Childs Nerv Syst (2015) 31:699–703
DOI 10.1007/s00381-015-2644-3

ORIGINAL PAPER

Histological structure of the medial and lateral walls of cavernous sinus in human fetuses

Cahit Kural · Gulcin Guler Simsek · Servet Guresci · Erhan Arslan · Cenk Kilic · Ozkan Tehli · Murat Geyik · Cem Erbas · Yusuf Izci

Received: 21 January 2015 / Accepted: 3 February 2015 / Published online: 18 February 2015

Abstract
Purpose The aim of this study is to elucidate the architecture of these fine structures in human fetuses.
Methods The histological examination of medial wall (MW) and lateral wall (LW) was performed in 15 normal human fetuses. Eleven fetuses were female and four were male. The gestational age ranged between 14 and 35 weeks. The weight ranged between 180 and 1750 g. The wall samples (two MW and two LW from each fetus) were obtained by microsurgical technique and underwent histological examination. Each wall was examined for the structure and composition of collagen and elastic fibers, ganglions, peripheral nerves, and vessels.
Results A total of 60 wall samples (30 MW and 30 LW) were examined in 15 fetuses. Loose connective tissue composed of type III collagen was observed in both of the walls. Elastic fibers were observed only in three wall samples (two MW and one LW). Ganglion was detected in 11 samples (nine in LW and two in MW), and peripheral nerve was found in 28 walls (18 LW and 10 MW). Vessels were observed in 51 samples (26 LW and 25 MW). None of the walls was stained with type I collagen.
Conclusions The structure of LW and MW of the cavernous sinus (CS) in fetuses is mainly composed of collagen tissue while some elastic fibers are supported by this tissue. Type III collagen is the main component of fetal CS walls. Because of the weak histological structure, CS may be more prone to tumor invasion in infants.

Keywords Cavernous sinus · Fetus · Histology

C. Kural · O. Tehli · Y. Izci (✉)
Department of Neurosurgery, Gulhane Military Medical Academy, 06018 Etlik, Ankara, Turkey
e-mail: yusufizci@yahoo.com

G. G. Simsek · S. Guresci
Department of Pathology, Kecioren Research and Education Hospital, Ankara, Turkey

E. Arslan
Department of Neurosurgery, Kecioren Research and Education Hospital, Ankara, Turkey

C. Kilic
Department of Anatomy, Gulhane Military Medical Academy, Ankara, Turkey

M. Geyik
Department of Neurosurgery, Gaziantep University, Gaziantep, Turkey

C. Erbas
Department of Neurosurgery, Bilgi Hospital, Ankara, Turkey

Introduction

The cavernous sinus (CS) is a paired structure on both sides of the sella turcica, pituitary gland, and sphenoid sinus. It has one of the most complex anatomical networks of the skull base and because of the diversity of its contents is involved in many pathological processes.

The term “cavernous sinus” was designated by Winslow [21] because he believed that it resembled the cavernous body of the penis. This name was discussed and considered inappropriate, later being changed by the term “lateral sellar compartment” [16].

The CS extends from the superior orbital fissure to the dorsum sellae, being the inferior limit of the upper border of maxillary nerve. CS has four walls: roof, lateral, medial, and posterior walls [18]. The roof of the sinus faces upward, and the lower edge, formed at the junction of the medial and lateral walls below the intracavernous segment of the internal carotid artery, gives the sinus a triangular shape in cross section. Venous blood flow, internal carotid artery with its branches, as

well as cranial nerve VI, the sympathetic plexus and adipose tissue take place within the walls of CS [2].

The anatomy of the medial wall (MW) of the CS, although thoroughly described [7, 18, 22–24], still generates controversy. It is classically thought that the pituitary gland is contained within a dural layer that limits the CS medially [8]. However, some reports suggest that there is no medial dural wall—rather, there exists a loose fibrous tissue that separates the pituitary capsule [5, 12], or merely its own capsule formed by fine collagen fibers that separate the gland [24]. All of these are anatomical studies that were applied in adults, except one morphological study in human fetuses performed by Hashimoto et al. [11]. But there is no detailed report on the fetal histological structure of MW including the types of collagen fibers in the literature.

