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HEAD AND NECK

Classification and volumetric study of the sphenoid sinus on MDCT images

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Abstract

Purpose We aimed to determine the position and size of the sphenoid sinus (SS) in our study and compare the results of the measurements relative to age, gender, and the presence of pituitary adenoma using multidetector computerized tomography (MDCT).

Methods We retrospectively evaluated the paranasal sinus computerized tomography (CT) images of 200 individuals (age range of all the individuals 4–84 years; 101 females, 99 males; age range of individuals with pituitary adenoma 15–63 years; 15 females, 9 males) with 24 pituitary adenomas. The shape of SS were identified and classified, volume were measured by MDCT also for individuals with pituitary adenoma.

Results It was determined that the volume averages were significantly affected by the type of SS. Among all the individuals studied, the sellar type of SS was most frequently observed (41.5%), followed by the postsellar type (38.5%), and the least observed was the presellar type (9%). The volume of the SS is bigger in males than females although the volume is not affected by the presence of pituitary adenomas. The development of the SS continues until the age of nine.

Conclusion The morphology and morphometry of the SS show individual differences. These anatomic variations are important for decision making and application for surgical interventions (especially transsphenoidal surgery).

Keywords Sphenoid sinus · Morphology · Morphometry · Variation · Multidetector computed tomography

Introduction

The development of the sphenoid sinus (SS) commences at the 8th week of intrauterine life with bilateral invaginations of the posterior nasal capsule to the os sphenoidale [1]. The non-pneumatic SS is usually present at birth [2]. Pneumatization of the SS has been reported to begin at age 2–3 years, although the reported age at onset differs in various studies [3, 4]. Jang and Kim [5] reported that the degree of pneumatization can be determined between the 8th week of gestation and 3 years of age in axial section and between the ages of 4 months and 6 years in sagittal section. Pneumatization was found to develop from the age of 1 year [6], 1–2 years [7], and 6 years [8]. The development period of pneumatization was reported as 3–5 years [1] and 6–10 years [6]. After its onset, pneumatization progresses in the inferior posterolateral direction [4]. The back edge of the SS extends to the anterior wall of the sella turcica at 7 years of age [1].

Several studies report a wide age range, between 10 and 18 years, for pneumatization to reach adult size [2–4, 6, 9],

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while Yonetsu et al. [7] reported that the expansion of the SS continuous until the end of the third decade of life.

Pituitary adenomas constitute the most common pituitary problems. Clinically diagnosed pituitary adenomas constitute 10–15% intracranial tumors [10]. The anatomical location of the SS is significant to neurosurgeons, because the SS is a way most accessible in approach to the pituitary gland [11]. Due to the close proximity of the SS to the pituitary gland its variability in shape, position and size is important in deciding and implementing surgery of the pituitary gland and its surroundings, in particular the transsphenoidal approach. To date, few articles have been published on the measurement of the volume of the sphenoid sinus in different populations [7, 12] and methods used were different as well as classifications [13–16].

Therefore, the aim of this study was to examine the development of the SS, to evaluate the shape and volume according to, age, gender and the presence of pituitary adenoma.

Materials and methods

This single-center retrospective study was approved by the local institutional review board with a waiver of the requirement for written, informed consent.

Scans were performed with a 256-slice multidetector computed tomographic scanner (Siemens Somatom Flash, Erlangen, Germany). Imaging parameters were as follows: kV = 120; mA = 160; rotation time = 0.5 s; collimation = 64 × 0.625; FOV = 220 mm. Images that included the paranasal sinus were analyzed retrospectively on a workstation (Snygo Via, Siemens, Germany). A total of 200 individuals (101 female, 99 male) who underwent measurements of the SS were studied in 8 different age groups according to gender, development of anatomical structures and the presence of pituitary adenoma. They were also grouped according to accepted age classification i.e. prepubertal, before 15 years; postpubertal, after 15 years and geriatric after 60 years [17, 18]. This grouping is based on the age limits reported in different studies [1–4, 6] for the development of the SS ranging from 4–9 years, 10–14 years, 15–19 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years and 60 years and over (Table 1).

Shape of the sphenoid sinus

While examining the shape of the SS, the relationship between the anterior and posterior wall of the sella turcica with the posterior wall of the SS was evaluated. The shape of the SS was examined in four groups including conchal, presellar, sellar and postsellar which were previously determined by different authors [11, 16].

Conchal type: the SS was as a small space in front of the anterior wall of the sella turcica (Fig. 1a, e).

