

Cribriform Plate Foramina Count in Patients With Acquired and Congenital Anosmia

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Abstract

Background: Cribriform foramina provide the openings for olfactory nerve fibers to cross from the nasal cavity to the olfactory bulb. Disruption of the olfactory nerve fibers is known to affect olfactory function, but little is known about the potential effects on the number of cribriform foramina in congenital anosmia.

Objective: This pilot study aimed to investigate whether there was a reduction in foramina in patients with acquired and congenital anosmia (including both Kallmann syndrome and isolated congenital anosmia) compared to controls with normal olfactory function.

Methods: Paranasal CT image stacks were analyzed from 20 patients with congenital anosmia ($n = 6$), acquired anosmia ($n = 6$), or normal olfactory function ($n = 8$). Cribriform foramina were counted by three observers from the slice revealing the crista galli and the ethmoidal slits. The two closest values for each subject were analyzed in comparison across the three groups using one-way analysis of variance.

Results: Patients with congenital, but not acquired, anosmia had significantly fewer cribriform foramina ($\bar{x} \pm SE = 10.17 \pm 1.23$) compared to healthy, normosmic controls ($\bar{x} \pm SE = 19.88 \pm 2.01$). There was no significant difference in foramina count between congenital and acquired anosmics ($\bar{x} \pm SE = 15.83 \pm 3.47$).

Conclusion: In this pilot study, a reduced number of cribriform foramina was found in individuals with congenital anosmia. Examination of cribriform foramina could be helpful in counseling patients with olfactory loss. Further investigation in larger studies with additional cohorts is warranted.

Keywords

anosmia, ethmoid bone, olfactory nerve, cribriform foramina, tomography, X-Ray computed, olfactory bulb, cribriform plate, crista galli, olfactory dysfunction, Kallmann syndrome

Introduction

Brain structures present differently in patients with congenital and acquired anosmia.^{1,2} Elucidating anatomical changes in the setting of congenital and acquired anosmia is of particular interest, specifically in the assessment of the cribriform plate foramina, which allow the passage of olfactory nerve fibers from the nasal mucosa to the olfactory fossa. Work examining patients with Kallmann syndrome, a rare genetic disorder characterized by anosmia and hypogonadotropic hypogonadism, did not find significant differences in the number of cribriform plate foramina despite other significant anatomical changes specific to the ethmoid bone and olfactory bulb.³ However, patients with Kallmann syndrome only have partially functional olfactory neurons, suggesting that their cribriform plate foramina may be altered due to

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neuronal agenesis.⁴ Such size reductions in cribriform foramina are known to occur in the cribriform plate alongside impaired olfactory function in geriatric patients.^{5,6} They may result from absence or atrophy of olfactory nerves, followed by bone apposition in the cribriform plate.

Prior work has correlated the noninvasive CT method of assessing the cribriform plate with anatomic dissection in cadavers.⁷ Therefore, this pilot study aimed to examine the number of foramina within the cribriform plate using CT image stacks in patients with congenital or acquired anosmia and compare these to healthy controls as a means of establishing normative values for foramina within the cribriform plate. Additionally, this work examined whether the number of foramina significantly differs between patients with congenital and acquired anosmia relative to those with normal olfactory function.

Materials and Methods

Demographics

Appropriate ethics approval for this study was obtained from Acibadem Healthcare Institutions Medical Research Ethics Committee (2023-15/521). In this case-control study, paranasal CT image stacks of 20 subjects with congenital ($n = 6$) or acquired ($n = 6$) anosmia and healthy controls ($n = 8$) were obtained from patients at the radiology department of Acibadem Taksim Hospital from 2018 to 2022 (Table 1). All patients were in general good health, and participants were excluded if they had disorders that might affect the sense of smell (eg, Parkinson's disease, severe renal dysfunction). The study complies with the Declaration of Helsinki for Medical Research involving Human Subjects.

