

# 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 nasal tissue. In the current investigation, we aimed to study the etiopathogenic role of sinonasal anatomical abnormalities and paranasal inflammatory pathologies in PANDO.

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

**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 the PANDO side of the subjects (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 an 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 the non-PANDO side of the studied cases.

**Conclusion:** 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 by 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 that 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-irritating make-up, female gender, smoking, history of dacryocystitis, and topical chloramide exposure are among the presumed predisposing factors for PANDO [2-5]. In addition, due to the proximity of paranasal sinuses and the 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, the association of lacrimal drainage system disease with paranasal pathologies is still controversial [6, 8-15].

In the current investigation, we retrospectively reviewed 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, in order to establish the relationship between sinonasal anomalies and nasolacrimal disease.

## Materials 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, all of whom were older than 18 years old, were reviewed retrospectively. All cases and controls were referred between April 2009 and March 2017 to the ear nose throat (ENT) clinic of Imam Hospital at Urmia University, a principal referral center in Northwest Iran. Subjects in the patient group were referred to the clinic by ophthalmologists and all presented with epiphora in one side of the face with no apparent cause. The diagnosis of PANDO was made according to classical symptomatic presentation along with conventional probing and syringing test. The diagnosis was confirmed by DCG with contrast.

Only patients with unilateral PANDO were included in the present investigation and the 200 individuals who had presented at 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=3, 1.5%), 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 incomplete information in their medical files were excluded as well. Sociodemographic (, age, gender) and clinical characteristics (, details of any previous sino-nasal disease, symptoms, and duration of PANDO) of the studied patients were extracted from medical files.

The older CT scans (between 2009 and 2014) were conducted using a multichannel Toshiba

scanner (Asteion 4, Otawara, Japan) with 3 mm of section thickness in the coronal plane. Axial cuts were taken whenever necessary. More recent CT scans (between 2014 and 2017) were performed using a spiral multislice Toshiba scanner (Activion 16, Otawara, Japan) with 1 mm of 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 a 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 the Chi-square test and Student t-test, respectively. Results were evaluated with a 95% confidence interval (CI). A  $p < 0.05$  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 the female: male ratio being 2.3:1. A total of 284 cases (61.9%) had PANDO on the

left side, whereas the right side-obstruction was observed in 175 patients (38.1%). The control group consisted of 129 (64.5%) women and 71 (35.5%) men. There was no statistically significant difference concerning the gender between the two groups (Chi-square test,  $p=0.168$ ). The mean ages of patients and controls were  $58.2 \pm 11.8$  years (range: 18-79 years) and  $53.9 \pm 12.4$  (range: 21-76 years) years, respectively (Student's t-test,  $p=0.618$ ).

Table I compares the rates of sinonasal pathologies between PANDO and non-PANDO sides of the patient group as well as between the patients and controls. A deviated nasal septum was found to be the only anatomic variation which showed significantly higher rates of occurrence, not only in the patient group vis a vis the control subjects ( $p < 0.001$ ) but also on the PANDO side vis a vis the non-PANDO side of the patients ( $p < 0.001$ ). The odds of septal deviation occurrence were 3.037 (95%CI: 2.303-3.990;  $p < 0.001$ ) times more on the obstructed than non-PANDO sides of patients. Agger nasi cells were 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 as compared to the control group. Our comparison, however, failed to detect a statistically significant difference between the obstructed and contralateral (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, either between cases and controls or between PANDO and non-PANDO sides of patients.

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

	Patients, both sides [n=918]			p*	p**
	PANDO side (n=459)	non-PANDO side (n=459)	Controls, both sides [n=400]		
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
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

## Discussion

PANDO is considered to result from fibrous stenosis secondary to local inflammation of the lacrimal drainage system [4, 8]. In previous research, certain sinonasal anatomic abnormalities have also been identified as trigger factors in its development. While cadaver studies and surgical findings have stressed 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 affected by PANDO, as compared to 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 their prevalence between populations with and without PANDO.

The relationship between sinonasal abnormalities and PANDO has been evaluated by multiple case-control studies with controversial results [6, 8-15]. However, it must be noted that the control groups included in these investigations included either the contralateral (unobstructed) sides of cases, patients who referred to ENT specialists with nasal symptoms, or non-PANDO cases with an 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".

Additionally, almost all of these investigations have been performed on only a small number 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-scale study designating 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].

According to our findings, a deviated nasal septum was statistically more prevalent not only in patients as compared to 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 also 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 patients 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 was conducted in 1996 by Kallman et al. [11] on 23 cases and 100 control subjects. Besides these studies, 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 et al. [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 a deviated nasal septum was found to be similar between the obstructed and unobstructed sides of 41 PANDO patients in a study by Habesoglu et al. [6]. Although the prevalence of nasal septal deviation was not related to PANDO incidence in the study by Yazici et al. [15], 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 ( $n=40$ ). Further, the rate of deviated nasal septum occurrence on the side of the obstruction was three-fold higher on the PANDO side (21 out of 40 cases) than that of the non-PANDO side (7 out of 40 cases) [15].

In our opinion, these controversies are partly due to a lack of consensus in the definition of the 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 toward a higher rate of Agger nasi cells on the PANDO side of the studied cases compared with the controls ( $p=0.023$ ). However, this association 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 lateral nasal wall at the area anterior and superior to the insertion of the middle turbinate. 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 the frontal sinus floor, and can partially or completely obstruct the nasofrontal duct [23]. There is also evidence in the literature that these cells may constrict the frontal recess without being pneumatized [24]. The association of these cells with PANDO incidence is still under discussion. 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 find evidence of an 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 consensus 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 the nasolacrimal duct from the nose and therefore cause serious damage to the 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]. The 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 did not seem to be a causative factor for 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 not found to be 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 et al. [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

the 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 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, the inclusion of only unilateral PANDO cases, and more robust inclusion criteria for the control group. The limitation is its design as a single-center, retrospective, case-control study, as this 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 as compared to the controls. Furthermore, unilateral acquired obstructive disease of the lacrimal drainage system was observed to be robustly associated with the 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, we cannot claim with certainty 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 the type, severity, extent, and dimensions of specific pathologies (anatomical, infectious, or inflammatory) and investigate their interactions with lacrimal drainage pathways.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Urmia University of Medical Sciences.

**Informed Consent:** Written informed consents were obtained from all participants before the study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – R.S., V.S., N.S.A.; Design - R.S., V.S., N.S.A.; Supervision - V. S., R. S.; Resources - R.S., V.S.; Materials - R.S., V.S., N.S.A.; Data Collection and/or Processing - R.S., V.S., N.S.A., N.F.;

Analysis and/or Interpretation - R. S., V.S., N. S.A., N. F.; Literature Search - R. S., V.S., N.S.A., N. F.; Writing Manuscript - R.S., V.S., N.S.A., N.F.; Critical Review - R. S., V.S., N.S.A.

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