Presellar type: the SS was found in front of the sella turcica but not moving to the rear. The posterior wall of the SS is located in front of the anterior wall of the sella turcica [16] (Fig. 1b, f).

Sellar type: the posterior wall of the SS is between the anterior and posterior wall of the sella turcica [16] (Fig. 1c, g).

Postsellar type: the posterior wall of the SS is located behind the posterior wall of the sella turcica [16] (Fig. 1d, h).

Volume of the sphenoid sinus

The boundaries of the sinus were drawn by evaluating each axial section in the area of the SS. The drawings in these sections were automatically saved in the computer memory. This process was repeated separately for each side. All sections were automatically evaluated by the computer program and the volume of the SS was calculated.

Volume measurements of the SS in the different shapes (conchal, presellar, sellar, postsellar) obtained were calculated separately (Figs. 2, 3).

Statistical analysis

In this study, SPSS version 22.0 for Windows (SPSS, Chicago, IL, USA) package program was used for statistical analysis of data. To compare possible differences between SS shape and volume averages according to gender, age group, presence of pituitary adenoma, the assumption of normality and homogeneity of variances was checked from the parametric test assumptions before applying the one way ANOVA. One way ANOVA was performed to determine any difference between the mean of the groups according to age and the volume of the SS.

Table 1 Distribution of individuals according to age and gender

	Age groups								
	4–9	10–14	15–19	20–29	30–39	40–49	50–59	60 years and over	Total
Female	10	11	13	13	13	15	13	13	101
Male	10	10	13	12	15	15	12	12	99