Olfactory function for all subjects was assessed using the Sniffin' Sticks test battery, which utilizes pen-like odor dispensers to measure odor Threshold (T), Discrimination (D), and Identification (I), resulting in a composite TDI score between 1 and 48 points.⁸ Congenital anosmia was diagnosed in patients who scored in the range of "total anosmia" (TDI <16.5),⁹ reported no sense of smell from birth and had no visible olfactory bulbs. Acquired anosmia patients also had TDI scores indicating total anosmia, reported anosmia for at least 1 year, and the etiology of their olfactory loss could be attributed to postviral (including

post-COVID-19) or posttraumatic causes. Healthy controls were recruited from patients presenting for a paranasal sinus CT scan to identify cephalgia etiology reporting a normal sense of smell and whose Sniffin' Sticks test score indicated normal olfactory function (TDI >30.5).⁹

Imaging

CT examinations were performed using a 128×2 detector dual source CT device (Flash Definition; Siemens, Erlangen, Germany). After screening the paranasal sinus area with 0.625 mm collimation in the axial plane, the olfactory cleft (OC) area was reformatted to 0.1 mm increment thickness per 0.4 mm slice using a smaller field of view.

Data Analysis

All images were assessed using MicroDicom DICOM Viewer (MicroDicom, Sofia, Bulgaria) at a 512×512 px resolution in the axial view. After observing all slices, foramina were counted bilaterally in the image within the stack showing both the crista galli and the bottom of the ethmoidal slits (Figure 1a-c). Cribriform foramina were identified in the cribriform plate between the anterior and posterior ethmoid arteries. Three trained scorers, blinded to the diagnosis of the participants (BH, AJ, and JJ), counted the foramina, and two closest values for each subject were chosen for further analysis.

Statistical Analyses

The statistical analysis was performed using IBM SPSS Statistics Version 29.0 (IBM Inc., Armonk, NY, USA). A one-way ANOVA along with post-hoc test with multiple comparisons (using the Tukey honest significant differences method) was conducted. Significance level was set at P -value less than .05 for all tests.

Results

Levene's test for equality of error variances found that the data did not violate the homogeneity of variances ($W = 3.16$, $P = .068$). The data for each observer met the assumption of normality by visual inspection through quantile-quantile plots and by Shapiro-Wilk's normality test (BH: $W = 0.92$, $P = .14$; AJ: $W = 0.94$, $P = .27$; JJ: $W = 0.96$, $P = .54$). Results of one-way ANOVA showed significant differences between groups for the number of cribriform foramina ($F [2, 17] = 4.34$, $P = .030$). Eta-squared $\eta^2 = 0.34$ indicates a large effect size of anosmia on cribriform foramina.

Post-hoc analysis revealed that controls had significantly more cribriform foramina as compared to patients with congenital anosmia (9.71, 95% CI [1.25 to 18.17], $P = .023$; Figure 2, Table 2). No significant difference existed between the control group and acquired anosmic group (4.04, 95% CI [-4.42 to 12.50], $P = .455$; Figure 2,

Table 1. Demographics of Study Subjects, by Type of Anosmia.

	Number of subjects	Age (years)	Sex
Acquired	6	7–60 ($\bar{x}$: 25.83 ± 21.46)	4 F, 2 M
Congenital*	6	11–35 ($\bar{x}$: 20.00 ± 8.76)	4 F, 2 M
Control	8	13–32 ($\bar{x}$: 21.00 ± 7.09)	3 F, 5 M
Summary	20	7–60 ($\bar{x}$: 22.15 ± 12.89)	11 F, 9 M

* Two subjects in the congenital group had Kallmann syndrome, while four had idiopathic congenital anosmia.

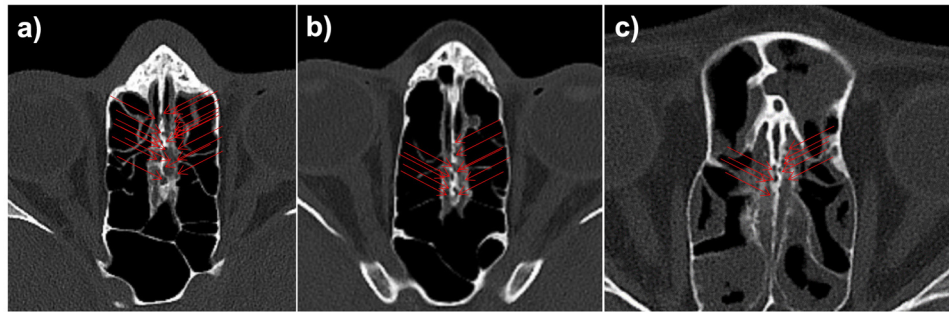


Figure 1. Examples of images used for analysis in control (a), acquired anosmia (b), and congenital anosmia (c) groups.

