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Clinical analysis of cavernous sinus anatomy, pathologies, diagnostics, surgical management and complications – Comprehensive review

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A R T I C L E I N F O

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A B S T R A C T

For decades, the cavernous sinus (CS) has been the subject of debates and scientific studies aimed at elucidating its anatomical variability, and at choosing the best method for accessing it so that optimal diagnoses and related surgical treatments can be decided. The present review considers a series of issues related to the CS. The anatomy of the CS and its features is explored first, and the most important structures, spaces and morphological variations are considered. This is followed by CS pathology and selected diagnostic methods that have proved useful in therapy, and then the management of these pathologies is discussed. Examples of therapeutic steps that have proved helpful in specific cases are taken from the literature. Finally, the various surgical accesses and complications that can be encountered during invasive interventions in the CS area are discussed. The aim of this study is to summarize up-to-date anatomical and clinical knowledge about the CS, citing the most informative scientific papers and aggregating their results. Morphological variations of the CS are common but have not been well described in the literature.
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1. Introduction

The cavernous sinus (CS) is a paired dural venous sinus in the middle cranial fossa on either side of the sella turcica of the sphenoidal bone, located between the endosteal and meningeal layers of the dura mater and containing the pituitary gland. Its anatomical boundaries are: anteriorly – extended into medial end of the superior orbital fissure, posteriorly - the petrous part of the temporal bone covered in two layers of dura mater, superiorly – a fold of meningeal layer of dura mater attached to anterior and middle clinoid processes, medially - the body of the sphenoidal bone overlaid with only the endosteal layer of dura mater, laterally – two layers of dura mater from the ridge of the roof to the floor of the middle cranial fossa, inferiorly – the endosteal layer of dura mater overlying base of sphenoidal bone. A characteristic feature of the CS is its anatomical division into smaller compartments. It is approximately 1 × 2 cm in size in a human adult (Rhoton, 2002a; Kiris et al., 1996).

Embryologically cavernous sinus develops from the rostral part of the primary head-sinus with its primary venous continuities to the orbit and nasopharynx, which later are an extension of bone drainage and late anastomoses that are secondary to bone drainage (Mitsuhashi et al., 2016).

The CS is clinically particularly important because it is close to many structures of the central nervous system and sense organs, and to some of the most important vessels in the head: the optic tract, optic chiasma, and internal carotid artery (ICA) superiorly; sphenoidal sinus inferiorly; the pituitary gland medially; the temporal lobe with uncus laterally; and the superior orbital fissure and orbit anteriorly (Janfaza, 2011; Kumar and Clark, 2005; Krayenbühl and Yaşargil, 1982).

Physiologically, it has many inflows because of connections with the surrounding venous network including the ophthalmic veins, sphenoparietal sinus, superficial middle cerebral vein (Sylvian vein) and pterygoid plexus located in the infratemporal fossa. The superior and inferior petrosal sinuses are continuations of the CS, changing during their further course into the transverse sinus and internal jugular vein (Janfaza, 2011; Mitsuhashi et al., 2016) (Fig. 1a). It is worth mentioning that there are several connections occurring between both CSs through intercavernous sinuses and basilar plexus, which also drain into inferior petrosal sinuses (Tubbs et al., 2007). Such an extensive vascular network is prone to hemangioma and sepsis, especially considering many venous inputs including the ophthalmic veins and the deep petrosal venous plexus draining into the CS (Chow et al., 2018). Mitsuhashi et al. (2016) in their study proposed a CS classification system distinguishing medial, intermediate and lateral axes. The medial venous axis carries venous drainage from the skull base, cartilaginous neurocranium (also called chondrocranium) and pituitary gland. The lateral axis corresponds to cerebral venous drainage and the intermediate axis, located between ICA and cranial nerves, carries venous drainage from the orbit with contributions from two other axes. Due to the novelty of this system, its clinical usefulness is still questionable, which indicates the need for further scientific work on this issue.

The anterior portion of CS is a venous space anterior to the cavernous part of the internal carotid artery (Charbonneau et al., 2013; Kawase et al., 1996; Sadasivan et al., 1991; Rhoton, 2002a). Its anterior apex reaches the superior orbital fissure (SOF), its superomedial wall is created by the base of the anterior clinoid process, and the sphenoidal bone limits it inferiomedially. Its lateral wall consists of dura, and the oculomotor, trochlear, ophthalmic, and maxillary nerves lie within it. Medially, the space is bordered by the cavernous part of the internal carotid artery. There is no medial dural wall limiting the CS, therefore both parasellar and the hypophysial compartment should be considered as a unique extradural space (Kehrli et al., 1998; Rhoton, 2002b).

Abducens nerve is located between cavernous part of the internal carotid artery and ophthalmic nerve, traveling through CS in its central part. (Charbonneau et al., 2013; Kawase et al., 1996; Kuybu, O Dossani, 2021; Sadasivan et al., 1991) (Fig. 1b). Pathologies particularly associated with this area are paraclinoid and carotid cave aneurysms (Sadasivan et al., 1991).

The posterior portion of CS contains lateral and posterior-superior venous spaces. Its roof is formed by the trigeminal ganglion and its floor by the apical portion of the pyramid-shaped petrous part of the temporal bone (Fisher E, 1938; Fukushima et al., 1996; Harris and Rhoton, 1976; Umansky et al., 1991). Pathologies particularly associated with this area are related to the contents of the space: abducens nerve from the entrance at abducens nerve canal to the ascending portion of the clinoid segment of the cavernous part of ICA (Fisher E, 1938; Fukushima et al., 1996; Harris and Rhoton, 1976). Neoplastic processes involving this space, either from within the CS or from the petroclival area, present difficulties for adequate surgical exposure (Fukushima et al., 1996). Owing to the accelerating development of neurosurgery, technology, methodology and anatomy directly affecting clinical practice during recent years, CS surgery has become significantly more frequent. The increasing number of medical procedures (Seo, 2006) has generated more scientific papers describing specific cases, methods used during surgery, and the effects of treatment (Alfieri and Jho, 2001a; D'Haens et al., 2009; de Keizer, 2003; Destrieux et al., 1997; Dolenc, 1983, 1989; Kim et al., 2000; McGrath, 1977; Melamed et al., 2009; O'Leary et al., 2002; Pamir et al., 2006; Umansky et al., 1991). However, surgeries requiring preparation of the CS still remain a challenge both technically and in deciding the appropriate surgical strategy, ensuring the best possible field of view and maneuverability while avoiding unnecessary complications related to the use of specific surgical accesses (Altay et al., 2012; Koga and Saito, 2012).

The wide range of possible surgeries in the same area raises questions, depending on their purpose and related clinical images: which method and which surgical access is the best for a given type of medical procedure, what are their distinctive traits, what aspects deserve special attention, and what possible complications and postoperative problems should clinicians consider before surgical intervention?

The aim of this review is to answer these questions as precisely as possible, gather the most up-to-date knowledge and use it to describe each topic individually, analyze its aspects and its clinical applications, and present the most relevant scientific studies from around the world.

2. Cavernous sinus anatomy and morphological variations

It is impossible to understand the clinical picture of any human disease without knowing the anatomy of the area affected by the pathological process. Therefore, in order to obtain an appropriate diagnosis and propose the most effective treatment, clinicians must have solid anatomical knowledge.

There are individual differences in the structure of the CS, as shown by studies describing it as a tetrahedral (Dolenc, 1983), pentahedral (Hakuba et al., 1989) or hexahedral (Kiris et al., 1996) space. In some specimens the sinus is large, while in others it is almost obliterated by the traversing nerves, arteries, and contained pituitary gland (Bergland et al., 1968 Feb). Scientific works do not emphasize, that these anatomical variants are of great clinical significance, however it is worth mentioning, that their shapes are often described differently among studies suggesting high individual variability.

Apart from the anatomical boundaries presented earlier, the most important surgical structures in the CS area are the cavernous part of the ICA and the cranial nerves (Fig. 2, Fig. 3, Fig. 4). Injury to these structures can cause massive intracranial haemorrhage or

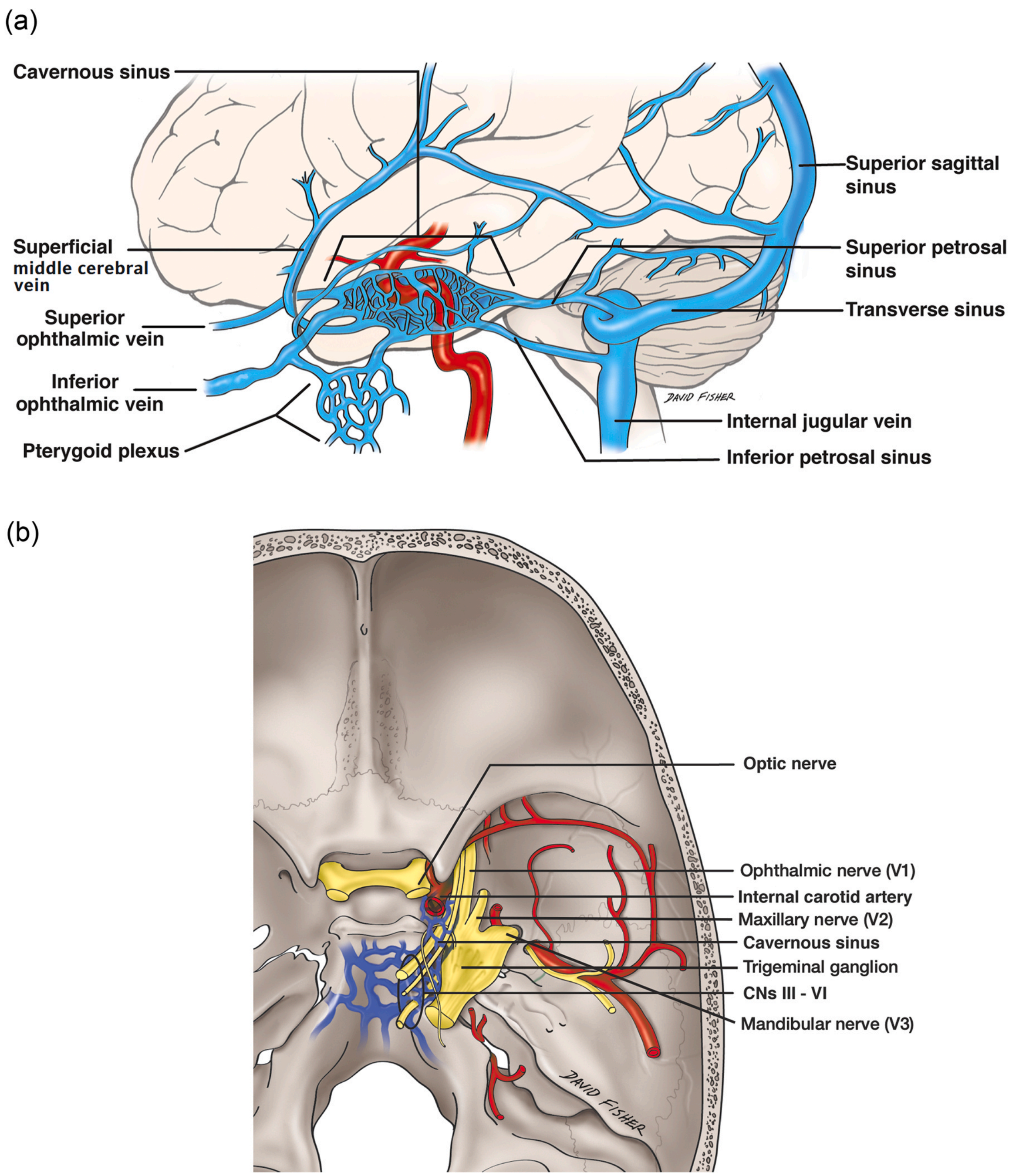

Fig. 1. a. Schematic drawing of the position and relationships of the cavernous sinus at the skull base, lateral view. b. Schematic drawing of the position and relationships of the cavernous sinus at the skull base, superior view. CNs III-VI – Cranial nerves III-VI (oculomotor, trochlear, trigeminal).

nerve dysfunction manifested by muscle paralysis (Frawley and Begley, 2005; Rush and Younge, 1981).