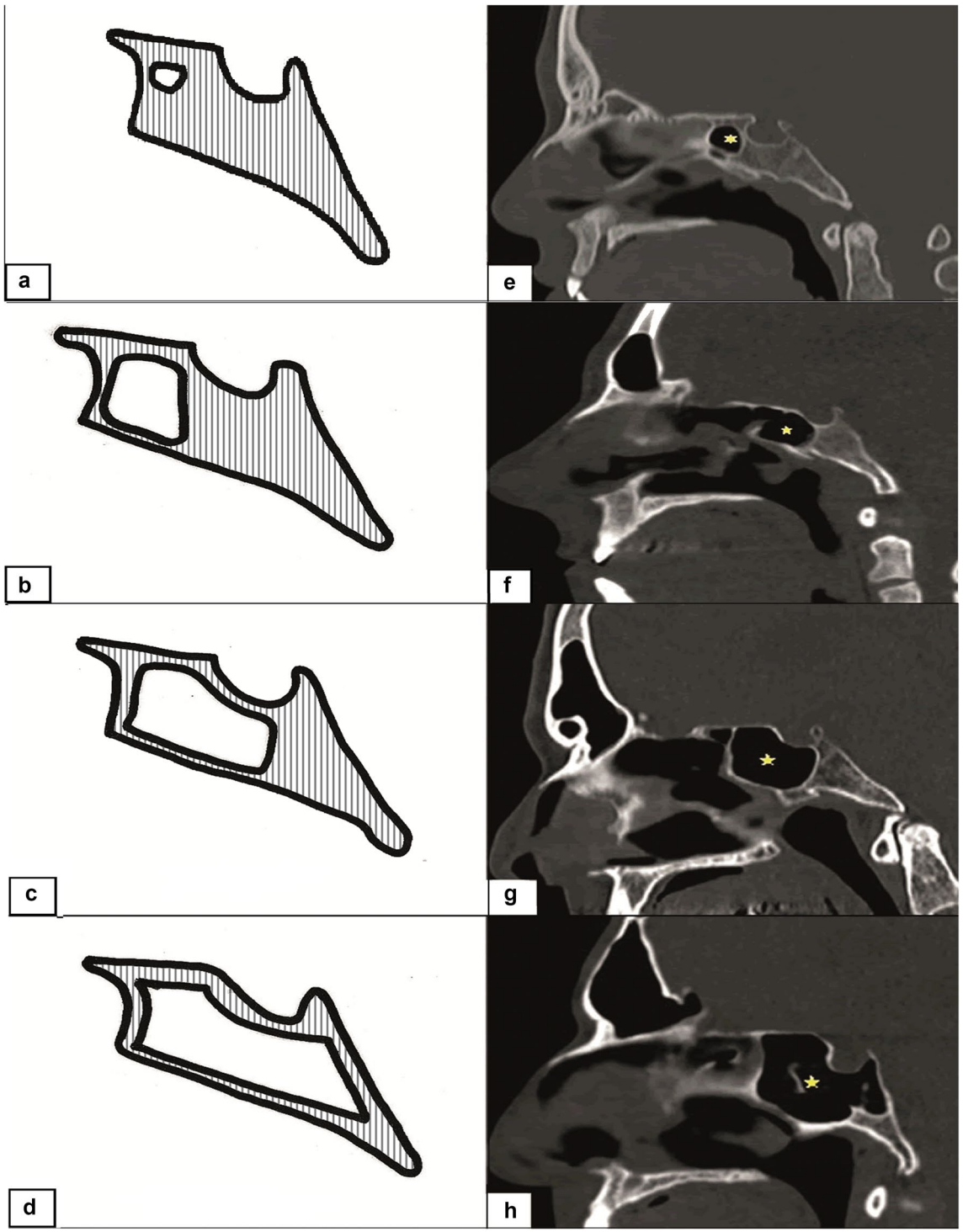

Fig. 1 Conchal, presellar, sellar, postsellar types; schematic diagram showing, respectively (**a**–**d**) [11] [Kayalioglu et al. [11] study has been modified.]; midsagittal MDCT images, respectively (**e**–**h**)

According to the analysis results, the difference in volume of the SS between the age groups was found to be statistically significant ($p < 0.05$). The Bonferroni multiple comparison statistical test was applied to determine the difference between age groups.

Results

In our study, according to the degree of pneumatization, the shape of the SS was examined in four types including conchal, presellar, sellar and postsellar.