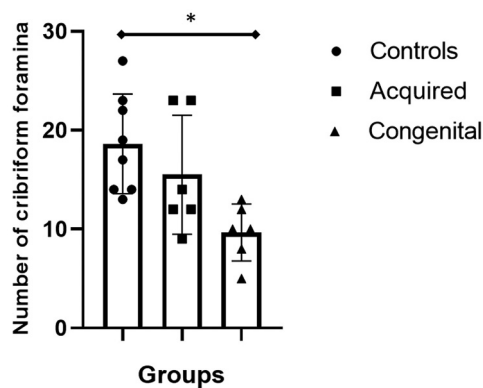


Figure 2. Barplot with overlaid data points depicting the significant difference ($P < .05$) in the number of cribriform foramina between control and congenital anosmia groups.

Table 2). Cribriform plate foramina did not significantly differ between patients with congenital and acquired anosmia (-5.67 , 95% CI $[-3.38$ to $14.71]$, $P = .27$).

Across the analysis, the two-way mixed intraclass correlation coefficient for average measures indicated moderate reliability between raters (0.642 , 95% CI $[0.21$ to $0.86]$). Figure 3 depicts the deviation across the three raters in a three-dimensional plot, highlighting the influence of two outlier points. This plot excludes two control subjects that were not assessed by one rater.

Power analysis for a future definitive study was conducted using the *pwr* package, with $k = 3$ groups, power = 0.8 , and a significance level of 0.05 . The observed η^2 of 0.34 corresponds to a large effect according to Cohen's f ($f = 0.72$); thus, effect size was estimated at $f = 0.4$ based on Cohen's benchmark for a large effect.¹⁰ This resulted in a target of 22 subjects per group to accomplish statistical power of 0.8 , using the effect size observed in this pilot study.

Discussion

Prior work examining counts of cribriform plate foramina did not find significant differences between congenitally anosmic

Table 2. Descriptive Statistics for Cribriform Foramina Count.

	<i>n</i>	Mean ($\pm$ SD)	Minimum	Maximum
Acquired	6	15.83 ($\pm$ 8.51)	7	33
Congenital	6	10.17 ($\pm$ 3.01)	6	17
Controls	8	19.88 ($\pm$ 5.69)	4	34
Total	20	15.75 ($\pm$ 7.10)	4	34

and control groups.³ However, this pilot study suggests that congenitally anosmic patients have fewer cribriform plate foramina compared to controls. The study by Maione et al was restricted to patients with Kallmann syndrome,³ while four of the six patients in this study were diagnosed with isolated congenital anosmia (ICA) and only two were diagnosed with Kallmann syndrome. Gender distribution was similar between all groups, and age distribution between the congenital anosmia and control groups was also similar. Notably, the mean number of cribriform plate foramina in the control group was 24.5 ± 5.4 , while Maione et al found the mean number was 8.0 ± 2.7 .³ Apart from the advanced imaging techniques used in the present study, this may be attributed to analysis using both the sagittal and axial planes, while the present study only examined foramina in slices from the axial plane.

The foramina estimates in normosmic controls also more closely align with the number of observed olfactory filaments (fila) in numerous studies. A cadaveric study found a combined average of 26 fila across the nasoseptal, middle turbinate, and superior turbinate mucosa, while another found approximately nine fila at the ethmoid roof and five at the septum.^{11,12} Endoscopic imaging indicates that cribriform foramina tend to allow for the passage of one filament each.¹² If so, this may provide more confidence to the preliminary estimates generated by the approach used in this study.

Other work also finds bony abnormalities such as a flattened ethmoid roof and shallower olfactory fossa in individuals with ICA, supporting the idea of the olfactory bulb and anterior skull base developing in an integrated manner.¹³ Given these findings, it seems that non-Kallmann congenital