The ICA supplies intracranial structures, orbit and scalp (Bergman et al., 1988). It runs diagonally at the base of the skull extradurally, measuring approximately 6 cm along its petrous and cavernous segments (Kiris et al., 1996).

Over the years, many classifications of the ICA have been presented, including those by Fisher (1938), Gibo et al. (1981), Lasjaunias and Santoyo-Vazquez (1984), Bouthiller et al. (1996), Ziyal et al. (2005), Labib et al. (2014), Shapiro et al. (2014), and Abdulrauf et al. (2016). Visualizations of those classifications are presented in Fig. 5.

Fisher's (1938) ICA classification (Fig. 5A) was the first modern attempt to describe ICA anatomy, however it was based on angiographic rather than anatomical observations. It was created in order to help clinicians to localize skull base lesions in consideration with their form and size correlated to ICA parts. Classification consisted of five segments designated: C1 – communicating, C2 – ophthalmic, C3 – clinoidal, C4 – cavernous and C5 – petrous. It remained standard for over forty years, however subsequent authors failed to recognize Fisher's intent of describing patterns of arterial displacement by tumors and this caused anatomically inaccurate nomenclature to appear. Other limitations were that this system numbered specific parts of ICA opposite to the direction of blood flow and the extracranial part of ICA was not included in classification.

First major classification proposal after Fisher (1938) was released by Gibo et al. (1981) (Fig. 5B), in which they presented a

Fig. 2. Cadaveric dissection of the cavernous sinus following removal of the brain but before opening of the dura mater. CN II – Cranial nerve II (optic); CN III – Cranial nerve III (oculomotor); CN IV – Cranial nerve IV (trochlear); CN V - Cranial nerve V (Trigeminal); CN VI – Cranial nerve VI (abducent).

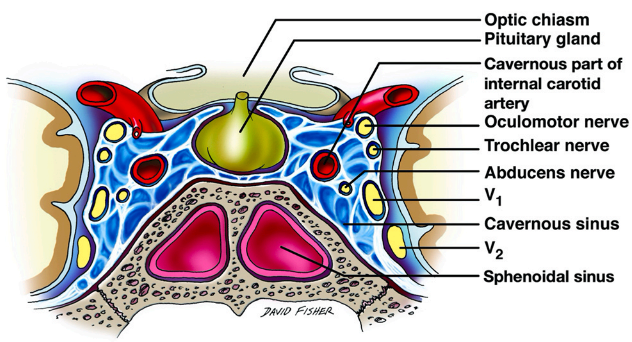

Fig. 3. Schematic drawing of the cavernous sinus and its contents in frontal section. V1 – Ophthalmic branch of trigeminal nerve; V2 – Maxillary branch of trigeminal nerve.

system based on locations of aneurysms: C1 – cervical segment (from common carotid artery bifurcation to the external aperture of the carotid canal), C2 – petrous segment (corresponding to part of the artery embedded within the petrous part of the temporal bone), C3 – cavernous segment (starting from cavernous sinus entry from the petrous part of the temporal bone and limited by distal dural ring) and C4 – supraclinoid segment, that was further divided based on the origin of its major branches into: ophthalmic part with ophthalmic artery (OA), communicating part with posterior communicating artery (PCA) and choroidal part with anterior choroidal artery (AChA). Subdivision enabled precise description of the supraclinoid segment of the ICA, however compared to subsequent works classification seems to not provide enough tools to describe other segments of ICA.

Six years later, Lasjaunias and Santoyo-Vazquez (1984) presented ICA classification (Fig. 5C), that was – for the first time – based on embryology. Authors divided ICA into 7 segments, which are correlated to origin of arterial branches, embryologic origin, and regional anatomical entities. First part - cervical segment – limited proximally with carotid sinus and distally with ICA cervical-petrous junction. Second part is limited by ICA cervical-petrous junction proximally and caroticotympanic artery distally. Third part is limited by caroticotympanic artery proximally and artery of pterygoid canal (also called Vidian artery) distally. Fourth part is limited by artery of pterygoid canal proximally and meningohypophyseal trunk (MHT) distally. Fifth part is limited by MHT proximally and inferolateral trunk (ILT) distally. Sixth part is limited by ILT proximally and OA distally. Seventh part is limited by OA proximally and PCOM distally. Limitation of this study is that it is unsuitable for most surgical interventions as authors did not took into consideration topographical anatomical relationships or any surgical and endoscopic experience during creation process of this classification.

Bouthillier et al. (1996) presented a classification system (Fig. 5D), that merges previous classifications with a more accurate description of specific segments, therefore making it more clinically useful than its predecessors. It divides ICA into seven segments: C1 – cervical – running in the carotid sheath with internal jugular vein, the vagus nerve and postganglionic sympathetic nerves from common carotid artery bifurcation to the external aperture of the carotid canal, C2 – petrous – travels through carotid canal to the posterior edge of the foramen lacerum, C3 – lacerum – from the internal aperture of the carotid canal, above foramen lacerum, creating lateral loop of the ICA to superior margin of the petrolingual ligament (PLL), which is a terminal part of periosteum of carotid canal, C4 – cavernous – from superior margin of PLL to proximal dural ring, C5 – clinoid (also called intradural segment of ICA) – proximal dural ring and distal dural ring, C6 – ophthalmic – from distal dural ring to posterior communicating artery (PCOM) origin and C7 – communicating – from PCOM origin to terminal bifurcation of the ICA into anterior and middle cerebral arteries.

Petrous segment (C2) is further divided into three smaller parts – a vertical portion, a bend (ICA posterior loop) and horizontal portion. Also, cavernous segment (C4) is subdivided into four smaller parts –

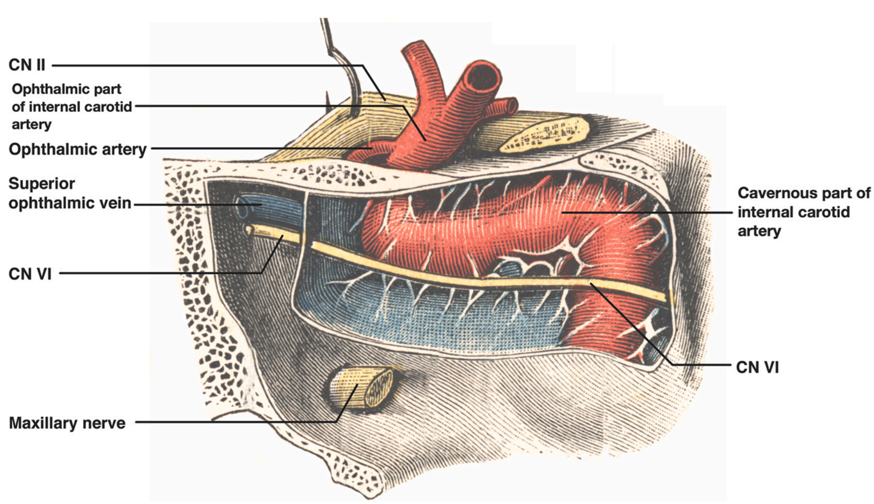

Fig. 4. Drawing of a lateral view of the cavernous sinus and its contents – cavernous part of the internal carotid artery and its branches. CN II – Cranial nerve II (optic); CN VI – Cranial nerve VI (abducent).

