Running title: New classification of the LLCP

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Title: Lateral lamella of the cribriform plate, a keystone landmark: proposal for a novel classification system

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SUMMARY

Background: the aim of this study is to propose a classification of the angle formed by the lateral lamella of the cribriform plate (LLCP) and the horizontal plane passing through the cribriform plate. In particular, the angle was classified into class I (> 80 degrees), class II (45 to 80 degrees, and class III (< 45 degrees)

Methodology: a total of 190 computed tomography scans were retrospectively reviewed in order to obtain four sets of measurements. 1) depth of the cribriform, 2) angle, 3) length of the LLCP, 4) width of the fovea ethmoidalis. The relationship among these measurements were analyzed.

Results: the angle was significantly correlated with the depth of the cribriform and the length of the fovea, while it was negatively correlated with the length of the LLCP. Significant negative correlation was also found between the length of the LLCP and the width of the fovea.

Conclusions: this angle classification is based on the theoretical risk of iatrogenic injuries, but it could be helpful also in clinical practice by providing indirect information on the thickness of the anterior skull base. As the angle decreases, in fact, the portion of the anterior skull base composed by the LLCP, increases.

Key words: anatomy; radiography, diagnosis, skull base, surgery

INTRODUCTION

Endoscopic sinus surgery (ESS) is a well established approach for the management of sinonasal diseases[1]. Although technological advances, proper instrumentation, surgical refinements, use of imaging techniques and better understanding of the regional anatomy have served to make surgeries more secure, ESS is not devoid of complications[2]. These latters can be divided into minor[3], and major ones, including cerebrospinal fluid leak (CSF-L) as well as ocular and intracranial injuries[4]. Most of these major complications occur during ethmoidectomy and can be related to anatomical variation of the anterior skull base[5].

The anterior skull base is composed by the cribriform plate and by the fovea ethmoidalis. These structures converge at the lateral lamella of the cribriform plate (LLCP) that delimits laterally the cribriform fossa, a weak area known to be a common site of iatrogenic skull-base injuries due to direct penetration or fracture during middle turbinate manipulation or lack of awareness of instrument placement[6]. This fossa, in fact, is the thinnest and the most vulnerable structure of the anterior skull base since the thickness of the LLCP can be only 0.05 mm[6].

According to Keros' classification[7] it is possible to distinguish between 3 types of cribriform fossa depending on its depth: type 1, 1-3 mm long, type 2, 4-7 mm long and type 3, 8-16 mm long. It has been previously reported that Keros type 3 patients have greatest risk of intracranial entry since the great extension in depth of the cribriform fossa and the thickness of its bone-wall make this area more susceptible to iatrogenic skull-base injuries[8]. Although Keros' classification is still commonly referred to, several authors highlighted the limitations of this classification system in fully describing the shape of the skull base and predicting the risk of intracranial entry[9-13]. In particular, Heaton et al. [9] in their retrospective case-control study reported that a greater slope of the anterior skull base in the coronal plane and a low cribriform height relative to the ethmoidal roof predispose the patient to CSF-L during ESS. It could be speculated that these anatomic characteristics may predispose the injuries of the medial part of the skull base during the dissection of the superior ethmoidal cells, when the surgical instruments are in close proximity to the cribriform plate[12].

Even if the role of olfactory fossa depth has been previously stressed[8,14], only limited data regarding the slope of the anterior skull base and, in particular, of the angulation of the LLCP in the coronal plane are available[12,13]. This angle might affect the level of the ethmoidal roof relative to the cribriform plate[12], and consequently could play an important role when approaching the frontal sinus and during the dissection of the more medial ethmoidal cells. The aim of this study is to propose a novel classification of the angulation of the LLCP in the coronal plane based on the theoretical risk of iatrogenic injuries in the thinnest and the most vulnerable structure of the anterior skull base. It must be noted that the evidence of an increased risk for complications related to the angulation of the LLCP is really very limited (only a case control study measured the angle or the fovea ethmoidalis at the level of the posterior ethmoid in a group of patients with CFS leak[9]). Therefore, the classification here proposed is strictly hypothetical, although it seems logical and reasonable. In addition, normative data of the angulation of the LLCP in the coronal plane obtained in a large sample of CT scans were provided. Finally, the relationship between this new classification and the Keros' one was assessed.

The importance of this study lies in the fact that this new classification in association with the Keros'

one, may lead to a deeper standardization and systematic approach during the preoperative sinus imaging assessment and could be of further help in preventing major complications.