There are few papers about the anatomy of lateral wall (LW) in the literature. Until Umansky and Nathan's publication in 1982 [20], the dural structure of the LW of CS and its relationship to cranial nerves III, IV, and V were not clearly understood. The LW of the CS has two layers [2]; the external one is thick and pearly grey, and the internal one is semitransparent and contains the cranial nerves; thus, the layers can be surgically separated to expose the III, IV, and ophthalmic cranial nerves. Both dural layers of the LW continue laterally with the dura covering the floor of the middle fossa, medially with the dura of the superior wall of the CS, anteriorly with the dura covering the concavity of the greater wing of the sphenoid bone, and posteriorly with the tentorium. There is a cleavage plane between both dural layers, which is important surgically because it permits access to the inner layer of the LW without entering the venous compartment of the CS and also allows exposure of the cranial nerves. The limits of the LW of the CS are the following [18]: (a) superiorly, the anterior petroclinoid ligament; (b) inferiorly, the superior border of the maxillary nerve; (c) anteriorly, the superior orbital fissure; and (d) posteriorly, an imaginary line that lies flush with the plane of the dorsum sellae. Few reports have focused on the anatomy of the LW of the CS which contains important neural structures [13, 20]. But histological features of the LW of CS were not investigated in detail until today.

The aims of this study are to elucidate the histological characteristics of the medial and lateral walls of the CS in normal human fetuses, to search any difference among fetuses of various gestational ages, and to compare our results with the previous studies.

Material and methods

Fifteen normal human fetuses were dissected for the histological analysis of the walls of CS (Fig. 1). The ethical approval for this study was obtained from the National Ethics Committee (approval number and date: B.10.4.ISM.4.06.68.49/25.04.2012). The study was conducted in Microsurgery Training and Research Laboratory of our institution. The fetuses were premature stillborns and were obtained from the Department of Obstetrics. Eleven of them were female and four were male. The gestational age was estimated by the last menstrual period of the mother and confirmed with the measurement of fetal foot by ultrasound. The gestational age of the fetuses ranged between 14 and 35 weeks, and the weight of them was between 180 and 1750 g. None of them had a malformation on the gross anatomical examination. The skull vault and the encephalon were removed to expose the skull base. A Carl Zeiss surgical microscope (OPMI-1 Lab) (Oberkochen, Germany), ×3 to ×25 magnification, was used. A Midas Rex high-speed drill was used to remove bone tissue (Legend Gold Touch, Medtronic; Minneapolis, MN, USA). After the exposure of sellar region, the pituitary gland was removed. The lateral and medial walls of the CS were entirely exposed (Fig. 2). Small parts of LW and MW of the CS, about 5-mm³ axial slices, were selected and taken for histological studies. The tissue specimens were fixed in 10 % formalin and embedded in paraffin. Serial longitudinal and transverse sections in 4-μm thickness were obtained on adhesive slides with a Leica CM1850 cryostat (Leica Microsystems, Nussloch, Germany). First sections were stained with hematoxylin-eosin (HE) for the light microscopic examination (Figs. 3 and 4). Masson trichrome (Bio-Optica, Milan, Italy) was used for staining the

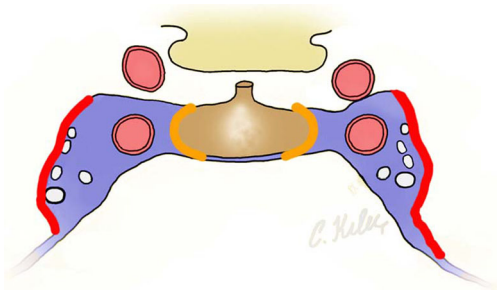

Fig. 1 The illustration showing the coronal section of the sellar region. *Red line* shows the lateral wall, and *orange line* shows the medial wall of the CS

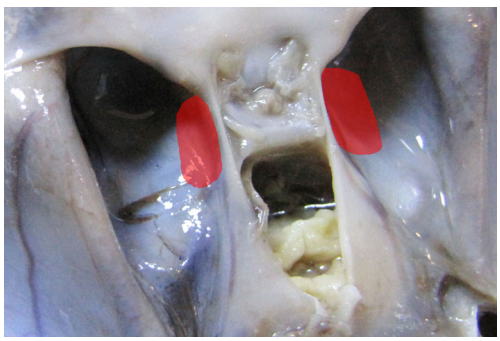

Fig. 2 Superior oblique view of the lateral sellar region. Lateral walls of both CS are shown with *red color* in a fetus before obtaining the sample for histological analysis. The cerebral tissue was removed, but the pituitary gland was still in place