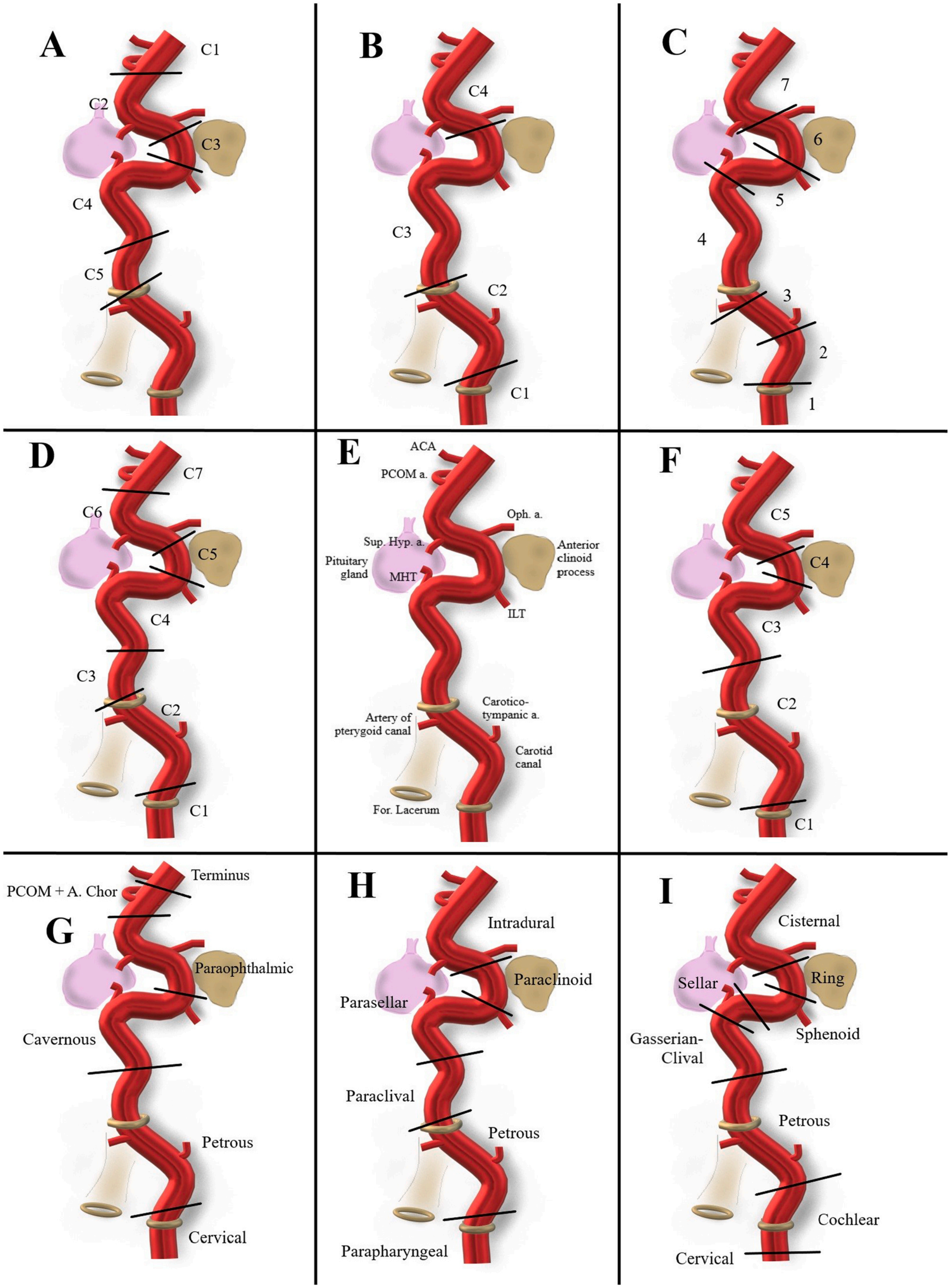

Fig. 5. Schematic drawing of the internal carotid artery classification systems. A – Fischer (1938), B – Gibo et al. (1981), C – Lasjaunias et al. (1984), D – Bouthiller et al. (1996), E – Description of presented structures, F – Ziyal et al. (2005), G – Shapiro et al. (2014), H – Labib et al. (2014), I – Abdulrauf et al. (2016) ACA – Anterior communicating artery; PCOM a. - Posterior communicating artery; Oph. A. - Ophthalmic artery; Sup. Hyp. A. - Superior hypophysial artery; MHT – meningohypophyseal trunk; ILT – Inferolateral trunk; Carotico-tympanic a. - Carotico-tympanic artery; For. Lacerum – Foramen lacerum; PCOM + A. Chor – Posterior communicating and anterior choroidal.

vertical portion, posterior bend (medial loop of the ICA), horizontal portion and anterior bend, which continues as clinoid segment (C5) and creates anterior loop of the ICA.

This system seems to be useful for surgeries with transcranial microscopic approach, however it has some limitations. Lacerum segment nomenclature can be misleading, due to fact, that ICA typically enters foramen lacerum at its middle level, then ascends – being inside the canal, however not passing through its whole extent. In addition, it is worth mentioning that clinoid segment is seen only during microsurgery, because imaging diagnostics does not allow it.

The fact that previous classifications are based on arterial blood flow without considering anatomical variations of the vessels raises a question – what if arteries, that set boundaries of specific ICA segments are originating in different part of ICA?

As a result of the appearance of newer scientific works in literature, among others, on the variable origin of ophthalmic artery - from clinoidal segment, cavernous segment, or middle meningeal artery (Kyoshima et al., 2000; Liu and Rhoton, 2001; Renn and Rhoton, 1975) – Ziyal et al. (2005) presented a classification (Fig. 5 F), that avoids setting segment limitations as arterial branches. They divided ICA into five segments: C1 – cervical - from common carotid artery bifurcation to carotid foramen, C2 – petrous – embedded in petrous part of temporal bone and limited by topographical point of PLL, C3 – cavernous – limited by superior margin of PLL and proximal dural ring, C4 – clinoidal – limited by proximal and distal dural ring, and C5 – cisternal, that continues inside subarachnoid space from distal dural ring and terminates at ICA bifurcation into ACA and MCA. One should keep in mind that some landmarks used in this classification system – PLL and distal dural ring cannot be found in clinical imaging.

Shapiro et al. (2014) driven by need for classification (Fig. 5G) optimized for endovascular procedures presented system, that is not based on alphanumeric nomenclature. ICA was divided into 7 segments: cervical, petrous, cavernous, paraophthalmic, posterior communicating, anterior choroidal and terminus. Cervical segment, similar to previous classifications, starts at common carotid artery bifurcation and extends to the external aperture of the carotid canal. The petrous segment travels within the petrous part of temporal bone and partially above foramen lacerum. Cavernous segment is limited by PLL and proximal dural ring. It is further subdivided into proximal ascending segment, proximal genu, horizontal segment with ILT, distal genu and distal ascending segment. Paraophthalmic segment starts at estimated distal border of the cavernous segment to the ostium of PCOM artery, that is also a proximal limitation of posterior communicating segment. The distal border of this segment is the anterior choroidal artery. Anterior choroidal segment starts at anterior choroidal artery and is limited by choroidal ostium. Terminus segment extends beyond choroidal ostium and terminates at ICA bifurcation.

Along with the increasing frequency of endonasal approach procedures, researchers started publishing ICA classifications, that would specifically apply to this surgical technique.

One of the most reliable classifications of that kind was presented by Labib et al. (2014). It aimed to present a system describing ICA anatomy from ventral endonasal perspective in order to lower the risk of ICA injury during the procedures (Fig. 5H). ICA was divided into parapharyngeal, petrous, paraclival, parasellar, paraclinoid and intradural segments. The parapharyngeal segment starts from the common carotid artery and is limited by the external aperture of the carotid canal. Petrous segment is limited by the external aperture of the carotid canal proximally and continues on three planes: posterior-to-anterior, inferior-to-superior, and lateral-to-medial ending at postero-lateral edge of foramen lacerum. The paraclival segment starts at postero-lateral edge of the foramen lacerum and continues to the superior limit of the petrous apex. Parasellar segment travels within cavernous sinus from superior limit of the petrous apex and the upper edge of the sphenopetrosal fissure and is limited by proximal dural ring of the ICA. Paraclinoid segment is bordered by proximal and distal dural ring. Ultimately, intradural segment is embedded within subarachnoid space and travels from distal dural ring to ICA final bifurcation. Without a doubt, this classification uses very precise and specific topographical terminology providing clinicians with an accurate system. However, the utility of this classification is questioned by the extent of the introduction of the new nomenclature, which can cause confusion and misunderstanding.

Abdulrauf et al. (2016) presented classification (Fig. 5I), that seeks to be useful both in lateral microsurgical approaches and ventral endoscopic procedures. A major benefit of this system is that it is based on radiological and anatomical observations. It divides ICA into eight segments: cervical segment limited by common carotid artery bifurcation and the external aperture of the carotid canal, cochlear segment (ascending segment of temporal bone) located at base of the styloid process towards the auditory tube (however preferably it should be called „tympanic" as it is more adjacent to the tympanic cavity than to the cochlea), petrous segment (horizontal segment), which starts at the crossing of the auditory tube superolateral to the ICA turn from vertical to horizontal at the genu, Gasserian-Clival segment (ascending segment of cavernous sinus) limited by proximal part of PLL and MHT, sellar segment (medial loop) starts at MHT and proceeds to sphenoidal segment (lateral loop in cavernous sinus) after crossing the trochlear nerve on the lateral aspect of cavernous part of ICA located laterally to sphenoidal sinus. It seems that preferably it should be called trigeminal-clival as, once again, this term is more adjacent to the related topography. The ring segment crosses the oculomotor nerve on lateral aspect of the ICA and is limited by two dural rings. Cisternal segment, which is the final one starts at distal dural ring and terminates at final ICA bifurcation. Despite its potential to be uniformly applied to all skull base surgical approaches, it also has its limitations. This classification is the most numerous one, and also introduces a lot of previously unused terminology, which can cause its reluctant use and confusion in the literature.

A summary of the discussed classifications with their limitations is presented in Table 1.

Course of ICA is morphologically variable, probably for embryological reasons (Carlson, 2018). Apart from different origin points of ICA branches (Kyoshima, Oikawa and Kobayashi, 2000; Liu and Rhoton, 2001) these variations can appear in the cervical part as coils, curved or kinked shapes (Arumugam and Subbiah, 2020; Metz et al., 1961; Osborn, 1999) and could be related to various neurological manifestations owing to altered blood flow dynamics (Derrick and Smith, 1962; Weibel and Fields, 1965).

The nomenclature of individual parts of ICA, including the cavernous section of the ICA has not been standardized and this can result in misunderstanding of its course. Apart from ICA classification systems, which are dividing ICA in correlation to anatomical landmarks, there are authors, that describe it strictly on the base of spatial arrangement - vertical lines, horizontal lines, loops, and bends. Inoue and co-workers (Inoue et al., 1990) distinguished the posterior vertical and horizontal and the anterior vertical segments, and the posterior and anterior bends. According to Kiris (Kiris et al., 1996), the posterior bend correlates to the medial loop and the anterior bend to the anterior loop. On the other hand, Dolenc et al. (Dolenc, 1995) differentiated not only the horizontal and vertical segments, as Inoue did (Inoue et al., 1990), but also the medial and anterior loops with the addition of an ophthalmic segment. However, the anterior loop seems to be confused with the anterior vertical segment. The division proposed by Fukushima and Day (Fukushima and Day, 1995) was another attempt to differentiate individual parts of vessel. They divided the ICA into: ascending

Table 1
Different ICA classifications presented over the years with their nomenclature and limitations.