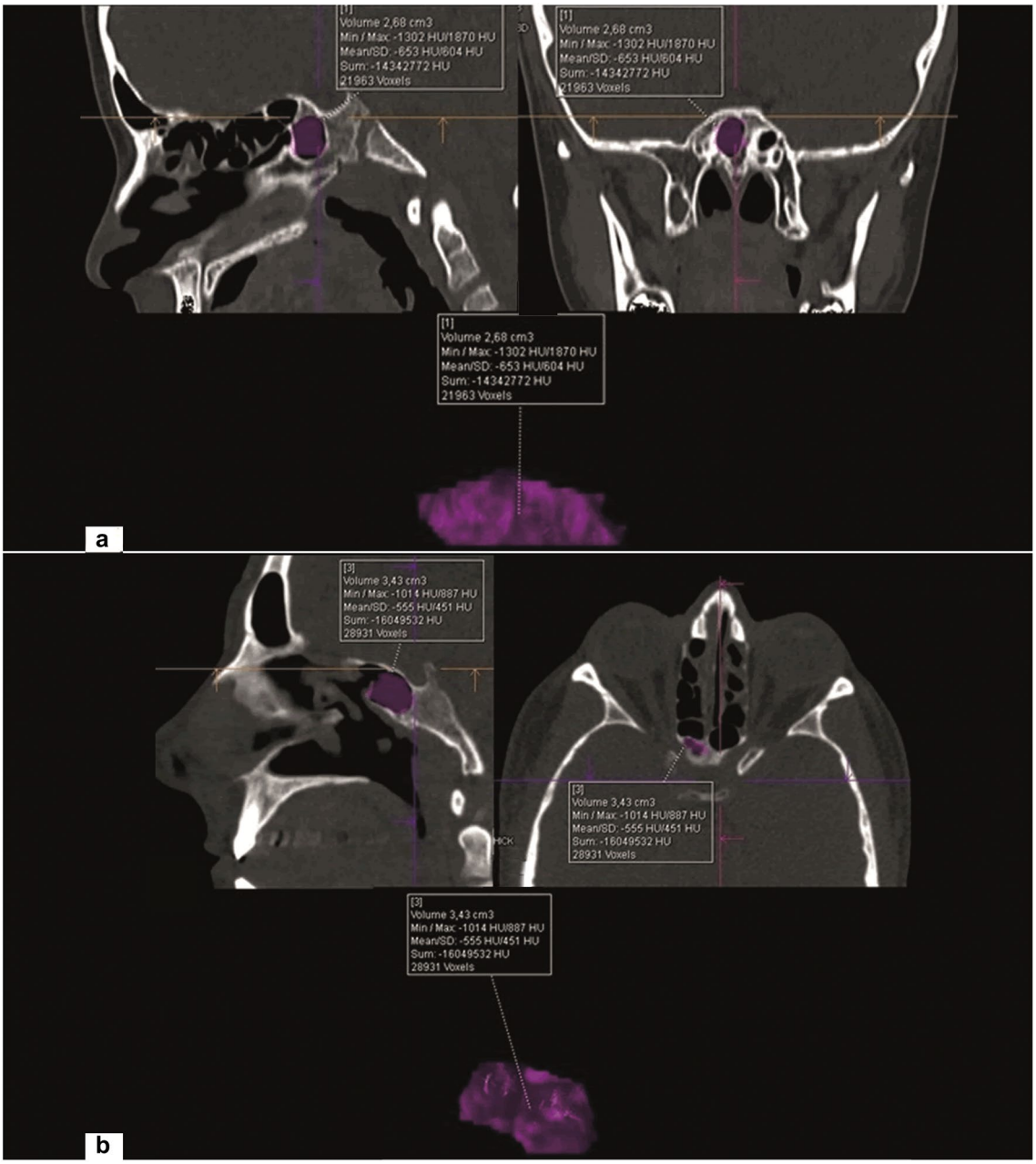

Fig. 2 Volume of conchal type (**a**) and presellar type (**b**) (purple)

The most observed was the sellar type (41.5%), followed by the postsellar type (38.5%), the conchal type (11%) and the presellar type (9%) in all individuals. Similarly, when evaluated the SS types in individuals with pituitary adenomas the most type was the sellar type (58.3%), followed by the postsellar type (16.7%), concal type (12.5%) and presellar type (12.5%). Statistically, it was determined that the presence of adenoma did not affect the sinus shape.

The most SS type in females was the sellar type (39.6%), followed by the postsellar type (36.6%), concal type (12.9%) and presellar type (10.9%). The most SS type in males was the sellar type (43.4%), followed by the postsellar type (40.4%) concal type (9.1%) and the presellar type sinus (7.1%).

Statistical analysis results showed that the volume average of the SS changed according to shape (Table 2). It was found that the volume of the SS was statistically greater in males than females ($p < 0.05$).

There was a statistically significant difference in the volume of the SS between the youngest age group,