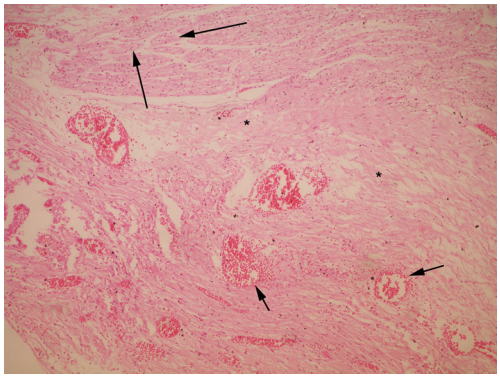

Fig. 3 Histological section of the lateral wall of a right CS shows peripheral nerve (*long arrows*) and loose collagen bundles (*asterisks*) associated with vascular structures (*short arrows*). (H&E, ×40)

nuclei, cytoplasm, collagen, and erythrocyte. Verhoeff-Van Gieson (Biostain, Manchester, England) stain was used for histochemical analysis of the elastic fibers. For immunohistochemical examination, antigen retrieval was done by citrate. Anti-collagen 1A1 (monoclonal, 1/100, Santa Cruz) and anti-collagen III (monoclonal, 1/100, BioGenex) primary antibodies were applied by indirect peroxidase method. Positive (normal skin tissue and gastric carcinoma, respectively) and negative controls were used during the process. The walls were histologically examined for the presence of peripheral nerve, ganglion, vessels, elastic fibers, and collagen bundles. The type of collagen was also determined as type I or type III (Fig. 5).

Results

A total of 60 wall samples (30 MW and 30 LW) were examined in 15 fetuses. The bulk of the CS is indeed composed of loose connective tissue and vascular and neural structures within this connective tissue. Vascular structures such as arteries, veins, and lymphatics were present in 51 samples, and the distribution of these structures was equally for both walls (26 in LW and 25 in MW). Peripheral nerve was found in 28 walls (18 in LW and 10 in MW). Ganglion was detected only in 11 samples (nine in LW and two in MW). These structures were mainly observed in LW of the CS. Elastic fibers were very rare and observed only in three CS samples (two in MW and one in LW). These fibers were surrounded by the arteries. Erythrocytes with nucleus were the proof of fetal tissues. Glial fibrillary acidic protein (GFAP) was negative in all samples. Collagen tissue was observed in all walls with different densities. All collagen bundles were stained with type III collagen. None of the samples was immunopositive for type I collagen. The important features of the walls were loose collagen bundles and thin vascular structures (Figs. 6 and 7). In addition, peripheral nerve and ganglion were mostly observed in LW of the fetal CS.

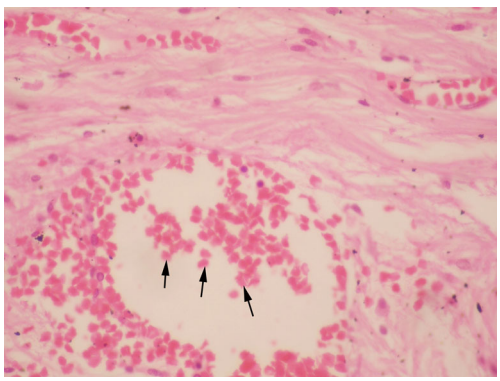

Fig. 4 Histological section of the medial wall of a left CS shows collagen fibers and vascular structures in which *black arrows* show erythrocytes with nuclei (H&E, ×400)

Discussion

The histological structure of the LW and MW of CS was analyzed in 60 samples from 15 fetuses. It was found that loose collagen tissue was the main component of these walls. This collagen tissue was composed of type III collagen, and elastic fibers were detected only in three samples. There was no glial tissue in the walls of fetal CS. Peripheral nerve and ganglions were mostly in LW, but vascular structures were equally distributed in both walls.

The walls of the CS are always under investigation by many scientists. Many papers were published in the literature on the anatomy and contents of these walls in order to facilitate surgical approach to the CS [2, 10, 13–15, 18, 22]. Few papers focused on the histology of these walls [17, 19, 23] to understand the invasion of the CS by adjacent tumors. Tobenas-Dujardin et al. [19] published a paper on the embryology of the internal carotid artery dural crossing, and they stated that the fetal period corresponds to the development of the meningeal structures and the superior, medial, and lateral walls of the CS appear on the fifteenth week of intrauterine life and do not change after that. But they did not give detailed histological information about the structure of the walls of CS. Our study is the first research focused on the histology of the medial and lateral walls of the CS in human fetuses.