MATERIALS AND METHODS

Participants

In this retrospective cohort study, computed tomography (CT) scans obtained in a group of one-hundred-ninety subjects (118 males and 72 females) who present themselves to our department for the investigation of possible or evident sinonasal disease were retrospectively reviewed. All CT scans were performed on high-speed spiral CT scanners using non-contrast axial 1.5-mm sections. Exclusion criteria were: age lower than 18 years, previous trauma, sinonasal tumor, sinonasal polyposis (that precluded the visualization of skull base anatomy), skull-base defects, previous ESS and congenital abnormalities of the facial growth. Scans that deviated from a true coronal plane by more than 5° from the perpendicular plane of the floor of the nose were also excluded. The study was carried out according to the Declaration of Helsinki and it was previously approved by the Institutional Review Board of our hospital.

Similar to Ramakrishnan et al. study[10], high-resolution direct non-contrast axial 1.5-mm sections were analyzed. A specialized computer software ‘‘picture archiving and communication system’’ (PACS) was used for morphological evaluation of the CT scans[15] in order to obtain four sets of measurements. These measurements were taken, using a 3-D multi-planar reconstruction (MPR), at the convergence between the LLCP and the most anterosuperior part of the anterior ethmoidal roof at the level of the posterior margin of the frontal recess[16] on the coronal plane, and at the level of the posterior margin of frontal recess on the sagittal plane (Figure 1). This point was selected since it is well identifiable and represent an important landmark for the dissection of the ethmoidal cells and during the approach to the frontal sinus.

- Depth of the cribriform: the first measurement was the depth of the cribriform plate, measured as the vertical height of the olfactory fossa in the coronal plane on each side (Figure 2). According to Keros’ classification system, each CT scan was defined as type 1 (1-3 mm depth), type 2 (4-7 mm depth) or type 3 (more than 7 mm depth). Asymmetry in the depth (difference of more than 3 mm) between the right and left cribriform plates was also recorded.
- Angle: the second measurement was the angle formed by the LLCP and the continuation of the horizontal plane passing through the cribriform plate (Figure 3). The angle was classified into 3 classes depending on its amplitude and on the hypothetical risk of iatrogenic injuries: class I (> 80 degrees, low risk), class II (45 to 80 degrees, medium risk) and class III (< 45 degrees, high risk). The cutoff angles were decided a priori. In particular, the 45 degrees was selected because it is very simple to assess and consequently it should quickly alert the surgeon of potential risk to have the LLCP in a sloped plane. For the same reasons, the other cutoff angle should be 90 degrees. However, preliminary measurements highlighted that no patients scored higher than 90 degrees. The 80 degrees was chosen because on a “quasi” vertical plane and consequently easily to assess.
- Length of the LLCP: the third measurement was the length of the LLCP (Figure 4), considered as the thinnest part of the angulated bony structure connecting the cribriform plate to the ethmoidal roof.
- Width of the fovea: the fourth measurement was the length of the portion of fovea ethmoidalis included between the LLCP and a vertical line passing at the level of the lamina papiracea in

the frontal plane reconstruction (Figure 5).

Each CT scan was reviewed by two independent raters (named rater 1 and rater 2), specialized in sinonasal disease and with an experience of at least 20 years in ESS. Correlations between the four sets of measurements were analyzed. In addition, in order to evaluate the inter rater reliability of these measurements, the results obtained by rater 1 and 2 were compared. Finally, in order to evaluate the intra rater reliability, rater 1 analyzed a random sample of 50 CT scans twice, with 2 weeks of interval. During the second evaluation the rater was blind to the results obtained during the first evaluation.

Statistical Analysis

Statistical tests were performed using the SPSS 21.0 statistical software (SPSS, Inc., Chicago, IL). Mean ± standard deviation and ranges were calculated for the measurements. The differences in the distribution of the measurements between males and females were evaluated through Student t for continuous variables and through Chi-square test for categorical variables. The degree of association between the angle width, LLCP length, depth of the cribriform plate and length of the portion of fovea ethmoidalis was estimated using Pearson's correlation coefficient. The same test was also used to analyze the inter- and intra-rater reliability of the measurements.

RESULTS

A total of 190 paranasal sinuses CT scans were retrospectively analyzed. The mean age of the patients included in the study was 43.6 ± 7.2 years (range, 19-67 years). One-hundred eighteen patients were males (62.1%), the remaining 72 patients were females (37.9%). The mean age of male patients was 43.2 ± 8.1 years (range, 19-66 years), while the mean age of female patients was 46.2 ± 6.9 years (range, 20-67 years). No differences were found in the distribution of age among males and females on Student t test ($p = 0.434$).