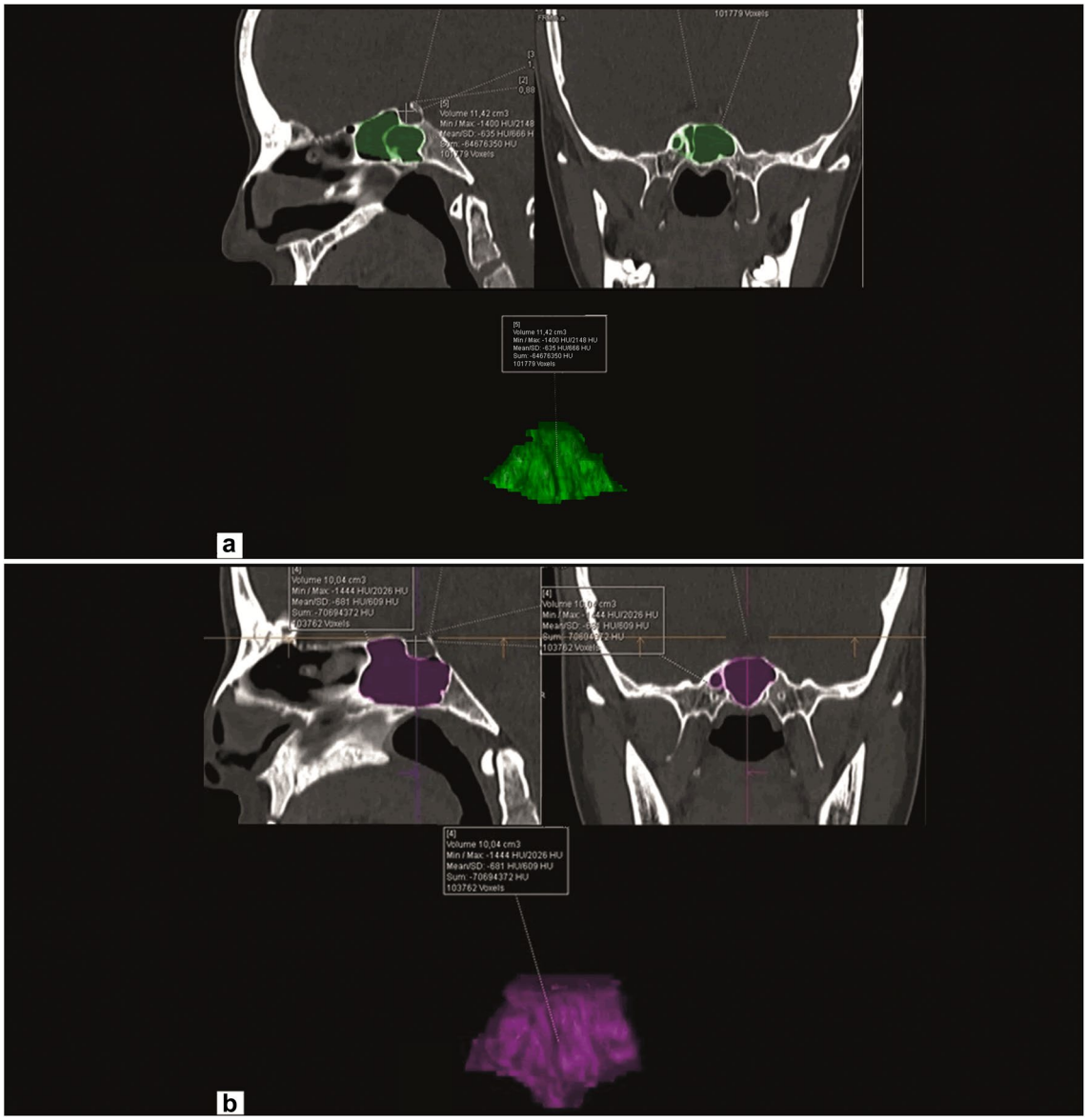

Fig. 3 Volume of sellar type (**a**) (green) and presellar type (**b**) (purple)

Table 2 Volume according to type of sphenoid sinus (SS) (cm^3)

Shape of SS	Minimum	Maximum	Mean ± SD
Conchal type	0.43	9.18	3.27 ± 2.08
Presellar type	3.2	13.58	6.52 ± 2.68
Sellar type	3.04	23.85	10.39 ± 3.39
Postsellar type	3.58	23.13	13.02 ± 4.09

SD standard deviation

4–9 years ($p < 0.05$) and the other groups. Differences between the measurement of volumes in the six other age groups was not statistically significant ($p > 0.05$).

There was no statistically significant difference in the volume of the SS between healthy individuals and individuals with pituitary adenomas ($p > 0.05$).

Discussion

The SS is quite an interesting structure for researchers. Different reports in the literature have defined the volume, anatomical variations and development of the SS in different populations. Some of the published reports are studies on cadavers [13], while others have studied radiological images (cone-beam computed tomography images, computed tomography images, magnetic resonance images,

X-ray images and helical computed tomography images) of living humans [12, 15, 16, 19, 20]. In addition, such studies compared computed tomography and magnetic resonance images [14], cadaver and computed tomography images [21]. We aimed to determine the shape, volume and anatomic variations of the SS and compare the results of the measurements relative to age, gender, and the presence of pituitary adenoma using MDCT.

The types of SS in different populations have been investigated, using different methods and classification types, summarized in Table 3. Some of these studies classify the three types as conchal, presellar and sellar [13, 21, 22], while others use a four type classification, adding the postsellar type to the other [11, 14, 16]. In our study, the SS was classified into four types and the most frequent respectively sellar type (41.5%) and postsellar type (38.5%) were observed. Although all the studies about SS classifying have changed rates, it is observed that the most common type was sellar type (Table 3). In addition, the incidence of the presellar type was third common in these studies, whereas the conchal type was third in our study.

The pneumatization of SS continues with age [1, 3, 4], so we think that the age of the examined individuals will affect the incidence and volume of SS types. Banna and Olutolu [13] examined adult cadavers, while other studies [14–16, 19, 21] examined individuals over the age of 18. In our study, we wanted to evaluate development of the SS, in subjects over a wide age range.

Güldner et al. [16] and Sheikh and Zahran [15] reported that the incidence of SS types were not affected by gender. In our study, the most common type of SS was the sellar type in males and females (respectively 43.4%, 39.6%), and the least common type was the presellar type (respectively 7%, 10.9%) (Table 3). Lu et al. [21], examined CT images of 200 (individuals over 18 years) and 18 cadavers, evaluated the types of SS separately. The most common type was the sellar type, while the least common was the conchal type in both groups. Hamid et al. [14], report that a total of 296 individuals over 18 years with SS type with adenomas were examined. The least common type in the Hamid et al. [14] study was the conchal type, while it was the presellar type in our study. This difference may be caused by the inclusion of individuals under the age of 18 years in our study.

