Functional anatomy of headache: circle of Willis aneurysms, third cranial nerve and pain

Anatomia functional da cefaleia: aneurismas do polígono de Willis, III nervo craniano e dor

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ABSTRACT

Patients with intracranial aneurysm located at the internal carotid artery-posterior communicating artery (ICA-PComA) often present pain on the orbit or fronto-temporal region ipsilateral to the aneurysm, as a warning sign a few days before rupture. Given the close proximity between ICA-PComA aneurysm and the oculomotor nerve, palsy of this cranial nerve may occur during aneurysmal expansion (or rupture), resulting in progressive eyelid ptosis, dilatation of the pupil and double vision. In addition, aneurysm expansion may cause compression not only of the oculomotor nerve, but of other skull base pain-sensitive structures (e.g. dura-mater and vessels), and pain ipsilateral to the aneurysm formation is predictable. We reviewed the functional anatomy of circle of Willis, oculomotor nerve and its topographical relationships in order to better understand the pathophysiology linked to pain and third-nerve palsy caused by an expanding ICA-PComA aneurysm. Silicone-injected, formalin fixed cadaveric heads were dissected to present the microsurgical anatomy of the oculomotor nerve and its topographical relationships. In addition, the relationship between the right ICA-PComA aneurysm and the right third-nerve is also shown using intraoperative images, obtained during surgical microdissection and clipping of an unruptured aneurysm. We also discuss about when and how to investigate patients with headache associated with an isolated third-nerve palsy.

Keywords: Aneurysm; Headache; Oculomotor nerve; Pain; Posterior communicating antery; Internal carotid artery, Anatomy.

RESUMO

Pacientes com aneurisma intracraniano localizado na artéria carótida interna na origem da artéria comunicante posterior (ACI-AComP) frequentemente apresentam dor na órbita ou na região fronto-temporal no mesmo lado do aneurisma, como sinal de alarme poucos dias antes da ruptura. Devido à proximidade do aneurisma da ACI-AComP do nervo craniano oculomotor, paralisia desse nervo pode ocorrer durante expansão aneurismática (ou ruptura), resultando em dilatação pupilar, visão dupla e ptose palpebral progressiva. Além disso, expansão aneurismática pode causar compressão não só do terceiro nervo craniano, mas também de outras estruturas da base do crânio sensíveis à dor (e.g. dura-mater e vasos), e dor homolateral ao aneurisma é previsível. Nós revisamos a anatomia funcional do polígono de Willis, nervo oculomotor e suas relações topográficas para melhor entender a fisiopatogenia relacionada a dor e paralisia do nervo oculo-motor causada pela expansão do aneurisma da ACI-AComP. Cabeças cadavéricas fixadas em formalina e injetadas com silicone foram dissecadas para apresentar a anatomia microcirúrgica do nervo oculomotor e sua relação topográfica. Também a relação entre o aneurisma da ACI-AComP e o terceiro nervo craniano é mostrada usando-se imagens intraoperativas, obtidas durante dissecção microcirúrgica e colocação de clipe em um aneurisma não roto. Nós também discutimos sobre quando e como investigar pacientes com cefaléia associada com uma paralisia isolada do terceiro nervo craniano.

Palavras-chaves: Aneurisma; Cefaleia; Nervo oculomotor; Dor; Artéria carótida interna; Artéria comunicante posterior; Anatomia.

INTRODUCTION

Patients with intracranial aneurysm located at the internal carotid artery-posterior communicating artery (ICA-PComA) often present pain on the orbit or fronto-temporal region ipsilateral to the aneurysm, as a warning sign a few days before rupture.[1,2] Given the close proximity between ICA-PComA aneurysm and the third cranial nerve (oculomotor nerve), palsy of this cranial nerve may occur during aneurysmal expansion (or rupture), resulting in progressive eyelid ptosis, dilatation of the pupil and double vision. In addition, aneurysm expansion may cause compression not only of the oculomotor nerve, but of other skull base pain-sensitive structures (e.g. dura-mater and vessels), and pain ipsilateral to the aneurysm formation is predictable (see Figures 1 and 2).