Authors	Nomenclature of segments	Limitations
Fisher (1938)	C1 – CommunicatingC2 – OphthalmicC3 – ClinoidalC4 – CavernousC5 - Petrous	– Parts of ICA are numbered opposite in the direction of blood flow. – Classification was not based on anatomical relationships, but rather displacement of ICA. – Lack of surgically important cervical segment of ICA.
Gibo et al. (1981)	C1 – CervicalC2 – PetrousC3 – CavernousC4 – Supraclinoid, subdivided into: – Ophthalmic part – Communicating part – Choroidal part	– Anatomical landmarks, that are used to set limitations of specific segments can be variable. – Lack of surgically important clinoid segment of ICA, making it difficult to differentiate extra- and intradural pathologies.
Lasjaunias and Santoyo-Vazquez (1984)	1. Cervical 2. Ascending intrapetrous 3. Horizontal intrapetrous 4. Ascending foramen lacerum 5. Horizontal intracavernous 6. Clinoid 7. Terminal	– Lack of any topographical relationships between ICA and surroundings. – Segments occur between branches of ICA making it unreliable due to the possibility of anatomical variations.
Bouthillier et al. (1996)	C1 – Cervical C2 – Petrous C3 – Lacerum C4 – Cavernous C5 – Clinoid C6 – Ophthalmic C7 – Communicating	– Clinoid segment is not visible in imaging diagnostics. – The lacerum segment of ICA can be misleading due to its nomenclature and the fact that ICA usually does not pass through its full extent.
Ziyal et al. (2005)	C1 – Cervical C2 – Petrous C3 – Cavernous C4 – Clinoidal C5 – Cisternal	– Clinoid segment is not visible in imaging diagnostics. – Lack of differentiation between parts of ICA, that give origin to ophthalmic artery and bifurcate into ACA and MCA.
Shapiro et al. (2014)	CervicalPetrousCavernous ParaophthalmicPosterior communicatingAnterior choroidalTerminus	– Classification is based on cerebral angiograms and has relatively poorly specified limitations of each segment of ICA, making it unsuitable for microsurgery procedures.
Labib et al. (2014)	ParapharyngealPetrousParaclivalParasellarParaclinoidIntradural	– Introduces new terminology making it potentially confusing. – Limited utility in transcranial microscopic surgeries, however useful in endonasal approach.
Abdulrauf et al. (2016)	CervicalCochlearPetrousGasserian-ClivalSellarSphenoidRingCisternal	– Most numerous classification – Introduces terminology, that is nearly entirely different than one, that was used before for a long time making it potentially confusing.

segment – C5, horizontal segment – C4, siphon segment – C3, and ophthalmic with paraclinoid segment – C2. The capital letter "C" does not refer to the cervical vertebrae, but to the division of the entire ICA. The biggest drawback seems to be the lack of specification of the posterior bend (according to the Rhoton and Inoue division), which makes this division system incomplete.

Other studies (Day, 1990; Kobayashi et al., 1989; Perneczky et al., 1988, 1985) of ICA and proposing other classification systems have been conducted, but in comparison with ones presented they seem to lack accuracy.

As has been shown, there have been many scientific papers aimed at the anatomical or topographical division of the ICA into smaller segments and therefore describing its course. On one hand, it is advantageous because clinicians can use a wide variety of tools, which are the classifications presented, depending on the purpose and needs. On the other hand, such a large variety of systems and associated nomenclature basically prevents its standardization and may be the cause of misunderstandings and errors. The most advisable and preferred choice is to navigate smoothly through all the frequently used classifications that have been presented previously. However, if one were to be chosen, the classification published by Bouthiller et al. (1996) would probably be the best option, due to its common acceptance both in clinical use and frequent appearance in publications. In addition, it subdivides cavernous part of ICA into four smaller parts: vertical portion, posterior bend, horizontal portion, and anterior bend. Petrous segment (C2) is also further divided into a vertical portion, a bend (ICA posterior loop) and horizontal portion. However, one must remember about the limitations of this system – ICA usually does not pass through foramen lacerum, despite the name of one of the segments and also, that there are cases, where arterial branches, that set boundaries can origin in different segment than presented in classification.

The cavernous part of the ICA shows no gender difference in length (13.6 ± 2.8 mm) (Farımaz et al., 2019), but three rather than two bends are sometimes observed, the third appearing between the other two (Farımaz et al., 2019; Vijaywargiya et al., 2017). The first bend can vary in its geometry, ranging from a gentle curve to a sharp acute bend; the bend is positioned higher as the angle becomes sharper. The second bend is usually around 45° and reverses the direction of the artery, constituting what is classically described as the carotid siphon (Vijaywargiya et al., 2017) (Fig. 6, Fig. 7).

According to Dolenc (Dolenc, 1995), the course and origin of the branches of the cavernous part of the ICA can vary. Author states, that main and most consistent branches – the meningohypophyseal (posterior caroticocavernous) and inferolateral (lateral caroticocavernous) trunks – form extremely important landmarks, injury to which can lead to serious complications including pseudoaneurysms and carotid-cavernous fistulae (Dolenc, 1995; Kiris et al., 1996). Meningohypophyseal (posterior caroticocavernous) trunk is the most proximal branch of the cavernous part of ICA, originating from the posterior bend (according to Inoue and co-workers (1990)), which is also called a medial loop (Kiris

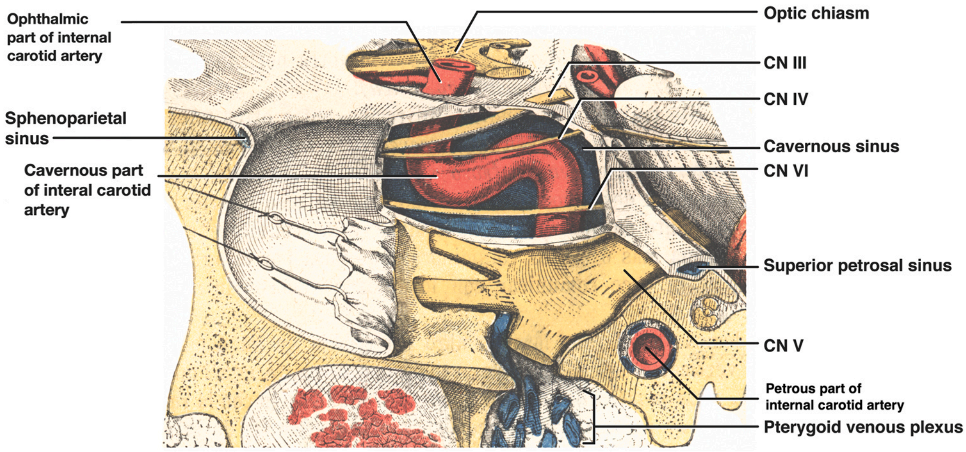

Fig. 6. Drawing of a lateral view of the cavernous sinus and its contents – nerve relationships. CN III – Cranial nerve III (oculomotor); CN IV – Cranial nerve IV (trochlear); CN V - Cranial nerve V (Trigeminal); CN VI – Cranial nerve VI (abducent).

et al., 1996), always medial to the abducens nerve, where it crosses the vertical segment of the cavernous part of ICA.

During its course it often gives off three branches: the tentorial basal branch, supplying the tentorium, anastomoses with the inferior hypophysial artery, supplying the posterior lobe of the pituitary gland and the dura of the sellar floor and the clival branches (clival meningeal artery), which further divides into branches supplying the clival dura and the abducens nerve within abducens nerve canal (Dolenc, 1995; Harris and Rhoton, 1976; Parkinson, 1965; Kiris et al., 1996).

Some studies suggest, that lateral caroticocavernous trunk, called inferolateral trunk (Dolenc, 1995) or the artery of the inferior CS (Morris, 2013) or truncus caroticocavernosus lateralis (Donkelaar et al., 2018), arises from the inferolateral part of the horizontal segment of the cavernous part of ICA, 5–8 mm distally to the meningohypophyseal (posterior caroticocavernous) trunk, and typically gives off three to four branches (Knosp and Müller, 1987): the anteromedial branch supplying the oculomotor, trochlear, abducens nerves and the ophthalmic nerve, anastomosing with branches of the maxillary artery after passing through the foramen rotundum together with the maxillary nerve; the posterior branch passing via the foramen ovale and anastomosing with the maxillary artery and/or the petrosal branch of the middle meningeal artery; and finally the superior branch supplying the trochlear nerve (Inoue et al., 1990).

Inoue et al. (1990) mention cases in which the tentorial basal branch of the meningohypophyseal (posterior caroticocavernous) trunk is absent and the tentorium is supplied by the marginal tentorial artery (also called Bernasconi and Cassinari artery or medial tentorial artery) originating from the inferolateral (lateral caroticocavernous) trunk. Other variations mentioned in that research are: a persistent trigeminal artery, intracavernous origin of the ophthalmic artery, and accessory hypoplastic ophthalmic arteries. Another variation observed is the capsular artery of McConnell (Kiris et al., 1996), which can arise from the medial aspect of the horizontal segment of the cavernous part of ICA and supplies the dura of the sellar floor, the anterior sellar wall and the capsule of the pituitary gland. It should be emphasized that those variants are rare and observed only in individual cases. However, knowledge about their possible occurrence may prove useful in clinical practice.

These results demonstrate, that when imaging diagnostics are obtained before invasive treatment, clinicians must be prepared for the third bend of the cavernous part of the ICA, which is not necessarily a symptom of vascular pathology but rather a physiological morphological variation. The numerous variants of the intracavernous branching patterns of the ICA confirm the obvious fact that to ensure the maximum safety margin for the patient, thorough knowledge of the anatomy and topography of the vascular and nervous areas of the CS is essential for every clinician in treatment planning, diagnosis and eventually surgical intervention.

Other extremely important structures from the anatomical and surgical points of view are rings around the ICA in specific parts of its course. A lateral ring made of a thick fibrous band of dura fixes the ICA at the horizontal segment of the petrous part of ICA (HSPICA)

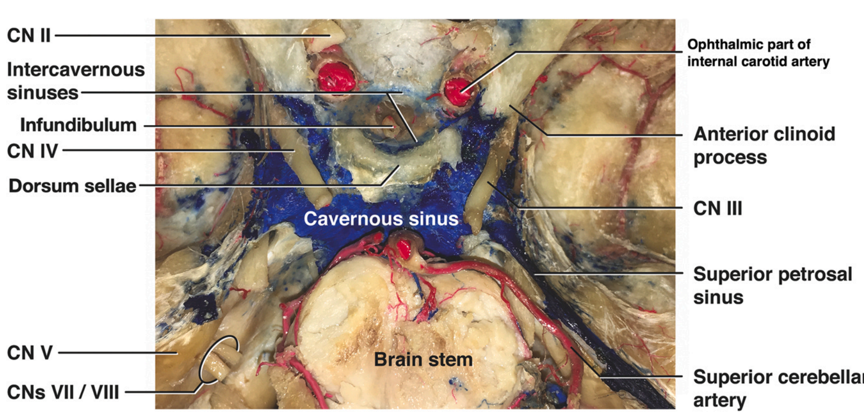

Fig. 7. Cadaveric dissection of the lateral view of the left cavernous sinus and its contents. CN III – Cranial nerve III (oculomotor); CN IV – Cranial nerve IV (trochlear); CN V - Cranial nerve V (Trigeminal); CN VII – Cranial nerve VII (facial); CN VIII – Cranial nerve VIII (vestibulocochlear).

crossing point in the vertical segment of the intracavernous part of the ICA (Kiris et al., 1996). During surgery, this can be confused with the abducens nerve if its position becomes more vertical and therefore parallel to the lateral ring. Moreover, the ICA is also surrounded at the zone of dural transition by two additional rings, proximal (cortico-oculomotor membrane) and distal (dural) (Kiris et al., 1996). The first of these is formed by a thin protective layer of dura between the anterior clinoid process and the oculomotor nerve. The second comprises strands of connective tissue radiating to the sphenoidal plane and anterior clinoid process, thinner on the medial and thicker on the lateral side (Kiris et al., 1996). If surgical dissection proceeds all the way to the proximal ring, there is an increased risk of CS venous plexus injury (Knosp et al., 1988; Perneczky et al., 1985).