The standard approach in the surgery of pituitary adenoma is the transsphenoidal approach. The variant ways to the sella turcica; transethmoidal, transnasal, transseptal, whether microscopic or endoscopic, finally pass through the SS to reach the sella turcica. Therefore, the anatomical variations of the SS have an important bearing on the surgical operation and the probability of complications [14]. Identification of the degree of pneumatization in the SS plays an important role for the surgeon because the various types of sinus pneumatization determine the surgical technique of the transsphenoidal approach. The thickness of the anterior wall of the sella turcica, an important measurement in transsphenoidal surgery, has been reported as 0.3–1.5 mm (mean 0.7 mm) in the presellar type and 0.1–0.7 mm (mean 0.4 mm) in the sellar type [23]. The conchal type SS was conceived as contraindication for the transsphenoidal approach to the sella turcica, but surgical advances and different devices have made this approach practical in the conchal type [14, 24]. High pneumatization disrupts the anatomical structure of the SS possibly leading to a thinning of the lateral wall, which may put pressure on the optic nerve and internal carotid artery. In addition, the relevant walls of the middle cranial fossa may also thin and be easily damaged during the operation [14].

The studies in which the volume of SS is evaluated in different populations using different methods are summarized in Table 4.

Yonetsu et al. [7] examined volume of the SS in nine different age groups between 1 and 80 years and reported that

Table 3 A comparison of the types of SS among various studies (%)

Method		Population		Conchal		Presellar		Sellar		Postsellar	
CADAVER	Banna and Olutola [13]	Unspecified		2.8		11.4		85.7		–	
BONES/CADAVERS/MR	Kayalioglu et al. [11]	Turkish		1.9		9		52.9		36.2	
CT/CADAVER	Lu et al. [21]	Chinese	CT	6		28.5		65.5		–	
			Cadaver	16		27		55			
CT/MRI	Hamid et al. [14]	Egyptian		2		21		54.7		22.3	
CONE-BEAM CT	Güldner et al. [16]	German		0.3		6.6		57.2		35.8	
X-ray	Sheikh and Zahran [15]	Arabian		–		37		63		–	
MDCT	Gibelli et al. [19]	Italian		–		10		74		16	
	Present study	Turkish		11		9		41.5		38.5	
				M	F	M	F	M	F	M	F
				9.1	12.9	7	10.9	43.4	39.6	40.4	36.6

CT computerized tomography, *MDCT* multidetector computerized tomography, *MRI* magnetic resonance imaging, *F* female, *M* male

Table 4 A comparison of volume of the SS among various studies (cm^3)

Methods	Authors	Population		
HELICAL CT	Yonetsu et al. [7]	Japanese	8.2	
MRI	Adibelli et al. [12]	Turkish	8.65	
CT	Cohen et al. [20]	Israeli	M 4.74	F 3.55
MDCT	Gibelli et al. [19]	Italian	8.96	
			M 10.0	F 7.92
MDCT	Present study	Turkish	10.26	
			M 11.23 ± 5.14	F 9.32 ± 3.97

CT computerized tomography, *MDCT* multidetector computerized tomography, *MRI* magnetic resonance imaging, *F* female, *M* male

the volume increased until third decade then it decreases. Yonetsu et al. [7] reported that there was no statistically significant difference in terms of age groups between male and female. The volume and shape of the SS are important because this structure must be examined when performing hypophyseal surgery. SS pneumatization is difficult to evaluate; thus, even a little information on its morphology might be useful [7].

Adibelli et al. [12] calculated manually the volume of the SS in subjects with an age range 0–18 years, while we calculated the volume of the SS automatically in a computer program. The mean volume of the SS was found to be smaller than in our results. The reason for this may be because we examined children and adult individuals in our study.

Cohen et al. [20] examined individuals 25 years of age and over, individuals classified as before and after 65 years of age group, the volume of the SS of the group before 65 years of age was reported to be significantly larger. Also, the volume of the SS was significantly greater in males than females.

Gibelli et al. [19] reported that the volume of the SS was significantly greater in males than females in all types of SS (conchal, presellar, sellar, postsellar). Differences of volume according to the type of SS were statistically significant.

In our study, there was a statistically significant difference between the age groups in terms of volume group averages, only in the 4–9 years age group ($p < 0.05$); the difference between the volumes of the SS in the other age groups was not statistically significant ($p > 0.05$). This result shows that the development of SS continues until the age of nine, and is reached to adult size at ten years. Scuderi et al. [4] reported that the SS reaches adult size at the age 14 years.