Thus, prompt evaluation of patients presenting recent third-nerve palsy is of vital importance with the aim of revealing an occult intracranial aneurysm, since most people are unaware of its presence, because of the lack of symptoms. In this regard, pain may even occur in the absence of a third-nerve palsy. In fact, most of the symptomatic ICA-PComA aneurysms are identified without any oculomotor or pupillary deficits.[3]

CLASSIFICATION OF THIRD-NERVE PALSIES

There are two main causes of oculomotor nerve palsy: (1) vasculopathic (commonly associated with diabetes mellitus and severe atherosclerosis) and (2) compressive (associated with ICA-PComA aneurysms).[4] Frequently, both forms of oculomotor palsy develop in an association with headache (e.g. retro-orbital pain). In practice, it is not an easy task to definitively distinguish one from the other exclusively on clinical grounds.[4] Unlike patients with ICA-PComA aneurysm, pain associated with vasculopathic lesions subsides after several days and spontaneous resolution of the third-nerve palsy is expected within 90 days.[4] Pupillary involvement is usually linked to parasympathetic fibers compressed by the aneurysm as the latter are located on the periphery (along the dorsomedial surface) of the third cranial nerve.

As a general rule (around 80% of the cases),[4] the pupil is spared in vasculopathic third-nerve palsy. However, it was reported that 14% (7/51 patients) of the ICA-PComA aneurysms are also associated with a pupillary-sparing partial third-nerve palsy.[5] Furthermore, patients presenting a pupil-sparing partial third-nerve palsy and harboring an unruptured intracranial aneurysm (UIA) may develop pupil dilation over time, as the compression progress.[5,6] Thus, we should assume that an aneurysm is the probable cause of a third-nerve lesion when there is even a slight degree of pupillary abnormality (the 'rule of the pupil' applied to isolated third-nerve palsies),[4] and immediate angiography is mandatory. Usually third-nerve dysfunction is associated with an aneurysm 9-11 mm in size, but smaller-sized aneurysms (5-6 mm) may also cause third-nerve palsy.[7,8] Aneurysms of the ICA-PComA are the most common aneurysm encountered in females.[2] And thunderclap headache in association with third-nerve palsy is characteristically found after subarachnoid hemorrhage due to ICA-PComA aneurysm rupture. The estimated frequency of third-nerve palsy in patients with ICA-PComA aneurysm is 30% to 40%.[3]

Aneurysms of the internal carotid artery are very common (30-40% of the aneurysms in most series), including aneurysms of the ophthalmic artery, superior hypophyseal artery, posterior communicating artery, anterior choroidal artery and carotid artery bifurcation. Unruptured ophthalmic artery aneurysm habitually is discovered during investigation of a recent side-looked unilateral headache without any cranial nerve deficit.