Both CSs receive blood from the superior and inferior ophthalmic veins. The superior ophthalmic vein joins the CS after passing through the SOF; the inferior ophthalmic vein can either join separately or join the superior ophthalmic vein before the CS (Ohmoto et al., 1991). The sphenoparietal and intracavernous sinuses are also tributaries of the CSs (Kiris et al., 1996). Furthermore, they are indirectly connected to the retina through the retinal vein, to nasopharynx by the pterygoid plexus (located within infratemporal fossa), to cerebral hemispheres by the superficial middle cerebral vein also known as the Sylvian vein (Maekawa and Hadeishi, 2015), and to the dura mater by middle meningeal vein (Gasecki and Barnett, 1995).

Cavernous sinuses are connected by intercavernous sinus (Bergland et al., 1968) and basilar plexus. Major part of venous blood flows from the cavernous sinuses into the internal jugular veins through superior and inferior petrosal sinuses, sigmoid sinus, and superior bulb of the internal jugular vein. Minor part of venous blood flows into pterygoid plexus through emissary veins, then into maxillary vein, retromandibular vein and into external jugular vein (Golub and Bordoni, 2022).

The intravascular division of the CS, studied by Harris and Rhoton (1976), Lang and Kageyama (1990) and Sadasivan et al. (1991), can be described as four or five venous spaces. The basic and most common four are named in relation to the intracavernous part of the ICA: anterior-inferior, posterior-superior, medial and lateral. The fifth space is a cavernous space anterior to the anterior bend (according to the Rhoton and Inoue (Inoue et al., 1990) division of the intracavernous part of the ICA). However, the presence of this space depends on the tortuosity and shape of the intracavernous part of ICA, and in specific cases it can overlap with the anterior-inferior space (Harris and Rhoton, 1976; Lang and Kageyama, 1990; Sadasivan et al., 1991; Kiris et al., 1996).

In addition to this complex circulatory system, the CS area contains many important nerve fibers, the exact locations of which should be determined prior to undertaking an invasive procedure. For this purpose, a broad and accurate understanding of the region's topography and observable neurovascular relationships is essential.

Most published research papers (Dolenc, 1995; Harris and Rhoton, 1976; Inoue et al., 1990; LN. Sekhar and Sen, 1990; Parkinson, 1990, 1965; Perneczky et al., 1988; Kiris et al., 1996; Umansky and Nathan, 1982) indicate that the abducens nerve along with the ICA and the associated sympathetic plexus goes through the CS proper, in contrast to the oculomotor, trochlear nerves and the ophthalmic and maxillary branches of the trigeminal nerve; these are located between the superficial and deep layers of the lateral CS wall, which can easily be separated intraoperatively (Umansky and Nathan, 1982). Umansky and Nathan (1982) also noted that the deep layer includes sheaths surrounding the cranial nerves, which alongside the reticular membrane (thin, delicate layer of reticular fibres) constitute its entirety. They also stated that the reticular membrane is often incomplete, especially between the oculomotor and trochlear nerves.

3. Cavernous sinus syndromes

According to Kuybu and Dossani (2021), the cavernous sinus syndrome (CSS) can be associated with any disease that affects the CS. Determining CSS etiology poses a challenge, even after diagnostic techniques have been improved by imaging and blood analysis. One reason is the difficulty of making a diagnosis based on CS tissue.

Etiologically, CS syndromes can be divided into five groups based on their principal causes: neoplastic (with differentiation into primary or metastatic), infectious, inflammatory, vascular and traumatic. It is important to note that individual groups are often not clearly distinguishable; the border between them is fluid and the etiology of the disease can take the form of a gradient created by several overlapping pathological processes (Broadbent, 2013, 2009; Fuller, 2018; Kuybu and Dossani, 2021). Jefferson (1938) classified CSSs using the extent of involvement of the trigeminal nerve. He distinguished three types: anterior, middle and posterior CSS (Jefferson, 1938). Ishikawa (1996) stated that this classification failed to correlate the anatomical and clinical dimensions and proposed new one, using the optic canal and maxillary nerve as differentiation factors. Both above-mentioned classifications of CSS (Ishikawa, 1996; Jefferson, 1938) are compiled in Table 2, with potential clinical implications.

The coexistence of the two classification systems prompted Bhatkar and co-workers (2016) to analyse and compare them against the background of clinical utility and in determining the etiology of diseases. Bhatkar and co-workers emphasize that using the Ishikawa (1996) classification, many more patients with CSS can be assigned to a specific group, mainly because the differentiating criteria are very precise and there are more classification groups (Bhatkar et al., 2016). However, Bhatkar and co-workers (2016) stated that the Jefferson (1938) scheme gave a better idea of the etiological background.

Overall, both classifications (Ishikawa, 1996; Jefferson, 1938) allow for a satisfactory research study with an appropriate group size, the Ishikawa classification having the advantage for large-group studies as it allows for more reliable statistical analysis. However, if the aim of the study is to determine the etiological background of a CSS as accurately as possible, Jefferson's classification (Jefferson, 1938) is better suited.

Epidemiological analysis of a CSS does not allow us to draw definite conclusions because so little research has been conducted on this topic (Bhatkar et al., 2017; Fernandez et al., 2007; Keane, 1996). Neither the average age nor a sex difference in incidence has been highlighted in any study, indicating that a CSS can occur at any age from 20 to 80 both in men and women (Bhatkar et al., 2017; Fernandez et al., 2007; Keane, 1996; Kuybu, O Dossani, 2021). One of the few findings that attract special attention is the general agreement that the most common etiological cause of CSS (30–64 %) are tumours (Kuybu and Dossani, 2021). The second most common cause recorded among the studies is either trauma (24 %) (Keane, 1996), vascular etiology (20 %) (Fernandez et al., 2007) or, exclusively in study conducted in Northern India, fungal infection (24.6 %) (Bhatkar et al., 2017). Other studies performed in the western world did not show such a high percentage of fungal infections in the etiology of CSS (Bhatkar et al., 2017; Fernandez et al., 2007; Keane, 1996; Kuybu and Dossani, 2021).

Table 2
Comparison of Jefferson (1938) and Ishikawa (1996) classifications of CSS with their potential clinical consequences.

	Jefferson classification		Ishikawa classification	
	Description	Clinical consequences	Description	Clinical consequences
Anterior cavernous syndrome	First branch of trigeminal nerve affected, with sparing of the other two.	Paralysis of superior branch of oculomotor nerve, or all nerves supplying mobility of the eyeball.	From the orbital apex to 3.5 mm posterior, i.e., the intracranial opening of the optic canal.	Optic neuropathy or isolated palsy of the superior or inferior branch of the oculomotor nerve (CNIII), regardless of involvement of other oculomotor nerves or the ophthalmic nerve.
Middle cavernous syndrome	First and second branch of trigeminal nerve affected, third division spared.	Paralysis of one nerve, usually of all nerves supplying muscles of the eye.	From 3.5 mm behind the orbital apex to 10 mm posterior- that is, at the site of entry of the maxillary nerve.	Concurrent oculomotor nerve and ophthalmic nerve involvement.
Posterior cavernous syndrome	Whole trigeminal nerve affected with ocular palsy, sometimes only abducens. Motor root of trigeminal affected but can escape.	If whole trigeminal nerve is affected it can result in significant neurosensory deficits and facial pain, and significant comorbidities due to changes in eating habits from muscular denervation of masticatory muscles or altered sensation of the oral mucosa.	From 10 mm behind the orbital apex to the posterior wall.	Involving the maxillary nerve or abducens nerve with Horner's syndrome.
Whole cavernous syndrome*			Whole CS affected.	Involving both optic nerve and maxillary nerve in addition to involvement of oculomotor nerves and ophthalmic nerve.
Unclassifiable*			Cases that do not provide sufficient evidence to qualify for either group.	

* - appears only in Ishikawa classification

Referring to and supporting the statistics presented, we will briefly characterize only the most commonly observed causes of CCS, i.e., those related to cancer and the circulatory system.

The cancers causing CSS can be primary, including meningiomas, schwannomas of CNIII, CNIV, CNV1/V2, CNVI, haemangiomas, hemangiopericytomas; or metastases from lung, breast or prostate, spreading through neural foramina (Kuybu and Dossani, 2021; Hirsch et al., 1993). Another possible intracranial tumour causing CSS is one associated with the pituitary gland or a spreading nasopharyngeal carcinoma (Azarpira et al., 2012).

Kuybu and Dossani (2021) divided vascular pathologies into three subgroups: carotid-cavernous fistulae (CCFs), carotid-cavernous aneurysms (CCAs) and CS thrombosis (CST). Useful information on these conditions in a clinical context is summarized in Table 3.

3.1. CSS diagnosis

One of the most important and oldest diagnostic tools for every doctor is the physical examination he/she performs. It allows the physician to confront the course of diagnostic thinking directly with the patient by examining various reflexes or using the senses to monitor the patient's condition (Artandi and Stewart, 2018; de de de Inocencio Arocena, 2016; Réthi, 1978).

Clinical exam findings can be divided into common symptoms of CCSs, which are often shared despite different etiologies, such as headache (90 %), diplopia (up to 90 %), painless/painful ophthalmoplegia, ptosis, proptosis, chemosis, facial sensory loss, visual deficit, fever, facial asymmetry, hearing loss, seizure, ocular and cranial bruits, papilledema, and retinal haemorrhages; and those that occur in patterns usually accompanying specific causes (Kuybu and Dossani, 2021). Selected pathologies and related symptoms are summarized in Table 4 (Cakirer, 2003; Kuybu and Dossani, 2021; Zhang et al., 2014).