The MW of the CS has been defined as a thin curtain that separates the CS from the sella and the pituitary gland capsule [6, 22]. It is believed that the MW plays a significant role in determining the direction of growth of pituitary adenomas and in planning pituitary surgery [4, 7, 22]. Tobenas-Dujardin et al. [19] analyzed the walls of the CS in human fetuses, and they divided the fetuses into two categories according to their ages. They found that the superior, medial, and lateral walls of the CS appear on the fifteenth week of intrauterine life and do not change after that. Hashimoto et al. [11] performed morphological study on the development of cavernous sinus in 14 fetuses, and they showed that the formation of CS occurs through the development of venous canals without smooth muscle layers,

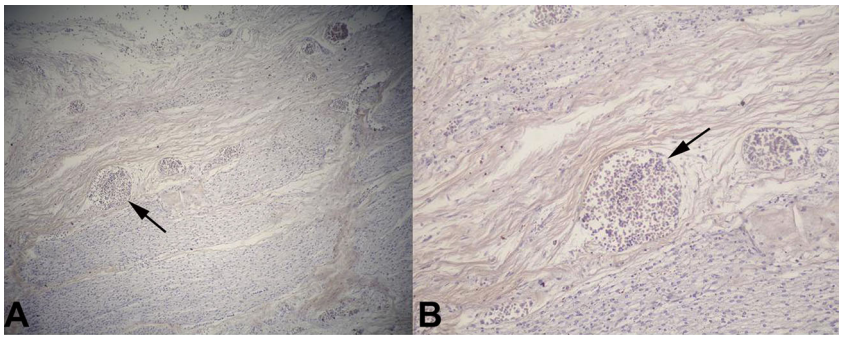

Fig. 5 Lateral wall of a right CS. Immunohistochemical examination shows collagen bundles composed of collagen type 3 between the vessels and nerve fibers. *Black arrows* show the vessels (streptavidin-biotin: **a** ×40 and **b** ×200)

followed by web formation by collagen fibers in the mesenchymal interstices. They also found that the formation of lateral sellar compartment is largely completed before birth. This study is similar to our study. But we mostly focused on the walls of CS, and we also analyzed the types of collagen in our study. Diao et al. [4] conducted a study on 16 adult cadavers, and they indicated that the MW of the cavernous sinus consists of both the meningeal dura and web-like loose fibrous network, which are located at the anterosuperior and posteroinferior aspects, respectively [4]. Yılmazlar et al. [23] analyzed histological structure of the MW of the CS in eight samples of adult cadavers. They obtained coronal sections and examined connective tissue. They found that the exposure of the medial venous space of the CS showed several fibrous bands extending from the inner side of basal dural layer to the carotid artery and MW of the CS. These bands were attached to the inferior aspect of the pituitary corner and were more prominent anteriorly than they were posteriorly. They suggested that the MW is a continuation of dura mater composed of loosely arranged collagen fibers. In our study, the youngest fetus was 14 weeks of gestational age and the walls of CS were detected in all fetuses. We showed that collagen fibers were the prominent tissue of the MW of CS, and peripheral nerve and ganglions were seldom observed within this tissue. Peripheral nerve and ganglions were less observed than the LW.

The anatomy of the LW of the CS has been described in detail, but the histological structure of the LW is also not well studied. Ultrastructural studies of the LW of CS have shown that the dura mater comprising this structure features three distinct layers: an external or periosteal layer that is attached to the inner surface of the skull, an internal or "meningeal" layer, and a layer of border cells that join this meningeal layer to the arachnoid membrane [9]. In our study, we did not observed three different layers in our samples. But we saw that LW has only one layer which was composed of peripheral nerve, ganglions, and vascular structures, and loose connective tissue consists of type III collagen bundles. According to Tobenas-Dujardin et al. [19], the LW appeared formed in the fetal stage by two layers: a lateral layer formed by meningeal cells, whose arrangement achieved a dense and resistant aspect, and a medial layer whose mesenchymatous cells created a looser network in the periphery of the cranial nerves. In our study, we did not observe two different layers in the LW samples of the fetal CS but we observed neural and vascular structures within a loose connective tissue which is mainly stained with type III collagen.