- Depth of the cribriform: the mean depth of the cribriform plate was 5.4 ± 1.7 mm (range, 2.4-10.3 mm). The mean depth of the cribriform plate in males was 5.6 ± 1.7 mm (range, 2.4-10.1 mm) while in females it was 5.2 ± 1.7 mm (range, 2.9-10.3 mm). These differences were found not significant on Student t test ($p = 0.909$). The most common anatomic variation was Keros type 2 (64.7% of cases), followed by Keros type 1 (20% of cases) and Keros type 3 (15.3% of cases). No significant differences in the distribution of Keros classification among males and females were found on Chi-square test ($p = 0.510$). Asymmetry in the depth of the cribriform plate was reported in 12.3% of patients. In 60.2% of them the height of the fovea ethmoidalis was lower at the right side compared to the left one.
- Angle: the mean degree of the angle formed by the LLCP and the continuation of the horizontal plane passing through the cribriform plate was 71.7 ± 12.1° (range 27-89°). The mean angle degree in males was 71.5 ± 13.7° (range, 27-87°) while in females it was 72.1 ± 10.7° (range, 32-89°). These differences were found not significant on Student t test ($p = 0.179$). In 62.7% of cases, the angle ranged from 45 to 80 degrees (class II, medium risk). In 32.6% of cases the angle measured more than 80 degrees (class I, low risk) and in 4.7% of cases the angle measure less than 45 degrees (class III, high risk). No significant differences in the distribution of angle classification among males and females were found on Chi-square test ($p = 0.108$).
- Length of the LLCP: the mean length of the LLCP was 4.7 ± 1.4 mm (range, 2.9-10.7 mm). The mean length of LLCP in males was 5.0 ± 1.5 mm (range, 2.9-10.7 mm) while in females it was 4.5 ± 1.7 (range, 3.1-10.4 mm). These differences were found not significant on Student t test ($p = 0.097$).
- Width of the fovea: the mean length of the fovea ethmoidalis was 8.8 ± 2.3 mm (range, 2.4-16.7 mm). The mean length in males was 8.8 ± 2.4 mm (range, 2.4-16.7 mm) while in females it was 8.9 ± 2.2 (range, 2.5-16.4 mm). These differences were found not significant on Student t test ($p = 0.276$).

The results of the correlation analysis are reported in Table 1. Figures 6-8 reported the scatterplots showing the relation between the angle formed by the LLCP and the continuation of the horizontal plane passing through the cribriform plate and the others parameters. The angle was positively correlated with the depth of the cribriform and the width of the fovea, while it was negatively correlated with the length of the LLCP. The length of the LLCP was negatively correlated with the angle and with the length of the fovea. In particular, class I patients (angle width more than 80 degrees), scored higher in the width of the fovea and in the depth of the cribriform. On the contrary, class III patients (angle width less than 45 degrees) presented higher values in LLCP length.

The results of intra- and inter-rater reliability analysis are reported in Table 2. The intra- and inter-rater reliability was higher than r = 0.82 for all the 4 measurements and reached the value of r = 0.92, p = 0.022 and r = 0.90, p = 0.32 for the intra- and inter-rater reliability of the measurement of the angle between the LLCP and the cribriform plate respectively.

The distribution of the angle classes and Keros types among the 190 enrolled patients is reported in Table 3. The majority of patients were classified as Keros type 2 and angle class II, followed by patients classified as Keros type 1 and angle class II and patients classified as Keros type 3 and angle class II.