WHEN AND HOW TO INVESTIGATE THE PATIENT WITH HEADACHE AND THIRD-NERVE PALSY

Patients with pupil-sparing third-nerve palsies should be initially evaluated with angio-MR or angio-CT[9] in order to disclose an unexpected aneurysm, especially the elderly, diabetic and those with arterial hypertension. Mathew and colleagues[8] reported that an intracranial aneurysm was the cause of isolated third-nerve palsy in 27/137 (19.7%) patients. All 27 aneurysms were detected by angio-CT and in no case was another lesion found by conventional cerebral angiography. They concluded that "multidetector computed tomographic angiography is a safe and effective diagnostic imaging tool in detecting clinically significant aneurysms when a patient presents with an acute isolated third nerve palsy".[8] However, if after 12 weeks of follow-up, no improvement in symptoms is observed, digital angiography is necessary, even in case of previously "normal" angio-MR or angio-CT. This is so because small aneurysms may undetected under those methods. Although, in the series of Mathew and colleagues,[8] only 81 of 110 (74%) of the individuals without an intracranial aneurysm made a complete spontaneous recovery. On the other hand, when the pupil is involved, a digital carotid and vertebro-basilar angiography is compulsory, since
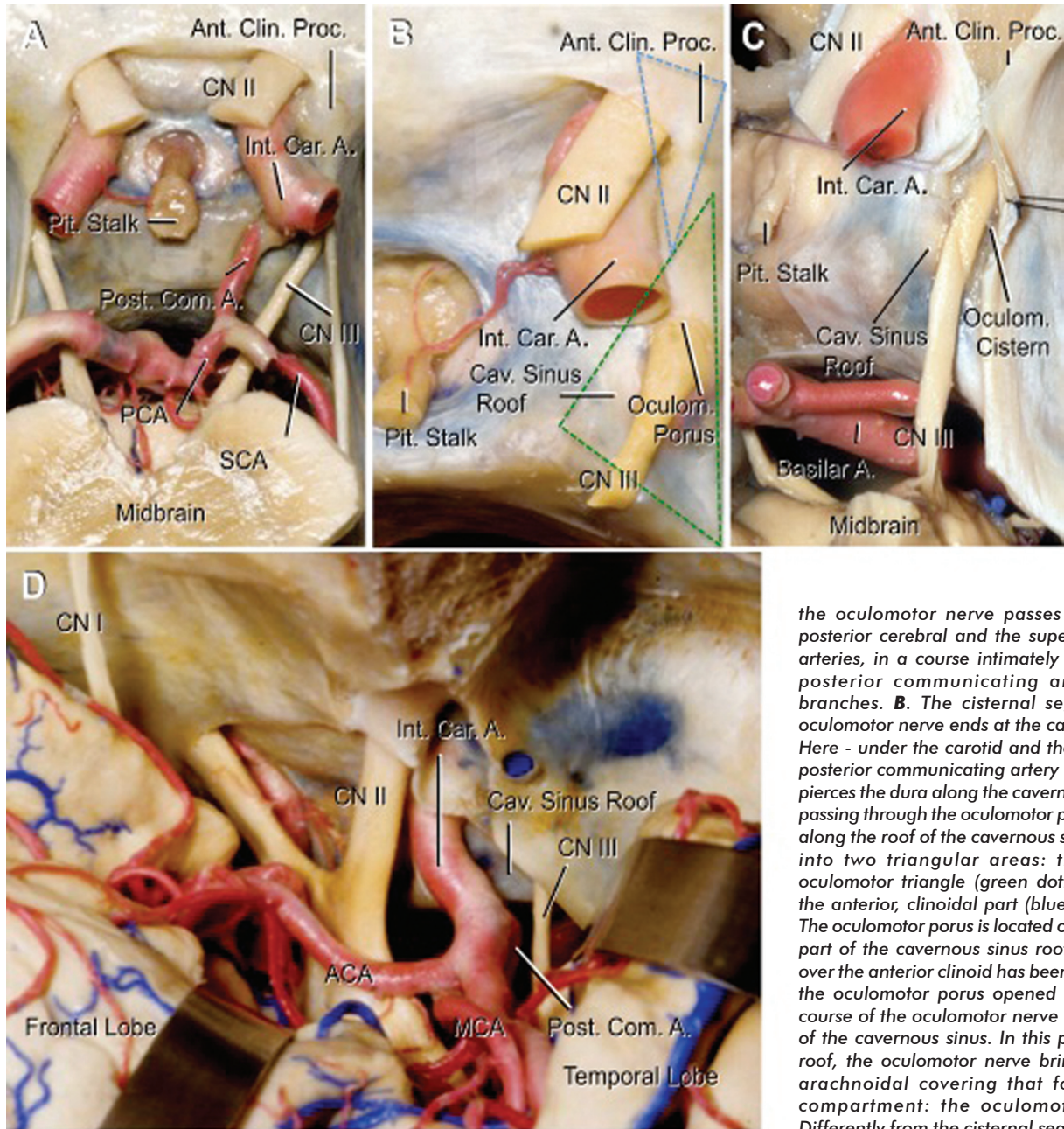
Figure 1. Silicone-injected cadaveric specimens have been dissected to demonstrate the microsurgical anatomy of the oculomotor nerve and its topographical relationships. **A**. A cut through the midbrain has been performed, allowing a view along the skull base and circle of Willis. The hypophyseal gland has been kept into the sellae, by cutting through the pituitary stalk. The optic nerve has been cut prior to the chiasm, as part of the right posterior cerebral artery. The posterior communicating artery is seen linking the internal carotid artery to the posterior cerebral artery. Although potent, this posterior communicating artery is not fetal - a term reserved for the posterior communicating artery which is the main supplier of the posterior cerebral artery and associated with an atretic segment linking this vessel to the basilar artery (P1). The oculomotor nerve emerges from midbrain along the lateral limits of the posterior perforated substance, starting its cisternal segment, on each side. The cisternal segment of