In human body, all connective tissues are composed of two basic components: intercellular matrix and cells [1]. The intercellular matrix of loose connective tissue is composed of various fibers and ground substance. There are three types of fibers in the intercellular matrix as follows: collagen fibers, reticular fibers, and elastic fibers. The most prevalent protein in the body is collagen. Each collagen fiber is made up of a variable number of smaller collagen fibrils. These fibrils are composed of type I collagen. Reticular fibers actually represent narrow bundles of type III collagen fibrils, which are produced by fibroblasts in loose connective tissue [1]. Peker et al. [17] studied the walls of the pituitary fossa and they found that the pituitary capsule and the dural layers in the lateral and inferior walls of the pituitary fossa were immunopositive for collagen types I and II. They detected collagen types III, IV, and V only in the pituitary capsule. In our study, we analyzed the walls for staining with type I and

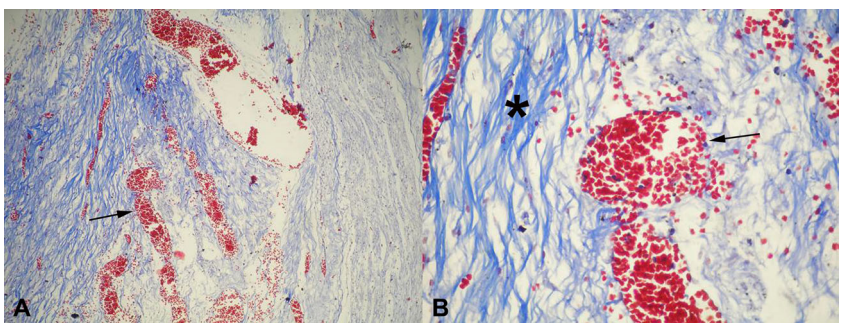

Fig. 6 Medial wall of a right CS. Histological examination with Masson trichrome shows collagen bundles between the vessels and peripheral nerves. *Black arrows* show the vessels, and *asterisk* shows the collagen bundles around the vessels (Masson reticulin: **a** ×40 and **b** ×400)

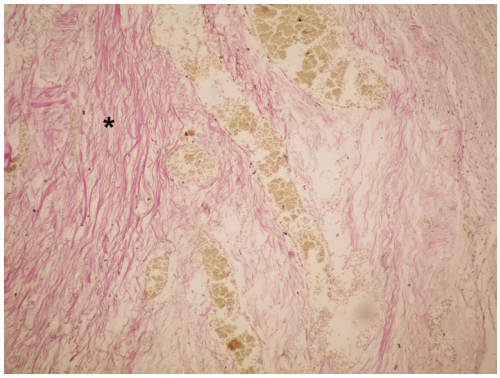

Fig. 7 Medial wall of a right CS. Verhoeff-Van Gieson staining shows collagen bundles (*asterisk*) between the vessels and peripheral nerves. (Verhoeff-Van Gieson: ×10)

type III collagens. We found that the lateral and medial walls were not immunopositive for type I collagen in the fetal CS. These walls were intensely stained for type III collagen. This shows that the structures of these walls are different from those of adults. So, lateral and medial walls are a weak barrier for the CS during the intrauterine life. Pituitary adenomas and middle fossa tumors could easily penetrate the CS due the loose connective structure of it in early age of the life.

Skull base is a unique area with compact arrangement, and surgery of this region in pediatric population has some special challenges. CS may be invaded by the skull base tumors, such as pituitary adenoma and meningioma. This invasion is clinically important because it makes the surgical procedure more difficult and less efficient. CS invasion increases the frequency of intraoperative vascular injury and postoperative cerebrospinal fluid leakage. Dural wall invasion usually implies partial surgical removal of the tumor and requires additional therapy, such as radiotherapy and chemotherapy [3]. Our study showed that the medial and lateral walls of the CS in fetuses have a less rigid structure than those in the adults. This may predispose infants to tumor invasion in the CS. Therefore, infants and young children with skull base tumors need meticulous and proper preoperative evaluation and planning to avoid additional neurological deficits.

In conclusion, the histological structure of the lateral and medial walls of the CS is different than those of the adults. The composition of these walls might not be changed after the birth. Children are more likely to have CS invasion than adults due to the weakness of the lateral and medial walls for the infiltration of the CS by pituitary and middle fossa tumors.