DISCUSSION

In this study the slope of the anterior skull base in the coronal plane and its relation with the Keros' classification was analyzed in a large group of patients complaining sinonasal disease. The underlining hypothesis is that a more pronounced slope of the anterior skull base on the coronal plane, may predispose to injuries of the medial part of the skull base during the dissection of the more medial ethmoidal cells and during the approach to the frontal sinus. In fact, during these surgical steps the instruments are in close proximity to the LLCP and the dissection is carried from posterior to anterior; thus it is possible that a more pronounced ethmoidal roof slope may predispose surgeons to inadvertent skull base violation. Consequently, a deeper understanding of this anatomical region is needed in order to reduce the risk of complications during ESS. To the best of our knowledge only few studies analyzed the slope of the anterior skull base[10,12,13] but scarce information is available regarding its relationship with other measurements of the ethmoid analyzed through computed tomography. In addition, in none of the previous studies the measurement of the degree of the ethmoidal roof slope in the coronal plane was performed. Only Heaton et al. [9] compared the slope of the skull base on the coronal plane in CSF-leak patients and in a control group and concluded that CSF-leak patients have a larger slope of the skull base than those of the control group. However, no information regarding the degree of the angle of the skull base were provided. In the present study, data on the degree of the angle formed by the LLCP and the continuation of the horizontal plane passing through the cribriform plate in a population complaining sinonasal disease were provided and a new 3-points classification of the slope of the anterior skull base in the coronal plane was proposed. In particular, we propose to classify the angle into 3 classes, depending on its amplitude and on the theoretical risk of iatrogenic injuries: class I (> 80 degrees, low risk), class II (45 to 80 degrees, medium risk) and class III (< 45 degrees, high risk). In the present series the large majority of the patients were classified as class I (low risk) and II (moderate risk), while only 4.6% of patients were classified as at high risk for iatrogenic injuries. Among the patients classified as class III angle, 3.6% demonstrated a Keros type 1, 0.5% demonstrated a Keros type 2 and 0.5% demonstrated a Keros type 3 on the right side, whereas 4.2% demonstrated a Keros type 1, 0.5% demonstrated a Keros type 2 and 0% demonstrated a Keros type 3 on the left side (Table 3). It might be consequently speculated that a significant percentage of patients classified as low risk according to Keros' classification, may have a high risk of iatrogenic injuries because of a more pronounced slope of the anterior skull base.

The distribution of Keros' classification across the 190 patients enrolled in this study was similar to the majority of previous reports[17-22] (see Table 4). Also in our sample a higher frequency of Keros type 2 (64.7%) was found, followed by type 1 (20%), and type 3 (15.3%). Guler et al. [21] found the mean height of the ethmoidal roof ranging from 3.9 mm to 4.5 mm at the right side and from 3.9 mm to 4.4 mm at the left side. Erdem et al. [23] found the mean height of the ethmoid roof as 6.1 mm at the right side and 6.3 mm at the left side. Meloni et al. [24] defined the mean depth of the cribriform as 5.9 mm in 106 Italian patients. This value appears very similar to the findings of the present study, and it is possible to speculate that the differences in the anatomic development in the ethmoidal roof might be related not only with heredity, environmental factors and previous chronic infections that could have affected the development of the sinuses, but also with ethnicity[25].

No differences in the distribution of Keros olfactory fossa or in the mean height of the ethmoidal roof was demonstrated between males and females. These results appear in contrast with those reported by Elwany et al.[1] who demonstrated that Keros type 2 was more common in men, while type 1 was commoner in women. However, also in Remarkrishan et al. [10] study no differences in the distribution of olfactory fossa height was found among males and females.

In the present study, asymmetry in the depth of the cribriform was reported in 12.3% of patients and in the majority of the cases the height of the fovea ethmoidalis was lower at the right side compared with the left side. These findings are similar to those of Lebowitz et al. [12], who analyzed 200 CT scans, and reported an asymmetry of the ethmoidal roof in 9.5% with a fovea ethmoidalis lower on the right side in the majority of cases. Dessi et al. [26], found the right fovea ethmoidalis lower than the left fovea ethmoidalis in patients with olfactory fossa asymmetry. Also Cumberworth et al (27) who analyzed through postal questionnaires (completed by members of the British Association of Otolaryngologist) the incidence of major complications during ESS, reported higher incidence of CSF leak on the right side, possibly related to asymmetry in the depth of the cribriform.

The high frequency of ethmoidal roof asymmetry further suggests careful preoperative review of the anatomical variations with CT scan in order to prevent the complications.

A significant positive correlation between the depth of the cribriform fossa, the length of LLCP and the degree of the angle between the LLCP and the cribriform plate was found. This agrees with the findings of Elwany et al. [1] who reported that the depth of the olfactory fossa depends upon the length and angulation of the lateral lamella. Also Souza et al. [19] observed that the ethmoidal roof asymmetry was related to the angulation of the lateral lamella. It must be noted that the length of the LLCP was negatively correlated with the length of the fovea ethmoidalis and the degree of the angle. These data suggest that subjects with a more pronounced slope of the anterior skull base on the coronal plane could have a longer LLCP and a shorter fovea ethmoidalis, than subjects with a less pronounced slope of the anterior skull base. It is consequently possible to speculate that the degree of the angle formed by the LLCP and the continuation of the horizontal plane passing through the cribriform plate could provide indirect information regarding the thickness of the anterior skull base since, as the angle decreases, the portion of the anterior skull base composed by the LLCP, increases. Interestingly, the correlation between the LLCP and the depth of the cribriform was the poorest of all, in addition, the depth of the cribriform appeared longer than the LLCP. This datum could be related to several factors. First of all, in this study we measured only the length of the LLCP (considered as the thinnest part of the angulated bony structure connecting the cribriform plate to the ethmoidal roof) and is consequently not surprising that the depth of the cribriform could be longer than the LLCP. Moreover, the poor correlation between the depth of the cribriform and the length of the LLCP could be also related to the angulation of the latter (for example in cases where the LLCP is long but very angulated on the coronal plane and consequently the depth of the cribriform was considered small).

