plane. Axial cuts were taken whenever necessary. More recent (2014-2017) CT scans were performed using a spiral multislice Toshiba scanner (Activion 16, Otawara, Japan) with 1 mm section thickness. Each side of the nasal cavity was investigated separately for the presence of anatomical variations. Therefore, the comparison of sinonasal CT images was performed as patients' nasolacrimal duct obstructed side (n = 459, PANDO side), patients' unobstructed side (n = 459, non-PANDO side), and control sides (n = 400). The primary author of the current article (R. S.) reviewed the CT images to reveal anatomical variations including deviated nasal septum, concha bullosa, paradoxical middle concha, osteomeatal complex disease, inferior concha hypertrophy, maxillary sinusitis, Agger nasi cell, Onodi cell, Haller cell, and pneumatized uncinate.

Statistical Analysis

Statistical analyses were performed using GraphPad prism software ver. 7.04 (GraphPad Software Inc., La Jolla, CA, USA). Qualitative and quantitative data were compared using Chi-square test and Student t-test, respectively. Results were evaluated with 95% confidence interval (CI). A p value <0.05 was considered to be significant.

Results

The medical records of 459 patients and 200 control subjects were examined in this study. Unilateral PANDO was observed in 321 (69.9%) female cases and 138 (30.1) male subjects with woman: man ratio being 2.3:1. 284 cases (61.9%) had PANDO on the left side, whereas obstruction restricted to the right side was observed in 175 patients (38.1%). The control group consisted of 129 (64.5%) women and 71 (35.5%) men. There was no statistical significant difference concerning the gender between two arms of the study (Chi-square test, $p = 0.168$). The mean ages of patients and controls were 58.2 ± 11.8 (range: 18 to 79 years) and 53.9 ± 12.4 (range: 21 to 76 years) years old, respectively (Student t-test, $p = 0.618$).

Table 1 compares the rates of sinonasal pathologies between PANDO and non-PANDO sides of the patient group as well as between cases and controls. Deviated nasal septum was found to be the only anatomic variation which showed significantly higher rates of occurrence not only in the patient group than in the control subjects ($p < 0.001$), but also on the PANDO side than on the non-PANDO side of the cases ($p < 0.001$). The odds of septal deviation occurrence were 3.037 (95% Confidence Interval (CI), 2.303-3.990; $p < 0.001$) times more on the obstructed than non-PANDO sides of patients. Agger nasi cells were also found to be more frequent on the diseased side of the patient group than in the controls ($p = 0.023$). Additionally, PANDO patients showed a marginally ($P=0.038$) higher frequency of maxillary sinusitis in their obstructed side compared with the control group. Our comparison however failed to detect statistically significant difference between the obstructed and contraleteral (non-PANDO) sides of the patients with regards to the prevalence of Agger nasi cell ($p = 0.171$) and maxillary sinusitis ($p = 0.324$). The occurrence of all other anatomic variations did not differ significantly, neither between cases and controls, nor between PANDO and non-PANDO sides of patients.

Discussion

PANDO is considered to result from a fibrous stenosis secondary to local inflammation of the lacrimal drainage system [4, 8]. Certain sinonasal anatomic abnormalities have been incriminated by earlier researches as trigger factors, among others, for its development. While cadaver studies and surgical findings have implicated the importance of the topographic knowledge of paranasal structures in the pathogenesis of primary acquired obstructive disease of the lacrimal drainage system [7, 16], cross-sectional descriptive studies and case series using radiologic imaging techniques or endoscopic assessments have found a higher relative incidence of one or more rhinologic anomalies or sinus diseases among patients suffered with PANDO compared with corresponding statistics obtained from whole population based studies [17-19]. However, the role of sinonasal abnormalities in the pathogenesis of PANDO can be better clarified by comparing the prevalence of sinonasal anatomic anomalies between populations with and without PANDO. The relationship between anatomic abnormalities of sinonasal region and PANDO has indeed been evaluated by multiple case-control studies, reaching controversial results [6, 8-15]. But it must be noted that the control groups included in these investigations were either the contralateral (unobstructed) sides of cases, patients who referred to ENT specialists with nasal symptoms, or non-PANDO cases with orbital inflammatory disease or traumatic lesion. Since nasal or orbital disorders are more prevalent in these control groups, most of the previous case-control studies suffer from so called "selection bias" problem. Additionally, almost all of these investigations have been performed on only tens of patients or controls. Such limitations reduce the precision of the research and restrain the generalizability of the findings. In order to eliminate these drawbacks, we conducted a relatively large scaled study using subjects with vertigo or headache as the control group in whom the incidence of nasal or orbital abnormalities was similar to the general population [15].