Imaging diagnostics are also undeniably powerful tools for a doctor. If a CSS proves demanding to diagnose, these techniques allow for a better examination of the orbits, sella and parasellar area, helping to determine the etiology of the disease process more accurately. Pre- and post-contrast scans are advisable (Kuybu and Dossani, 2021). CT provides better visualisation of bone and calcium; MRI gives better detail of all soft tissues contained in the sinuses. In order to complete the clinical picture, an angiographic examination is also performed.

Table 5 presents some of the diagnostic steps that can prove valuable in evaluating a neoplastic or vascular etiology (Kuybu and Dossani, 2021; Zhang et al., 2014). Biopsies of CS tumours are rarely needed for diagnosis of primary tumours, provided no tumours have spread from another source (Kuybu and Dossani, 2021). Inflammatory and infectious etiologies are not discussed because our research focuses on the surgical aspects of CSS treatment, which have not proven useful for those etiologies.

Based on the tumor origin and growth pattern, Chotai and coworkers (2018) divided tumors associated with CS into three groups:

1) Type-I: tumor originating from CS
   Hemangiomas are benign and the only primary intracavernous tumour. They account for 13% of all intracranial cavernous hemangioma, 3% of benign tumors of the CS area, 2% of all tumors within the CS area, and 0.4–2% of intracranial vascular malformations (Zabramski et al., 1993; Goel, 1997).
   The second category of tumors that can be classified in this group are metastasis to CS. They are usually associated with poor prognosis and therapy restricted to palliative methods. which are associated with poor prognosis and treatment is largely palliative (Chotai et al., 2018).

Table 3
Vascular pathologies of the CS distinguished by Kuybu (Kuybu, O Dossani, 2021).

	Carotid-cavernous aneurysms	Carotid-cavernous fistulae	Cavernous sinus thrombosis
Cause and division	The etiology of CCAs can be traumatic, infectious, or idiopathic (Eddleman et al., 2009).	Can arise spontaneously or as a result of trauma, CCAs or venous thrombosis (Barrow et al., 1985; Kuybu and Dossani, 2021). Can be classified as indirect, direct, low-flow, high-flow or dural CCF (depending on connection between the intracavenous carotid artery and the CS) (Barrow et al., 1985).	Mostly occurs as aseptic or infectious. Rare but dangerous complication of CS infections (Weerasinghe and Lueck, 2016). Infections often result from spread from the nasal furuncle (50 %), sphenoidal sinus or ethmoidal cells (30 %), or the teeth (10 %) (Kuybu and Dossani, 2021). Aseptic causes are observable typically after surgery or trauma (Kuybu and Dossani, 2021; Weerasinghe and Lueck, 2016). Aseptic thrombosis can be associated with hypercoagulable states or lymphoproliferative disorders (Kuybu and Dossani, 2021).
Potential complications	Do not carry major risk of subarachnoid haemorrhage (Kuybu and Dossani, 2021). When traumatic or spontaneous CCA rupture does occur, the formation of a CCF can be expected (Eddleman et al., 2009). Diplopia from single or multiple oculomotor nerve paresis, decreased visual acuity from compressive or ischemic optic neuropathy, corneal and facial anesthesia, or hypoesthesia from involvement of the trigeminal nerve, and facial pain (Goldenberg-Cohen et al., 2004).	Intracerebral hematoma, subarachnoid haemorrhage, intraorbital haemorrhage, epistaxis, and otorrhagia (Dohrmann et al., 1985; Halbach et al., 1987; O'Reilly et al., 1986; Turner et al., 1983); blurred vision or loss of vision caused by secondary glaucoma or intraorbital haemorrhage (Halbach et al., 1987; Kupersmith et al., 1986); cerebral ischemia (Halbach et al., 1987); progressive proptosis (Halbach et al., 1987; Kupersmith et al., 1986); limitation of ocular movements (Halbach et al., 1987; Kupersmith et al., 1986).	Diplopia, partial or complete external ophthalmoplegia, limited eye movement (most commonly abduction), internal ophthalmoplegia resulting in mydriasis, numbness, paresthesias, loss of corneal blink reflex and facial pain (Plewa et al., 2021).

CCA, carotid-cavernous aneurysm; CCF, carotid-cavernous fistula; CST, cavernous sinus thrombosis

Table 4
Selected pathologies of CS and related symptoms.

Disease	Associated symptoms
CS tumours	Isolated or combined ophthalmoplegia, painful ophthalmoplegia, anaesthesia in oculomotor nerve (CNIII), unitemporal or bitemporal visual field defects, acromegaly, and galactorrhoea.
Carotid-cavernous fistulae	Ocular bruit (commonly auscultated), proptosis, chemosis, conjunctival injection, ocular and/or orbital pain, headache, diplopia, blurry vision.
CS thrombosis	Signs of infectious processes often involving the paranasal sinuses, orbital cellulitis, conjunctival injection, chemosis and proptosis.
Tolosa-Hunt syndrome	Usually unilateral, painful ophthalmoplegia, diplopia from cranial neuropathy, Claude Bernard-Horner's syndrome in the event of injury to periarterial sympathetic fibres.
Sarcoidosis	Uveitis, ophthalmoplegia and facial diplegia, and systemic signs.

2) Type-II: originating from lateral wall of CS
The most common primary tumors originating from lateral CS wall are meningiomas and schwannomas.
Meningiomas can occur due to arachnoid granulations of cranial nerves in lateral cavernous sinus wall. Usually, they appear between the outer and inner layer of dura. Extension or invasion into surrounding structures is possible. If tumour does not extend beyond dural layers, complete resection is possible (Chotai et al., 2018). However, in case of invasive meningioma, full resection may be challenging due to significant morbidity associated with the risk of ICA and CN damage (O'Sullivan et al., 1997).
Schwannomas in that area originate from the trigeminal ganglion in the outer layer of lateral wall of the cavernous sinus and can be classified precisely based on the origin. Trigeminal schwannomas can expand from the posterior part of lateral wall into the posterior cranial fossa. Epidural and intradural middle cranial fossa approaches can achieve complete resection of the tumor – partially due to fact that it rarely invades ICA, cranial nerves or venous plexus (Muto et al., 2010).
3) Type-III: extraneous origin and occupying CS

This category includes pituitary adenomas, chordoma and chordosarcomas, nasopharyngeal carcinoma, petroclival meningioma and meningioma originating through sphenoidal ridge.

Pituitary adenoma appears in 15–20 % of cases (Ceylan et al., 2011; Frank and Pasquini, 2006). Invasion of this tumor remains

Table 5
Diagnostic steps in determining neoplastic and vascular etiologies of CSS.

	Etiology	
	Neoplastic	Vascular
Diagnostic aspects	Determination whether mass is primary, metastatic or local spread. CT, MRI and thorax/abdomen/pelvic CT in search of the primary tumour focus. Lumbar puncture with cytological examination.	Can be seen on CTA, MRI, MRA and angiography. Digital subtraction angiography is gold-standard test for diagnosis of CCF CCF also possible to visualize using orbital and transcranial USG. Intraocular pressure should be checked on patients with ocular sequelae If CST is suspected, infectious workup, D-dimer, MRV or CTV should be performed.

Table 6
CS pathologies related to vascular etiology and selected practices that have proved useful in clinical practice.

Disease	CCA	CCF	CST
Treatment strategy	Lowest rate of rupture for unruptured cerebral aneurysms (Morita et al., 2012). Cost-effectiveness analyses showed that preventive treatment was ineffective or not cost-effective for large (greater than 25 mm) aneurysms (Wiebers, 2006), therefore surgical intervention is not recommended. In case of aneurysm rupture, opinions are divided as to whether to use endovascular coils or extravascular clips (Byrne, 2006; Nichols et al., 2002).	Depends on classification, onset of symptoms and long-term neurological impairment; 20–60% of indirect CCFs close spontaneously (de Keizer, 2003; Kuybu and Dossani, 2021). Direct CCFs, which are unlikely to close spontaneously, should be closed at risk of progression with attendant morbidity. The technique of choice is endoscopy with trans-arterial or transvenous embolization (Kuybu and Dossani, 2021; O'Leary et al., 2002). When endovascular treatment is not possible or ineffective, surgery should be considered (Cowan et al., 2007; Debrun et al., 1989). If the medical facility can provide appropriate conditions and equipment, it is also possible to consider stereotactic radiosurgery. However, not all cases are eligible for this type of procedure (Lunsford, 1994; Myrseth et al., 2009; O'Leary et al., 2002; Schreuder et al., 1998; Yi et al., 2000).	Should include antimicrobial management with or without surgical drainage of air sinuses (Desa and Green, 2012). Retrospective analysis suggests that treatment with heparin reduces mortality in carefully selected cases of septic CST (Southwick et al., 1986).

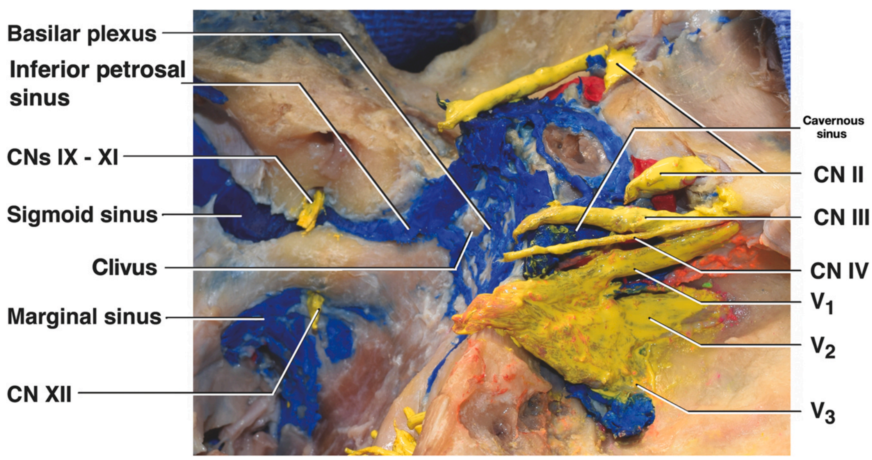

Fig. 8. Cadaveric dissection of the superolateral view of the right cavernous sinus and its contents. CN II – Cranial nerve II (optic); CN III – Cranial nerve III (oculomotor); CN IV – Cranial nerve IV (trochlear); CNs IX-XI – Cranial nerves IX-XI (glossopharyngeal, vagus, accessory); CN XII – Cranial nerve XII (hypoglossal); V1 – Ophthalmic branch of trigeminal nerve, V2 – Maxillary branch of trigeminal nerve; V3 – Mandibular branch of trigeminal nerve.

controversial as some authors indicate, that pituitary adenomas are biologically benign and parasellar invasion occurs due to histological defect in medial CS wall (Yokoyama et al., 2001; Ceylan et al., 2011). Other authors suggest that biological behavior aids infiltration (Yasuda et al., 2004). As neuroimaging techniques failed to delineate the medial CS wall, distance between two sides of ICA is measured to determine adenoma invasion. Frank and Pasquini (2006) presented a five-graded endoscopic classification for CS invasion, where score equal two or more is associated with CS invasion. There are also authors that state that pituitary adenoma does not invade CS, but rather growing mass of tumor pushes the medial wall toward the CS pressuring it and causing symptoms (Chotai et al., 2018).