the oculomotor nerve passes between the posterior cerebral and the superior cerebelar arteries, in a course intimately related to the posterior communicating artery and its branches. **B**. The cisternal segment of the oculomotor nerve ends at the cavernous sinus. Here - under the carotid and the origin of the posterior communicating artery (A) - the nerve pierces the dura along the cavernous sinus roof, passing through the oculomotor porus. The dura along the roof of the cavernous sinus is divided into two triangular areas: the posterior, oculomotor triangle (green dotted area) and the anterior, clinoidal part (blue dotted area). The oculomotor porus is located on the posterior part of the cavernous sinus roof. **C**. The dura over the anterior clinoid has been removed and the oculomotor porus opened to expose the course of the oculomotor nerve along the roof of the cavernous sinus. In this path along the roof, the oculomotor nerve brings with it an arachnoidal covering that forms a small compartment: the oculomotor cistern.[26] Differently from the cisternal segment, the part of the nerve coursing along the roof is considerably fixed, being susceptible thus to external compression. **D**. The right sylvian fissure has been opened in another specimen, to simulate the surgical view into this area. The carotid cistern is the expansion of the subarachnoidal space that extends from the anterior clinoid process (removed) to the carotid bifurcation, just above the cavernous sinus roof and Liliequist's membrane. It contains the supraclinoid carotid