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According to our findings, deviated nasal septum was statistically more prevalent not only in cases than in the controls ($p < 0.001$), but also on the obstructed side than on the contralateral side of the patients ($p < 0.001$). A statistically significant difference was still observed when the comparison was made between the control group and both patients' sides combined ($p < 0.001$). This was in full agreement with a recent case-control study conducted by Singh *et al.* [13] showing that ipsilateral deviated nasal septum is associated significantly with unilateral PANDO, and cases had more septal deviation (30 cases out of 50, 60%) than the control group (18/50, 36%). A similar result has also been reported by one of the pioneering studies in this field which had been conducted in 1996 by Kallman *et al.* [11] on 23 cases and 100 control subjects. Besides, facial asymmetry analyses have revealed that unilateral PANDO is more likely observed on the side in which the nasal septal deviation has been developed [20-21]. In contrast, Sefi and her colleagues [12] failed to establish a significant difference in terms of nasal septum deviation prevalence between 20 PANDO patients and 20 age- and sex- matched controls using paranasal CT dacryocystography examination. In addition, the frequency of deviated nasal septum was found to be similar between the obstructed and unobstructed sides of 41 PANDO patients in Habesoglu *et al.*'s study [6]. Although the prevalence of nasal septal deviation was not related to PANDO incidence in Yazici *et al.*'s [15] study, the laterality of septal deviation, and not its localization (anterior, posterior and central) or angle, was differently distributed among the obstructed and unobstructed sides of patients (n=40). Indeed, the rate of deviated nasal septum occurrence on the side of the obstruction was three fold higher (21 out of 40 cases) than that of non-PANDO side (7 out of 40 cases) in that study [15]. These controversies in our opinion are partly due to a lack of consensus in the definition of deviated nasal septum. The term nasal septal deviation refers to the irregularities of the septal cartilage in general and does not elucidate the nature of the pathology (e.g. cartilaginous, osteocartilaginous or osseous) or its impact on normal physiology. In the current research,

deviated nasal septum was defined as any deviation that blocked at least half of the nasal cavity.

In our study, there was a significant trend towards a higher rate of Agger nasi cells on PANDO side of the studied cases compared with the controls (p = 0.023). This association however, lost its significance when the prevalence of Agger nasi cells was compared between the control group and both sides of patients as a whole (PANDO side plus non-PANDO side) (p = 0.066). Agger nasi cells are the most anterior ethmoid air cells that are located in the area anterior and superior to the insertion of middle turbinate at the lateral nasal wall. It has been observed that these cells can invade the lacrimal bone or the ascending process of maxilla [22]. Expanded cells can even encroach upon the medial aspect of frontal sinus floor, and narrow or obstruct the nasofrontal duct [23]. There is also evidence in the literature that these cells may constrict the frontal recess without being pneumatized [24]. Reports differed concerning whether these cells are associated with PANDO incidence or not. While Kallman *et al.* [11] noted a significant association between the presence of Agger nasi cells and increased risk of PANDO, Habesoglu *et al.* [6] and Yazici *et al.* [15] could not reach an evidence of increase in the prevalence of Agger nasi cells among PANDO cases. Our analysis also demonstrated that the laterality of Agger nasi cell did not change the rate of PANDO occurrence between the diseased and the contralateral sides of the patient group, which was in accordance with previous studies [6, 15]. Like the deviated nasal septum, there is no accordance between researchers regarding the definition of Agger nasi cell as the reported prevalence varies widely among different studies (2-98%) [22, 25].