References

1. Bergman RA, Afifi AK, Heidger PM (2013) Connective tissue. Atlas of microscopic anatomy. Anatomy Atlases. Curated by Bergman RA. Available at http://www.anatomyatlases.org. Accessed 12 Sept 2013
2. Campero A, Campero AA, Martins C, Yasuda A, Rhoton AL Jr (2010) Surgical anatomy of the dural walls of the cavernous sinus. J Clin Neurosci 17(6):746–750
3. Cottier JP, Destrieux C, Brunereau L, Bertrand P, Moreau L, Jan M, Herbreteau D (2000) Cavernous sinus invasion by pituitary adenoma: MR imaging. Radiology 215(2):463–469
4. Diao Y, Liang L, Yu C, Zhang M (2013) Is there an identifiable intact medial wall of the cavernous sinus? Macro- and microscopic anatomical study using sheet plastination. Neurosurgery 73(1 Suppl Operative) ons106–110
5. Dietemann JL, Kehrli P, Maillot C, Diniz R, Reis M Jr, Neugroschl C, Vinclair L (1998) Is there a dural wall between the cavernous sinus and the pituitary fossa? Anatomical and MRI findings. Neuroradiology 40: 627–630
6. Dolenc VV (1989) Relation of the cavernous sinus to the sella. In: Dolenc VV (ed) Anatomy and surgery of the cavernous sinus. Springer-Verlag, Wien, pp 118–130
7. Gonçalves MB, de Oliveira JG, Williams HA, Alvarenga RM, Landeiro JA (2012) Cavernous sinus medial wall: dural or fibrous layer? Systematic review of the literature. Neurosurg Rev 35(2):147–153
8. Gray H (1995) Angiologia. In: Williams PL, Warwick R, Dyson M, Bannister LH (eds) Gray anatomia, vol 1. Guanabara Koogan, Rio de Janerio, pp 754–755
9. Haines DE, Harkey HL, Al-Mefty O (1993) The "subdural" space: a new look at an outdated concept. Neurosurgery 32:111–120
10. Harris FS, Rhoton AL Jr (1976) Anatomy of the cavernous sinus. J Neurosurg 45:169–180
11. Hashimoto M, Yokota A, Yamada H, Okudera T (2000) Development of the cavernous sinus in the fetal period: a morphological study. Neurol Med Chir (Tokyo) 40(3):140–150
12. Kehrli P, Ali M, Reis M Jr, Maillot C, Dietemann JL, Dujovny M, Ausman JI (1998) Anatomy and embryology of the lateral sellar compartment (cavernous sinus) medial wall. Neurol Res 20:585–592
13. Kırıcı Y, Kılıc C, Kocaoglu M, Ozan H (2010) Radiological and anatomical evaluation of the cranial nerves running lateral wall of the cavernous sinus. Gulhane Med J 52:162–166
14. Knappe UJ, Konerding MA, Schoenmayr R (2009) Medial wall of the cavernous sinus: microanatomical diaphanoscopic and episcopic investigation. Acta Neurochir (Wien) 151(8):961–967
15. Marinkovic S, Gibo H, Vucevic R, Petrovic P (2001) Anatomy of the cavernous sinus region. J Clin Neurosci 8(Suppl 1):78–81
16. Parkinson D (1995) Lateral sellar compartment. History and anatomy. J Craniofac Surg 6:55–68
17. Peker S, Kurtkaya-Yapicier O, Kilic T, Pamir MN (2005) Microsurgical anatomy of the lateral walls of the pituitary fossa. Acta Neurochir (Wien) 147(6):641–648
18. Rhoton AL Jr (2002) The cavernous sinus, the cavernous venous plexus, and the carotid collar. Neurosurgery 51(Suppl 1):375–410
19. Tobenas-Dujardin AC, Duparc F, Ali N, Laquerriere A, Muller JM, Freger P (2005) Embryology of the internal carotid artery dural crossing: apropos of a continuous series of 48 specimens. Surg Radiol Anat 27(6):495–501
20. Umansky F, Nathan H (1982) The lateral wall of the cavernous sinus. J Neurosurg 56:228–234
21. Winslow JB (1734) Exposition anatomique de la structure du corps humain. N. Prevast, London, Vol II, pp 29
22. Yasuda A, Campero A, Martins C, Rhoton AL Jr, Ribas GC (2004) The medial wall of the cavernous sinus: an anatomical study. Neurosurgery 55:179–190
23. Yılmazlar S, Kocaeli H, Aydiner F, Korfali E (2005) Medial portion of the cavernous sinus: quantitative analysis of the medial wall. Clin Anat 18(6):416–422
24. Yokoyama S, Hirano H, Moroki K, Goto M, Imamura S, Kuratsu JI (2001) Are nonfunctioning pituitary adenomas extending into the cavernous sinus aggressive and/or invasive? Neurosurgery 49(4): 857–862