Another types of tumors, that we can categorize into this group are chordoma and chordosarcomas. In comparison to pituitary adenoma, these tumors tend to compress cavernous sinus, rather than invading it (Chotai et al., 2018). Chotai and co-workers (2018) also emphasize that it would be safer to categorize these tumors as Type I, due to fact, that compression of CS can lead to thin and weakened wall, which can be missed to observe during surgery and this can cause direct inadvertent entry to CS. Radical removal of these type of tumors is possible and was accomplished with acceptable surgical morbidity (Lanzino et al., 1993).

Nasopharyngeal carcinomas tend to invade cavernous sinus, usually from lateral and inferior walls. Main goal of surgical treatment is to release the compression of cranial nerves, which is most commonly done by partial resection (Chotai et al., 2018).

Petroclival meningiomas are associated with anatomical space packed with cranial nerves, dural folds and vessels. This type of tumour similar to nasopharyngeal carcinoma tends to compress CS walls (especially posterior and lateral), rather than invading it (Chotai et al., 2018). Radical resection is extremely challenging given that tumour extends into cavernous sinus. However, novel studies describe endoscopic-assisted techniques to be a possible solution for these scenarios (Koerbel et al., 2009; Ebner et al., 2009).

Meningiomas originating through sphenoidal ridge and invading CS are the last type of tumor, that can be classified as Type III. Characteristics of these tumors can be compared to Type-II meningiomas originating in lateral wall of CS, which are described above.

3.2. CSS management

Clinical information collected during the diagnostic process, during a physical examination, a series of imaging diagnostics, and often hematology tests, directly affects the therapeutic strategies that a clinician can suggest for the patient (Balogh et al., 2015). If the cause of the pathology is infection or inflammation, pharmacological treatment in accordance with the latest recommendations should be started (Desa and Green, 2012; Plewa et al., 2021; Weerasinghe and Lueck, 2016). However, if the ethology is more complex, having neoplastic or vascular components, and conservative treatment is ineffective, invasive therapy is probably inevitable (Inoue et al., 1990; O'Reilly et al., 1986; Seo, 2006).

A vascular etiology of CSS indicates a few different clinical scenarios, which are presented in Table 6.

Neurological microsurgery operations in the head are extremely challenging (Dolenc, 1983, 1985; Kim et al., 2013; O'Leary et al., 2002; Parkinson, 1965; Yasuda et al., 2005) owing to the lack of any margin of error for the surgeon. Any mistake can cause injury to an extremely important anatomical structure such as a nerve, causing paralysis, or a vessel, the interruption of which can result in massive haemorrhage and serious complications. Figs. 7 and 8 present the cavernous sinus and its contents – note the topographical relationships between nerves and vessels.

Stereotactic radiosurgery remains an attractive alternative to classical surgery if the tumour diameter is ≤ 3 cm. Not only does it not require the disruption of tissue continuity, but in many cases, for example meningiomas, it also provides excellent tumour control (94–98% tumour control rate) (Lee et al., 2002; Pollock et al., 2012). Limitations of that technique include the reduced efficacy of stereotactic radiosurgery at recurrence, and if the tumor is highly infiltrative, making the lesion difficult to define as the target (Koga and Saito, 2012). Therefore, in most CS tumors such as pituitary adenomas, the procedure of choice is classical surgery (Kuybu and Dossani, 2021). However, if the patient qualifies for endoscopic intervention, consideration of this therapeutic option is justified by a higher gross total remission rate (GTR) than microscopic surgery and this improves with experience (Dhandapani et al., 2016). Importantly, some studies have shown a higher morbidity rate with endoscopic surgery and some lower; therefore, we recommend further research and meta-analysis (D'Haens et al., 2009; Dhandapani et al., 2016). It should also be added that gamma-knife radiosurgery can be successfully used to treat recurrent or residual adenomas (Sheehan et al., 2011).

If the tumour is not eligible for radiological surgery or/and the vascular lesion in the CS cannot be removed with endovascular treatment, clinicians rely on direct microsurgical intervention (Ammirati et al., 2013; Debrun et al., 1989; Lunsford, 1994; Myrseth et al., 2009; Schreuder et al., 1998; Yi et al., 2000). The procedure is associated with the selection of an appropriate surgical approach, individually for each patient, depending on the operational strategy and the clinical picture.

3.3. Surgical accesses to the cavernous sinus

The surgical procedure ensuring the safest possible intervention in the CS area depends on the physiological anatomical spaces in which the density and topography of structures are optimal (Alfieri and Jho, 2001b; Chung et al., 2016; Dallan et al., 2017; Kim et al., 2000; Yasuda et al., 2005) (Fig. 8). For this reason, the establishment of surgical access is adjusted according to the results of analysis of the CS anatomical triangles (Chung et al., 2016; Watanabe et al., 2003). Different pathologies require different procedures to ensure optimal vision of the surgical field, which is possible though multiple pathways (Alfieri and Jho, 2001b; Harris and Rhoton, 1976; Kurata et al., 2012). Each operating procedure must be preceded by detailed analysis of the risks posed by the operation, which can be achieved by determining the placement of important anatomical structures passing through or forming the boundaries of the triangles of the CS (Krisht et al., 1994; Ohmoto et al., 1991, 2002b).

Table 7
Medial group of CS triangles according to Chung et al. (Chung et al., 2016).

	Medial Group			
Triangles	Superioposterior	Superior	Middle	Inferior
Definitions	Anterior clinoid process, posterior clinoid process, apex of petrous part of temporal bone	Optic nerve, oculomotor nerve before entering SOF, dural fold between dural entries of optic and oculomotor nerves	Oculomotor nerve, trochlear nerve, dural fold between dural entries of oculomotor and trochlear nerves	Trochlear nerve, ophthalmic nerve, dural fold between dural entries of trochlear and ophthalmic nerves
Nomenclature used in other studies (Dolenc, 1989; Fujimoto et al., 1992; Goel, 1997; Hakuba et al., 1989; Isolan et al., 2005; Watanabe et al., 2003)	Oculomotor triangle	Anteromedial triangle, clinoidal triangle, Dolenc's triangle	Paramedial triangle, paramedian triangle, supratrochlear triangle	Superolateral triangle, infratrochlear triangle, Parkinson's triangle
Related surgical accesses	Interhemispheric approach		Pterional approach	

Table 8
Lateral group of triangles according to Chung et al. (2016).

Triangles	Lateral group: Anteromedial	Anterolateral	Posterolateral	Posteromedial
Definitions	Ophthalmic nerve, maxillary nerve, space between the superior orbital fissure and the foramen rotundum	Maxillary nerve, mandibular nerve, space between the foramen rotundum and foramen ovale	Mandibular nerve, greater petrosal nerve, space between foramen ovale and hiatus for greater petrosal nerve	Trigeminal ganglion, greater petrosal nerve, space between hiatus for greater petrosal nerve and apex of petrous part
Nomenclature used in other studies (Dolenc, 1989; Fujimoto et al., 1992; Goel, 1997; Hakuba et al., 1989; Isolan et al., 2005; Watanabe et al., 2003)	Anterolateral triangle, Mullan's triangle	Lateral triangle	Posterolateral triangle, Glasscock's triangle	Posteromedial triangle, Kawase's triangle
Related surgical accesses	Pterional approach		Middle cranial fossa approach	

Over the decades, many articles (Chung et al., 2016; Dolenc and Rogers, 2009; Dolenc, 1989; Goel, 1997; Hakuba et al., 1989; Isolan et al., 2007; Parkinson, 1965; van Loveren et al., 1991) have described the triangles of the CS. Unfortunately, the definitions of boundaries and the contents of individual triangles and their terminology differ across the literature. Therefore, the nomenclature has not been properly standardised and this often hinders the proper interpretation and comprehensive understanding of scientific findings. In our opinion, the most consistent and complete description of these anatomical structures was provided by Chung et al. (2016), who not only named, distinguished and unified the previous nomenclature but also introduced an additional division, grouping specific triangles according to their topographical locations. Table 7 presents triangles classified to the medial group, Table 8 to the lateral group and Table 9 to the posterior group. Clinical examples are matched to each group, in the course of which appropriate access proved to be useful.

The interhemispheric approach can be performed by drilling the central portion of the frontal bone to reach the superoposterior and superior triangles of the medial group. This route can be used to treat carotid-ophthalmic aneurysms. Moreover, it provides optimal access to the superior and inferior parts of the carotid siphon (Chung et al., 2016; Watanabe et al., 2003). Renn and Rhoton (1975) state, that there are anatomical variabilities in the sellar region that are disadvantageous specifically to transfrontal approach, including:

1) a prefixed chiasm (observed in 10% of cases) and a normal chiasm with 2 mm or less between the chiasm and tuberculum sellae (observed in 14% of cases).

2) an acute angle between the optic nerves as they entered the chiasm (observed in 25% of cases).

3) a prominent tuberculum sellae protruding above a line connecting the optic nerves as they exit the optic canals (observed in 44% of cases).

4) carotid arteries approaching within 4 mm of midline within or above the sella turcica (observed in 12% of cases).

The pterional approach is carried out by drilling the pterion area - where the frontal, parietal, temporal, and sphenoidal bones join, through the middle and inferior triangles of the medial group or the anteromedial and anterolateral triangles of the lateral group and enables the carotid-cavernous fistula to be accessed (Gonzalez et al., 2005; Kim et al., 2013; Yoon et al., 2012). Moreover, the anterolateral triangle provides a side of the cavernous-pterygoid venous anastomosis (Watanabe et al., 2003). The pterional approach is also used to reach the inflamed abducens nerve through the inferior triangle of the medial group and its distal section through the anterolateral triangle of the lateral group (Chung et al., 2016).

The middle cranial fossa approach has a wide range of surgical applications, allowing access to the petrous part of ICA aneurysms or petroclival meningioma (Abla and Lawton, 2014; Gonzalez et al., 2000). The subsequent operational steps consist of temporalis muscle retraction, opening the pterion, lifting the temporal bone and locating the posterolateral and posteromedial triangles. The rhomboid space expanded from the posteromedial triangle can provide a greater margin of movement for the surgeon (Tripathi et al., 2015). On the other hand, posterolateral triangle access is extremely useful in cases of carotid siphon haemorrhage, allowing the ICA to be temporarily occluded (Chung et al., 2016).