It is believed that acute infectious and inflammatory pathologies of the sinuses may ascend into nasolacrimal duct from the nose and therefore cause serious damage to lacrimal membranous conduit which in turn may lead to permanent fibrous obstruction [1, 8]. However, solid clinical

evidence is still lacking in this area [8]. Osteomeatal complex represents the final common channel for ventilation and drainage of the frontal sinus, anterior ethmoid air cells, and maxillary sinus [26]. Variations in any of these clefts, cells, cavities or recesses could increase the occurrence rate of PANDO. In order to evaluate the impact of ascending infectious and inflammatory pathologies on PANDO development, we investigated the prevalence of osteomeatal pathologies and ethmoidal/maxillary sinusitis among our patients. Based on our data, ethmoidal sinusitis and osteomeatal complex disease seemed not to be a causative factor to PANDO. This is in agreement with the findings of Sefi *et al.* [12] and Yazici *et al*. [15] who did not detect any significant association between PANDO incidence and the prevalence of ethmoidal and osteomeatal pathologies. Maxillary sinusitis was also found to be no more frequent in PANDO patients than in controls ($p = 0.09$) according to Yazici *et al*.'s analysis [15]. In a recent assessment, Borges Dinis and his colleagues [8] examined the presence of chronic sinusitis in 60 patients with PANDO and 40 control participants using the Lund McKay sinus CT scoring system. Neither the frequency nor the extent of inflammatory sinus pathologies was found to be associated with PANDO incidence in that investigation. In our study however, a borderline level of significance ($p = 0.038$) was noted between PANDO side of patients (27.0 %) and the control group (20.6 %) with regards to the prevalence of maxillary sinusitis. Yet, the prevalence of maxillary sinusitis was statistically comparable between controls and patients when the both sides of the case group were considered as a whole ($p = 0.070$)

Strengths of the present study with respect to previous related investigations include the large sample size collected over a period of 8 years, inclusion of only unilateral PANDO cases, and a more robust inclusion criterion for the control group. The limitation is its design as a single-centre, retrospective, case–control study which prohibits causal inferences.

In conclusion, nasal septal deviation showed a strong association with PANDO incidence. We also found that the prevalence of Aggar nasi cells and maxillary sinusitis were higher in PANDO patients compared with the controls. Furthermore, unilateral acquired obstructive disease of the lacrimal drainage system was observed to be robustly associated with ipsilateral deviated nasal septum. Considering the results obtained, we believe that some anatomic variations in the paranasal sinuses and nasal cavity may play a role in the development of unilateral PANDO. Since the precise role of certain etiopathogenic parameters and confounding factors have not yet been elucidated, one could not certainly claim that sinonasal pathologies are independent causative factors for primary acquired obstructive diseases of the lacrimal drainage system. To find out the exact effects of sinonasal abnormalities on etiology of PANDO, multicenter studies are needed to evaluate not only the rate of sinonasal variations, but also type, severity, extent, and dimensions of specific pathologies (anatomical, infectious, or inflammatory) and investigate their interactions with lacrimal drainage pathways.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Table 1. Comparison of anatomic and inflammatory/infective variations between patients and controls as well as between PANDO sides and non-PANDO sides of the investigated cases

	Patients, both sides [n=918]		Controls, both sides [n=400]	p Value*	p Value**
	PANDO side (n=459)	non-PANDO side (n=459)			
Deviated nasal septum, n (%)	254 (55.3)	133 (29.0)	113 (28.3)	**<0.001**	**<0.001**
Agger nasi cell, n (%)	67 (14.6)	53 (11.5)	38 (9.5)	0.171	**0.023**

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Maxillary sinusitis, n (%)	123 (27.0)	110 (24.0)	83 (20.6)	0.324	**0.038**
Concha bullosa, n (%)	158 (34.4)	138 (30.1)	129 (32.3)	0.158	0.501
Paradoxical middle concha, n (%)	42 (9.2)	33 (7.2)	28 (7.0)	0.278	0.251
Osteomeatal complex disease, n (%)	98 (21.4)	87 (18.6)	77 (19.3)	0.365	0.446
Inferior concha hypertrophy, n (%)	130 (28.3)	108 (23.5)	98 (24.5)	0.097	0.206
Onodi cell, n (%)	46 (10.0)	35 (7.6)	33 (8.3)	0.200	0.370
Haller cell, n (%)	61 (13.3)	65 (14.2)	69 (17.3)	0.701	0.106
Pneumatized uncinate, n (%)	19 (4.1)	27 (5.9)	15 (3.6)	0.226	0.770

* Chi-square test between PANDO and non-PANDO sides of the case group

** Chi-square test between diseased sides of patients and both sides of controls

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