Spaeth et al. [9], reported that up to the age of 5–6 years, sinus volume is greater in girls than in boys of same age and then the situation tends to reverse. Understanding these changes in the volume of the SS will also be useful in interpreting radiological images and evaluating normal SS development [4].

In addition, the difference in volume of the SS between healthy individuals and individuals with pituitary adenoma was not statistically significant ($p > 0.05$). This result shows that the volume of the SS is not affected by the presence of pituitary adenomas.

Barotrauma of the SS may cause headaches, blindness and pressure to the internal carotid artery, therefore, the volume of the SS is particularly important in divers [25], and for individuals associated with this sport because the volume of the SS may be considered as criteria for safe diving.

SS mucocele may cause serious complications such as permanent blindness due to pressure on the optic nerve [26]. The degree of pneumatization of the SS may cause defects in the wall of the sinus and due to its proximity the sinus can protrude into the internal carotid artery. For example, in the postsellar type SS clivus may get thinner and, therefore, might be damaged in basillar plexus operations [27]. Posterior or lateral enlargement of the SS may cause compression to the parasellar and paraclival sections of the internal carotid artery [22].

Posterior ethmoidal cells may sometimes become Onodi cells which may protrude into the lateral and/or superior areas of the SS. The optic nerve may lie within this sphenoethmoid cell, as well as in the lateral wall of the SS. It is important for surgeons to understand the location of the Onodi cells because of proximity to the optic nerve, the internal carotid artery and the pituitary gland. Onodi cells are frequently confused with SS often causing complications in sphenoidotomy [28]. Therefore, it is important to determine the shape and normal volume of the SS according to age and gender for successful diagnosis and surgery.

In conclusion, this study provides information about the development of sphenoid sinus and the close relationship between its volume and shape. The development of the SS continues until the age of nine, reaching adult sizes from the age of ten years. The volume of the SS is bigger in males than females. Additionally, the presence of pituitary adenoma does not affect the volume of the SS. Therefore, in pituitary adenomas that fill the sella turcica and extend to the suprasellar area, or in cases such as pituitary apoplexy, the pressure effect moves up and/or sideways may affect the important soft structures in the proximity (optic chiasm, cavernous sinus and inside the cranial nerves, the internal carotid artery and branches).

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Compliance with ethical standards

Conflict of interest None of the authors have a personal conflict of interest to declare.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval (approval number 2016/205) was given by the Non-Intervention Clinical Research Ethics Committee of the Medical Faculty.

Informed consent A formal informed consent procedure was waived due to the retrospective nature of this study.