Information regarding the intra- and inter-rater reliability of ethmoidal measurements were provided for the first time. Both intra- and inter-rater reliability were high for all the 4 measurements suggesting a good reproducibility over time. This data might be related to the anatomical landmarks used for the measurements. All the measurements, in fact, were performed at the convergence between the LLCP and

the most anterosuperior part of the anterior ethmoidal roof at the level of the posterior margin of the frontal recess[17] on the coronal plane, and at the level of the posterior margin of frontal recess on the sagittal plane. Consequently, it is possible that the use of a well identifiable landmarks as well as of MPR could have improved the reliability of the measurements.

In conclusion, in the preoperative evaluation of a patient with sinonasal disease, careful evaluation of the CT scan is mandatory. In the past years, the height of the ethmoidal skull base was considered as the most important factor for identification of high-risk anatomic situations within the ethmoid. However, the presence of significant correlations among different ethmoidal measurements highlights the importance of assessing more than just the height of the ethmoidal skull base. In particular, the evaluation of the angle formed by the LLCP and the continuation of the horizontal plane passing through the ethmoidal plate could provide indirect information regarding the thickness of the anterior skull base, which is, in the opinion of the Authors, crucial before surgery. A better analysis of the convergence between the frontal sinus and the ethmoid on the skull base could assure a 'safer' surgical approach to this area. We believe that the application of the classification system here proposed could be consequently useful in the preoperative assessment of sinus imaging in order to prevent major complications. However, future studies including patients with CSF leak caused by injuries at the level of LLCP occurred during ESS procedures are required to validate the classification here proposed.

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AUTHORSHIP CONTRIBUTION

Gera R[1], Mozzanica F[1], Karligkiotis A[2], Preti A[2], Bandi F[2], Gallo S[2], Schindler A[3], Bulgheroni C[1], Ottaviani F[1], Castelnuovo P[2]

Gera R, Castelnuovo P, Schindler A, Ottaviani F: Substantial contributions to the conception or design of the work, revising it critically for important intellectual content, final approval of the version to be published.

Preti A, Bandi F, Gallo S: Substantial contributions to the acquisition of data for the work, revising it critically for important intellectual content and final approval of the version to be published.

Mozzanica F, Karligkiotis A: Substantial contributions to the analysis and interpretation of data for the work. Drafting the work. Final approval of the version to be published.

CONFLICT OF INTEREST

None of the authors have any conflict of interest to declare

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FIGURES

Table 1: Results of the correlation analysis among the ethmoidal measurements.

	Depth of the cribriform	LLCP	Angle	Width of the fovea
Depth of the cribriform	1	0.338*	0.553**	0.385*
LLCP	0.338*	1	-0.397*	-0.342*
Angle	0.553**	-0.397*	1	0.336*
Width of the fovea	0.385*	-0.342*	0.336*	1

* = $p < 0.05$

** = $p < 0.01$

Table 2: Results of inter- and intra-rater reliability analysis.

	Intra-rater	Inter-rater
Depth of the cribriform	0.85	0.82
LLCP	0.90	0.87
Angle	0.92	0.90
Width of the fovea	0.89	0.86

Table 3: Distribution of Keros classification and angle formed by the LLCP and the continuation of the horizontal plane passing through the cribriform plate.

	Right (%)			Left (%)		
	Class I	Class II	Class III	Class I	Class II	Class III
Keros 1	3.2	13.1	3.6	3.2	12.6	4.2
Keros 2	20.3	43.8	0.5	21.1	43.2	0.5
Keros 3	8.5	6.5	0.5	10.1	6.3	-
Total	32	63.4	4.6	33.2	62.1	4.7

Table 4: Distribution of Keros' classification in previous studies.

Author	N° patients	Keros' classification		
		1	2	3
Basak et al [15]	61	9%	53%	38%
Jang et al [16]	205	30.5%	69.5%	-
Anderhuber et al [17]	272	14.2%	70.6%	15.2%
Souza et al [18]	200	26.3%	73.3%	0.5%
Sahin et al [19]	100	10%	61%	29%
Guler et al [20]	300	26%	66%	8%
Remarkrishan et al [10]	200	42%	50%	8%
Peber et al [21]	109	81.6%	17.9%	0.5%