In the case of lesions around the CS and anterior part of parahippocampal cortex, the trans-zygomatic middle fossa approach presented by Melamed et al. (2009) provides a wider surgical corridor for visualizing extradural structures such as trigeminal nerve divisions with minimal temporal lobe retraction.

The retromastoid suboccipital approach provides optimal access to small branches of the cavernous part of the ICA and can be performed by drilling the occipitomastoid suture and locating both triangles of the posterior group, medial and lateral (Quiñones-

Table 9
Posterior group of triangles according to Chung et al. (Chung et al., 2016).

	Posterior group	
Triangles	Lateral	Medial
Definitions	Dural entry of trochlear nerve, dural entry of abducens nerve, apex of petrous part	Dural entry of trochlear nerve, dural entry of abducens nerve, posterior clinoid process
Nomenclature used in other studies (Dolenc, 1989; Fujimoto et al., 1992; Goel, 1997; Hakuba et al., 1989; Isolan et al., 2005; Watanabe et al., 2003)	Inferolateral triangle	Inferomedial triangle
Related surgical accesses	Retromastoid suboccipital approach	

Hinojosa, 2012). The literature states that surgeons should take care with their actions because the basilar venous plexus is nearby (Chung et al., 2016).

Anatomical structures that are accessible via specific routes can be identified from the contents of Tables 7, 8 and 9.

In addition to the surgical accesses presented through the triangles of the CS area, clinicians have developed several alternative routes for CS-related invasive procedures, some of which are presented below.

The lateral orbital wall approach presented by Altay et al. (2012) enables lesions with primary or secondary involvement of the CS to be accessed without the need for brain retraction and interruption of the temporalis muscle. It can be performed by a lateral canthal incision, lateral orbit rim and anterior lateral wall removal, reflection of the dural covering of the CS and deletion of the anterior clinoid process.

The superior intradural approach is directed through a frontotemporal craniotomy, removing the anterior clinoid process and opening the optic canal (Dolenc, 1983, 1985). During that procedure, care should be taken because of the increased risk of orbital periosteum injury (Hashimoto and Kikuchi, 1990). This approach can be used with great success to expose the oculomotor and trochlear nerves, but the trigeminal and abducens nerves are seldom observable (Dalgic et al., 2010; Sekhar et al., 1987).

The inferomedial transnasal-transsphenoidal approach can be performed to expose the medial wall of the CS (Fujii et al., 1979; Inoue et al., 1990). Generally, the major steps in this operation are mucosa elevation and removal of the lateral wall of the sphenoidal sinus to expose the bone between the cavernous and sphenoidal sinuses. However, it is possible to observe very thin bone or no bone at all, exposing the dura or the medial part of the CS. Medial retraction of the cavernous part of the internal carotid artery provides excellent exposure of the lateral venous space and access to the origin of the inferior part of the CS and the abducens nerve (Dalgic et al., 2010).

Yilmazlar et al. (2008) provide a lot of technical information on carrying out transsphenoidal access (TSS) operations, including the safety margin working area in patients with macroadenomas, which, according to the study, is approximately 15.0 (+/- 2.6) x 10.3 (+/- 2.1) mm. In relation to the basal dura, the posterior segment of the common carotid artery was observed to have more caudal position than the anterior segment, which should be considered during extended exposure. In addition, authors advise precautionary measures aimed at prior identification of morphological variations in this area, which can be beneficial for detection of the boundaries of dissection. This is particularly important in the basal portion of CS, where variable course of internal carotid artery may transform the anatomical configuration - slowly growing pituitary adenomas stretch out both internal carotid arteries from medial to lateral directions and can cause widening of distances between parts of the vessel. One should remember about the limitations of this study - processes to which the cadaveric tissue was subjected to compared to physiologically hydrated tissues may influence the accuracy of measurements and therefore they should be handled with some caution. The authors also state that their measurements are significantly different than those in the radiologic images when arterial blood under pressure is in the arteries as well as when venous blood fills the cavernous sinus as is the case in vivo.

Transsphenoidal approach is also discussed in Renn and Rhoton (1975) work about disadvantageous anatomical configuration of the sellar region, when deciding which surgical approach will be most appropriate. Unlike the transfrontal approach, the transsphenoidal approach is described as disadvantageous in as many as eight scenarios:

1) large anterior intercavernous sinuses extending anterior to the gland just posterior to the anterior sellar wall (observed in 10% of cases).

2) a thin diaphragm in 62%, or a diaphragm with a large opening (observed in 56% of cases).

3) carotid arteries exposed in the sphenoidal sinus with no bone over them (observed in 4% of cases).

4) carotid arteries that approach within 4 mm of midline within the sella turcica (observed in 10% of cases).

5) optic canals with bone defects exposing the optic nerves in the sphenoidal sinus (observed in 4% of cases).

6) a thick sellar floor (observed in 18 % of cases).

7) sphenoidal sinuses with no major septum in 28 % or a sinus with the major septum well off midline (observed in 47 % of cases).

8) a presellar type of sphenoidal sinus with no obvious bulge of the sellar floor into the sphenoidal sinus (observed in 20 % of cases).

The zygomatic approach to the CS is another technique successfully used to treat chordoma (Aversa and Al-Mefty, 2021). The author states that this route minimizes the depth of field and is highly advantageous in chordoma located mainly lateral to the cavernous part of internal carotid artery. Tumor extensions to the sphenoidal sinus, sella, petrous apex, and clivus are also removable (Aversa and Al-Mefty, 2021).

In addition to traditional surgery, it is also possible to use endoscopic access to the CS in specific cases. This leads to a shorter hospitalization period, reduced mortality and less postoperative discomfort (Lee et al., 2008; White et al., 2007). Depending on the need and the specific appearance of the clinical case, it is possible to choose from a number of endoscopic methods: the direct superior ophthalmic vein approach related to embolization (Lee et al., 2008); transorbital access through the meningo-orbital band (most superficial dural band that tethers the fronto-temporal dura) (Dallan et al., 2017); the transvenous facial vein approach for carotid-CS fistulae (Thiex et al., 2014); the transvenous inferior petrooccipital vein approach presented as a route that can be used when others are not possible (Kurata et al., 2012); and endonasal approaches representing adjunctive techniques, which have proved useful in cases of intracavernous soft tumours not invading the vessels and nerves (Alfieri and Jho, 2001b).

Selected complications resulting from procedures performed in the area of the CS are presented in Table 10.

The clinical aspects related to the CS presented here clearly demonstrate the complexity and multidimensionality of health problems and related therapeutic issues that clinicians must address in

Table 10
Selected complications resulting from procedures performed in the area of the CS.

Procedure	Complications related to procedure
Proximal left ICA endovascular sacrifice; left maxillectomy with orbital exenteration and radical resection of left CS; anterolateral thigh free flap reconstruction (Rennert et al., 2018).	Thigh hematoma requiring evacuation; recurrent cerebrospinal fluid leak requiring two revision surgeries for placement of a fat graft followed by a shunt; meningitis (Rennert et al., 2018)
Surgical treatment for CS tumours (not specified) (Landeiro et al., 2001)	Death from uncontrollable intracranial hypertension caused by ischemic infarction in the immediate postoperative period (1/16; 6.25 %), clinical recurrence confirmed by MRI, reoperated on; the histopathological study revealed that it was a malignant meningioma resulting in death 12 months after continuous tumor growth, with brainstem compression, ear invasion and clivus destruction (1/16; 6.25 %), extensive cerebral infarction (2/16; 12.5 %), tumor bed small hemorrhages, brain edema, minimal bruises, oculomotor nerve palsy (Landeiro et al., 2001)
En bloc resected CS meningioma (Larson et al., 1995)	Oculomotor nerve palsy, trigeminal nerve palsy (Larson et al., 1995)
CS sampling (Tanriover et al., 2017)	Guidewire breakage (Tanriover et al., 2017)
Subtotal meningioma resection via frontotemporal craniotomy concurrently with decompression of the CS and ipsilateral optic nerve (Gozal et al., 2020)	Cranial nerve palsy involving CN III–VI (70 %), a visual deficit (62 %), headaches (52 %), or proptosis (44 %); radiographic recurrence was noted in 10 % of cases, with a median time to recurrence of 4.6 years (Gozal et al., 2020)
CS surgery for benign tumors (not specified) (Cusimano et al., 1995)	Cerebral infarctions (5/124; 4 %), meningitis (2/124; 0.016 %), hydrocephalus with chiasmal prolapse (1/124; 0.008 %); complications occurred only in cases of meningiomas or pituitary adenomas; tumor recurrence (12/124; 10 %) (Cusimano et al., 1995)
Radiosurgical management of benign CS tumors (Chen et al., 2001)	Cranial nerve deficits - VIth cranial nerve palsy (1/69; 0.001 %), bilateral VIth cranial nerve palsy (1/69; 0.001 %) (Chen et al., 2001)
Radical CS resection (Katzir et al., 2016)	Cavernous part of internal carotid artery pseudoaneurysm (Katzir et al., 2016)
CS surgery for meningiomas (technique not unified) (Newman, 2007)	30 % of patients suffered vision worsening, including 20 % whose vision deteriorated to no light perception, 11 % developed newly acquired optic neuropathy, 100 % of patients had evidence of some cranial nerve dysfunction (III, IV, V, or VI) immediately after surgery, 16 % had evidence of aberrant regeneration of the third nerve and 21 % developed neurotrophic keratitis (Newman, 2007).

their practice. Solid, complete and transcendent knowledge of the anatomy of the CS, the diagnostic processes, pathologies associated with it, symptoms of various disease syndromes, the principles of operational strategies and preparation for various scenarios along with the high manual skills of the neurosurgeon, are indispensable for optimal, safe and effective treatment of patients with the presented complaints.

4. Conclusions

The clinical aspects of the CS have been analyzed from many perspectives. Using carefully selected literature and analyzing the results of many scientific studies, current knowledge about the diagnosis and treatment of pathologies related to the CS was summarized. Errors and misunderstandings between individual research papers were also observed and potential solutions were proposed. The CS remains an object of interest to clinicians and anatomists, and there is still need for research into optimal therapies, taking account of the distinctiveness of disease processes among patients. Further research is required to acquire more information and establish reliable conclusions.

Ethical approval and consent to participate

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Ethical approval and consent to participate

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Data Availability

Please contact authors for data requests (Łukasz Olewnik PhD - email address: lukasz.olewnik@umed.lodz.pl).

Competing interests

The authors declare that they have no competing interests.

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