artery, the origins of the ophthalmic, posterior communicating, choroidal, middle cerebral and anterior cerebral arteries. The oculomotor nerve pierces the roof of the cavernous sinus in close relation to the carotid artery and the origin of the posterior communicating artery. A.: Artery, ACA: Anterior Cerebral Artery, Ant.: Anterior, Car.: Carotid, Cav.: Cavernous, Clin.: Clinoid, CN: Cranial Nerve, Com.: Communicating, Int.: Internal, MCA: Middle Cerebral Artery, PCA: Posterior Cerebral Artery, Oculom. Oculomotor, Pit.: Pituitary, Post.: Posterior, Proc.: Process, SCA: Superior Cerebellar Artery.
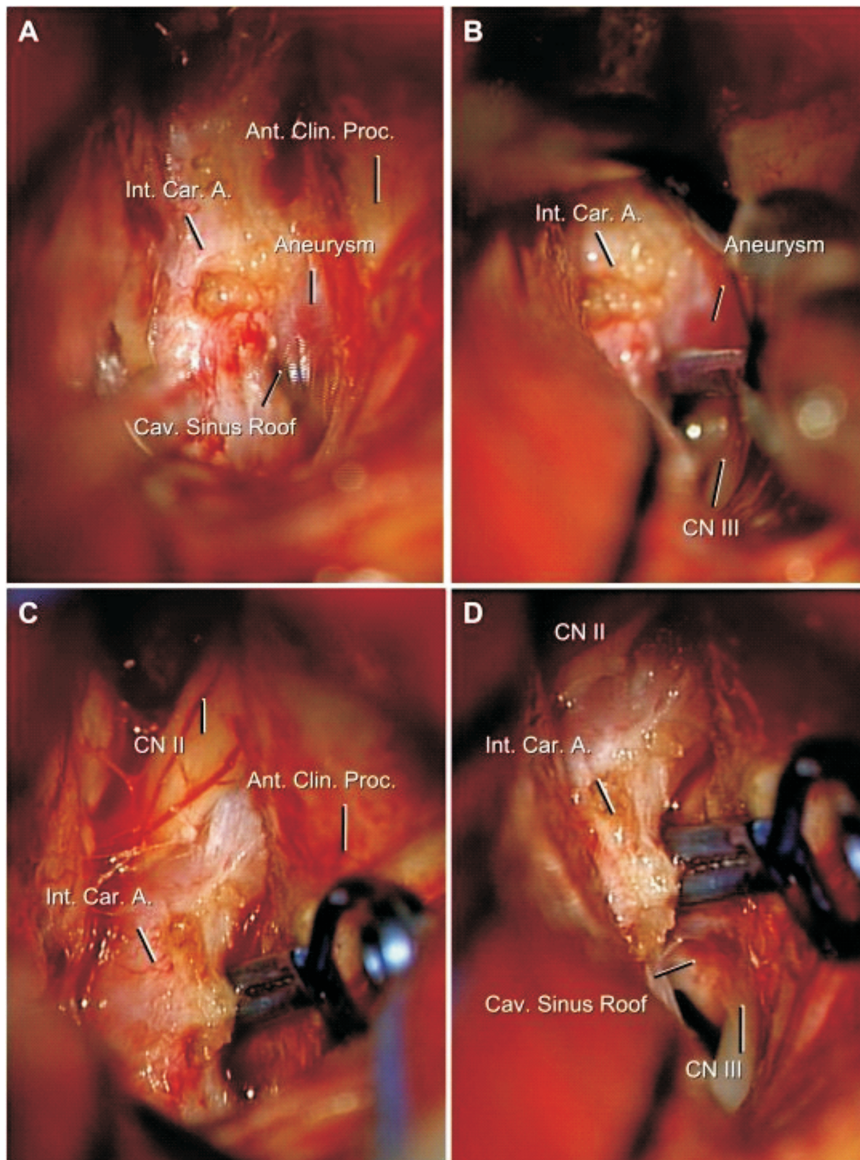
Figure 2. Intraoperative images. A. Lateral view into the right carotid cistern. The internal carotid artery is seen, just medial to the dura covering the anterior clinoid process. Extensive fibrotic tissue involves the aneurysmatic sac and roof of the cavernous sinus (this patient underwent a previous aneurysm operation 6 years before). B. The aneurysmal neck has been exposed by careful microsurgical dissection. The oculomotor nerve, entering into the cavernous sinus, is now seen. C. The aneurysm has been secured, preserving the posterior communicating artery. D. Shrinkage of the aneurism dome allows view into the posterior part of the cavernous sinus roof. The oculomotor nerve can be followed from its cisternal segment up to the oculomotor porus. A.: Artery, Ant.: Anterior, Car.: Carotid, Cav.: Cavernous, Clin.: Clinoid, CN: Cranial Nerve, Com.: Communicating, Int.: Internal, Post.: Posterior, Proc.: Process.