References

1. Som PM, Lawson W, Fatterparker GM et al (2011) Embryology, anatomy, physiology and imaging of the sinonasal cavities. In: Som PM, Curtin HD (eds) Head and neck imaging, 5th edn. Elsevier Health Sciences, St. Louis, pp 99–141
2. Reittner P, Doerfler O, Goritschnig T et al (2001) Magnetic resonance imaging patterns of the development of the sphenoid sinus: a review of 800 patients. Rhinology 39(3):121–124
3. Leclerc JE, Leclerc JT (2009) Sphenoid sinus development in choanal atresia. Int J Pediatr Otorhinolaryngol 73(12):1746–1750
4. Scuderi AJ, Harnsberger HR, Boyer RS (1993) Pneumatization of the paranasal sinuses: normal features of importance to the accurate interpretation of CT scans and MR images. AJR Am J Roentgenol 160(5):1101–1104. https://doi.org/10.2214/ajr.160.5.8470585
5. Jang YJ, Kim SC (2000) Pneumatization of the sphenoid sinus in children evaluated by magnetic resonance imaging. Am J Rhinol 14(3):181–185
6. Park IH, Song JS, Choi H et al (2010) Volumetric study in the development of paranasal sinuses by CT imaging in Asian: a pilot study. Int J Pediatr Otorhinolaryngol 74(12):1347–1350. https://doi.org/10.1016/j.ijporl.2010.08.018
7. Yonetsu K, Watanabe M, Nakamura T (2000) Age-related expansion and reduction in aeration of the sphenoid sinus: volume assessment by helical CT scanning. AJNR Am J Neuroradiol 21(1):179–182
8. Tan HK, Ong YK, Teo MS et al (2003) The development of sphenoid sinus in Asian children. Int J Pediatr Otorhinolaryngol 67(12):1295–1302
9. Spaeth J, Krugelstein U, Schlondorff G (1997) The paranasal sinuses in CT-imaging: development from birth to age 25. Int J Pediatr Otorhinolaryngol 39(1):25–40. https://doi.org/10.1016/S0165-5876(96)01458-9
10. Lake MG, Krook LS, Cruz SV (2013) Pituitary adenomas: an overview. Am Fam Phys 88(5):319–327
11. Kayalioglu G, Erturk M, Varol T (2005) Variations in sphenoid sinus anatomy with special emphasis on pneumatization and endoscopic anatomic distances. Neurosciences 10(1):79–84
12. Adibelli ZH, Songu M, Adibelli H (2011) Paranasal sinus development in children: a magnetic resonance imaging analysis. Am J Rhinol Allergy 25(1):30–35. https://doi.org/10.2500/ajra.2011.25.3552
13. Banna M, Olutola PS (1983) Patterns of pneumatization and septation of the sphenoidal sinus. J Can Assoc Radiol 34(4):291–293
14. Hamid O, Fiky LE, Hassan O et al (2008) Anatomic variations of the sphenoid sinus and their impact on trans-sphenoid pituitary surgery. Skull base 18(1):9–15. https://doi.org/10.1055/s-2007-992764
15. Sheikh BY, Zahran MF (2006) Radiological anatomy of the sella turcica and sphenoid sinus. Pan Arab J Neurosurg 10(1):46–49
16. Guldner C, Pistorius SM, Diogo I et al (2012) Analysis of pneumatization and neurovascular structures of the sphenoid sinus using cone-beam tomography (CBT). Acta Radiol 53(2):214–219. https://doi.org/10.1258/ar.2011.110381
17. Chauhan P, Kalra S, Mongia S et al (2014) Morphometric analysis of sella turcica in North Indian population: a radiological study. Int J Res Med Sci 2(2):521–526. https://doi.org/10.5455/2320-6012.ijrms20140529
18. Alkofide EA (2007) The shape and size of the sella turcica in skeletal Class I, Class II, and Class III Saudi subjects. Eur J Orthod 29(5):457–463. https://doi.org/10.1093/ejo/cjm049
19. Gibelli D, Cellina M, Gibelli S et al (2018) Volumetric assessment of sphenoid sinuses through segmentation on CT scan. Surg Radiol Anat 40(2):193–198. https://doi.org/10.1007/s00276-017-1949-1
20. Cohen O, Warman M, Fried M et al (2018) Volumetric analysis of the maxillary, sphenoid and frontal sinuses: a comparative computerized tomography based study. Auris Nasus Larynx 45(1):96–102. https://doi.org/10.1016/j.anl.2017.03.003
21. Lu Y, Pan J, Qi S et al (2011) Pneumatization of the sphenoid sinus in Chinese: the differences from Caucasian and its application in the extended transsphenoidal approach. J Anat 219(2):132–142. https://doi.org/10.1111/j.1469-7580.2011.01380
22. Dal Secchi MM, Dolci RLL, Teixeira R et al (2018) An analysis of anatomic variations of the sphenoid sinus and its relationship to the internal carotid artery. Int Arch Otorhinolaryngol 22(2):161–166. https://doi.org/10.1055/s-0037-1607336
23. Rhoton AL Jr, Hardy DG, Chambers SM (1979) Microsurgical anatomy and dissection of the sphenoid bone, cavernous sinus and sellar region. Surg Neurol 12(1):63–104
24. Massoud AF, Powell M, Williams RA et al (1997) Transsphenoidal surgery for pituitary tumours. Arch Dis Child 76(5):398–404
25. Schipke JD, Cleveland S, Drees M (2018) Sphenoid sinus barotrauma in diving: case series and review of the literature. Res Sports Med 26(1):124–137. https://doi.org/10.1080/15438627.2017.1365292
26. Li E, Howard MA, Vining EM et al (2018) Visual prognosis in compressive optic neuropathy secondary to sphenoid sinus mucocele: a systematic review. Orbit 37(4):280–286. https://doi.org/10.1080/01676830.2017.1423087
27. Wiebracht ND, Zimmer LA (2014) Complex anatomy of the sphenoid sinus: a radiographic study and literature review. J Neurol Surg B Skull Base 75(6):378–382. https://doi.org/10.1055/s-0034-1376195
28. Wada K, Moriyama H, Edamatsu H et al (2015) Identification of Onodi cell and new classification of sphenoid sinus for endoscopic sinus surgery. Int Forum Allergy Rhinol 5(11):1068–1076. https://doi.org/10.1002/alr.21567