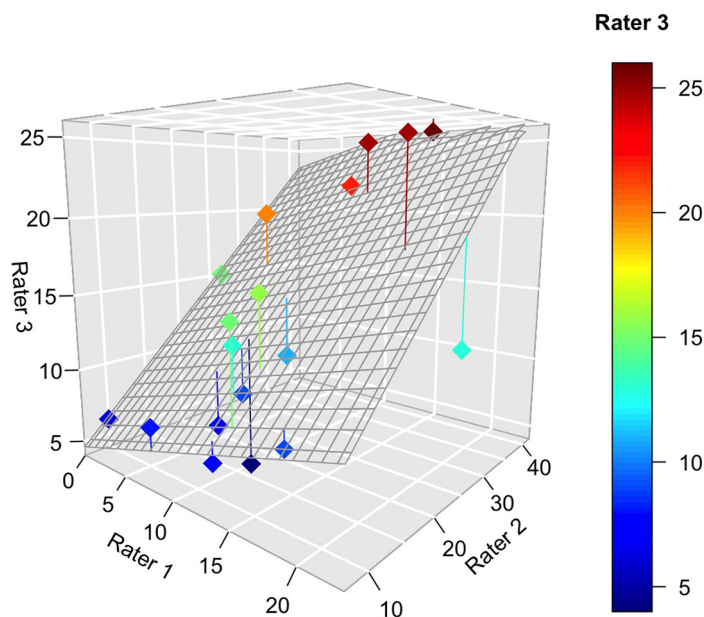


Figure 3. Three-dimensional scatterplot illustrating interrater reliability. The grid plane represents the predicted values from a linear regression of raters 1 and 2 on rater 3.

anosmic syndromes result in alterations to cribriform foramina numbers. However, these are relatively rare disorders which are frequently grouped together under ICA.¹⁴ The anterior skull base was found to vary in individuals with ICA based on the presence of the olfactory bulb, suggesting that development in this region can adjust to the absence of olfactory structures.¹⁵ This underscores the importance of continuing to examine potential bony abnormalities in congenital anosmia syndromes, and of developing a unified system for assessing the number of cribriform plate foramina using CT image stacks.

Subjects in the present study included children, and in the case of patients with acquired anosmia, ranged from 7 to 60 years of age, presenting a potential limitation to the analysis. Nevertheless, research has shown that the anterior skull base fully ossifies by age 4.¹⁶ The cribriform plate is considered the earliest to complete growing—by age 4—in the anterior cranial base.^{17,18} Inclusion of children above this age is not expected to affect findings regarding the cribriform plate foramina. A prior CT study found no age-related differences in olfactory foramina stenosis, although conflicting cadaver studies have observed changes in the area of foramina in the cribriform plate with age.^{5,19} More comprehensive analysis of the olfactory foramina could be accomplished with 3D reconstructed CT scans,²⁰ but this method is not suitable in most cases due to the elevated radiation exposure.

Although not significant in this analysis, the differences in foramina between the acquired and control groups would be of particular interest, as it suggests that even acquired anosmia can be associated with bony abnormalities which may contribute to the severity of the anosmia. Under the

assumption that foramina only exist in the presence of nerves traversing the cribriform plate, such findings may indicate either that (a) patients with acquired anosmia are equipped with fewer olfactory nerves and hence are more susceptible to olfactory loss,²¹ or (b) acquired olfactory loss is due to atrophy of olfactory fibers, followed by a decrease of olfactory nerves, resulting in bony appositions to the cribriform plate and fewer foramina. Further analysis will include a larger sample size of patients with acquired anosmia that has persisted over a longer period, as this subset of patients may be more likely to reflect these changes to the cribriform plate foramina.

In addition to the limitations of sample size and age distribution, cribriform foramina were analyzed in this study by count alone, which can mirror the clinical assessment of foramina but does not account for differences in foramina size and morphology. These results can be supported in future studies by a volume-of-interest analysis of the cribriform plate to calculate bone composition.⁷ Assessing cribriform foramina count may be clinically relevant in identifying the propensity for recovery of olfactory function in those with anosmia. Three-dimensional reconstruction in MRI tractography illuminates the pathways through which the olfactory nerve filaments advance to the olfactory bulb.²² As further studies investigate the role of olfactory filaments in the prognosis for olfactory training in anosmics,²³ recognizing the existing olfactory architecture for each patient will serve a greater clinical purpose. The number of these pores identified using CT can serve as a proxy for quantifying the olfactory filaments in cases where MRI is contraindicated or inaccessible.

Conclusion

Overall, this pilot study suggests that there are less cribriform foramina in people with congenital anosmia compared to controls. Further investigation is warranted to confirm these preliminary findings with larger sample sizes in additional cohorts of anosmia. Future studies may also focus on longitudinal changes in patients with acquired olfactory loss.

Data Availability

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Approval

Ethics approval for this study was obtained from Acibadem Healthcare Institutions Medical Research Ethics Committee (2023–15/521). Written informed consent was obtained from participants.

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