chances of an aneurysm being present are higher. Yet, the most sensitive tool for detection of intracranial aneurysms is digital subtraction angiography. Although it is an invasive study – with low risk of permanent neurologic deficit (<0.1%)[10] – it should be used in order to avoid missing small aneurysms.

HEADACHE AND UNRUPTURED INTRACRANIAL ANEURYSMS

During the lifespan of the individual, an intracranial aneurysm may develop in up to 10% of the population. Nowadays, as a result of the widespread use of neuroimaging techniques, it is not uncommon to become aware of the existence of an UIA during an investigation of a patient with headache. Nonetheless, the literature addressing the relationship between headache and the so-called 'incidental' UIA is scarce. The vast majority of vascular neurosurgeons would consider the finding of an UIA as an incidental event in a patient with headache.[11] In a recent study, Choxi and colleagues[11] reported that a remarkable improvement of the previous headache is expected after surgical or endovascular treatment of an UIA.

We have previously reported[12] that the stabbing headache formerly regarded as benign (characterized by a sharp pain of short duration on the surface of the head) might be a warning sign of intracranial, potentially dangerous abnormalities, such as UIA, vascular malformations or tumors (pituitary adenoma, meningioma, acoustic schwannoma). Some of the characteristics of these

secondary stabbing headache attacks (referred by us as 'alarm bell headache') are the following: (a) a gradual increase in pain severity with an increased frequency over the previous few months or years (crescent pattern); (b) a dura-mater contact with the lesion; (c) repeatedly confined to one or just a few points on the head; (d) unilateral on the same side as the lesion; (e) precipitated by head movements or the Valsalva maneuver.

In 2007 we reported[13] that ICA-PComA aneurysms may cause cluster headache-like symptoms and surgical clipping of the aneurysms resolved the cluster pain, suggesting a relationship between peripheral lesions located in the parasellar/sellar region and the appearance of cluster headache symptoms.

In addition, headache during the preoperative period in a patient with a known UIA is also to be expected as the result of a recent cerebral angiography performed in a patient with an UIA (6.5.5 [G44.810] Angiography headache, ICHD-II).[14] It is estimated that half of the patients submitted to angiography experienced headache within 24 hours.[15,16] On the other hand, both headache attributed to intracranial endovascular procedures (6.5.4 [G44.810], ICHD-II)[14,17] and post-craniotomy headache (5.7 [G44.88], ICHD-II)[14,18,19] may occur postoperatively.

CLASSIFICATION OF UNRUPTURED INTRACRANIAL ANEURYSMS BASED ON THE FORM OF DIAGNOSIS

An UIA may be diagnosed in a number of different conditions such as (1) incidentally; (2) associated with a ruptured aneurysm in a patient with multiple aneurysms (as expected in 15-35% of cases, mainly in females); or during investigation of (3) family members with familial aneurysms, (4) patients with a mass-effect due to a large or giant aneurysm (i.e. cranial nerve palsy or brainstem compression), and (5) patients with symptomatic headache simulating a primary type of headache (e.g. migraine, tension-type headache, stabbing headache, cluster headache or other trigemino-autonomic headaches).[12,13,20]

'RED FLAGS' SIGNALING UNRUPTURED INTRACRANIAL ANEURYSMS

Headache may be interpreted as a 'red flag' signaling that an UIA may be its cause, mainly when at least one of the following is present: (1) it is of recent onset, (2) side-looked unilateral pain with no side shift, (3) gradual increase in severity, (4) patient's age >50,

(5) precipitated by Valsalva maneuvers or head movements.[20] Some authors also recommend neuroimaging evaluation of patients with trigemino-autonomic headaches, such as cluster headache.[13,21] Thus, studies evaluating headache associated with UIA are of great importance to allow for early diagnosis before catastrophic rupture occurs.

MICROSURGICAL ANATOMY OF THE CIRCLE OF WILLIS AND OCULOMOTOR NERVE

The location of an aneurysm in the circle of Willis is closely related to the specific anatomical arterial configuration. There is a relationship between the lack of visualization of a unilateral A1 segment and detection of anterior communicating artery (AComA) aneurysms, whereas ICA-PComA aneurysms are related to the fetal type of posterior cerebral artery.[22] In this regard, an illustrative, case (36-year-old woman) is presented (Figure 3). The MR-angiography clearly shows the internal carotid artery aneurysm, related to the origin of a right, fetal pattern, posterior cerebral artery.

Figure 3. Magnetic resonance angiography (MRA). Right side, profile: Internal carotid artery aneurysm, related to the origin of a right, fetal pattern, posterior communicating artery. A.: Artery, ACA: Anterior Cerebral Artery, Car.: Carotid, Com.: Communicating, Int.: Internal, MCA: Middle Cerebral Artery, Post.: Posterior.

We recently analyzed a consecutive series of 158 patients with cerebral aneurysms originating in one of the three following locations: IC-PComA, AComA, and middle cerebral artery (MCA).23 The frequency of fetal-PCA was significantly higher in the group of patients with IC-PComA aneurysms (24% vs. 2% AComA and 3% MCA aneurysms).[23]

Silicone-injected, formalin fixed cadaveric heads were dissected to present the microsurgical anatomy of the oculomotor nerve and its topographical relationships (Figure 1). The relationship between the right internal carotid artery aneurysm at the origin of the posterior communicating artery and the right third-nerve is also shown in a 42-year-old woman with an unruptured aneurysm. Intraoperative images, obtained during surgical dissection, through a Zeiss Opmi Pentero Surgery Microscope camera, display the adhesions between the lesion and the entire roof of the cavernous sinus.

In this area, where the supraclinoidal internal carotid artery is situated, three main nerve systems are encountered: (i) the sympathetic nervous system, (ii) the parasympathetic nervous system, and (iii) the trigeminal nervous system. The sympathetic nerves, which innervate orbital structures, originate from the superior cervical ganglia and take an upward direction, by the side of the internal carotid artery to reach the parasellar region via the internal carotid nerve, which divides into two branches: the lateral branch, which distributes to the internal carotid artery (internal carotid plexus), and the medial branches, which also distributes filaments to the internal carotid artery and, continuing onward, forms the cavernous plexus. Trigeminal nerve fibers are diffusely distributed all over the parasellar structures, together with vessels and dura-mater.[24] As the internal carotid artery is surrounded by trigeminal and sympathetic fibers, aneurysm formation with gradual saccular growth may stretch and stimulate the nerve endings and this may cause pain in the periorbital and/or temporal regions. Aneurysmal compression of pain sensory afferent fibers of the ophthalmic division of the trigeminal nerve present around the oculomotor nerve and into parasellar dura is seen by some as cause of orbital pain.[25]

In conclusion, we reviewed the functional anatomy of circle of Willis, oculomotor nerve and its topographical relationships in order to better understand the pathophysiology linked to pain and third-nerve palsy caused by an expanding ICA-PComA aneurysm.

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COMMENT

To study headaches with consistent unilateral presentations (especially at the same side), in addition to study head pain sufferers with isolated third-nerve palsies is crucial to determine anatomo-pathological relationships between structural lesions in the vicinity of the oculomotor nerve emerging branches as well as its topographic relationship with the internal carotid artery-posterior communicating artery (ICA-PCA).

In this review, the authors discuss not only the anatomical perspective but also the clinical features. The pain frequently reported as ipsilateral, representing a warning sign few days before the rupture of aneurysms occurring in this internal carotid artery branch is emphasized. Expatiating about oculomotor palsies and the importance of excluding the aneurysms of the internal carotid artery-posterior communicating artery, the authors present the classification of the third-nerve palsies and when and how to investigate the patients presenting it. Discussion on whether an angiography is indicated and the arterial territories in which they have to be performed, is presented in this review, which also presents important data on available reports from specialized literature.

Patients presenting unilateral headache around the eye are common in daily neurological clinics, but the difficulties in evaluating these subjects based on clinical findings only, especially when a third-nerve palsy is also manifested and the pain is atypical warrants the need for reviewing unusual headache types. Since the authors present their own experience and compare it with other author's cases, discussion presented herein is useful for clinicians willing to get update.

Special interest is devoted to the classification of unruptured intracranial aneurysms based on the form of diagnosis and to the "red flags" signaling unruptured intracranial aneurysms such as its recent onset, age over 50 years, side-looked unilateral pain with, gradual increase in severity and precipitation by Valsalva maneuvers or head movements. Attention should be dedicated as well to the complementary examinations mandatory to evaluate these patients. It is a must-read review.

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