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ORIGINAL ARTICLE

Ophthalmic artery originating from the anterior cerebral artery: anatomo-radiological study, histological analysis, and literature review

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Abstract The ophthalmic artery has an anomalous origin in 2–3 % of cases and rarely arises from the anterior cerebral artery. Herein, we provide the first anatomical, radiological, and histological description of such an anomalous origin, together with a literature review. During the anatomical dissection of an 81-year-old Caucasian male, the absence of the right ophthalmic artery in its usual location was evident from an endonasal transsphenoidal perspective. The specimen was then studied in detail, through multiple dissections, corrosion casting, high-resolution CT, and histological analysis. The English literature on anomalous origins of the ophthalmic artery was reviewed, together with reported associated pathologies. Anatomo-radiological analysis documented that the right ophthalmic artery arose from the inferior surface of A1 tract of the anterior cerebral artery (A1) and passed over the optic nerve in its subarachnoid tract. A meningo-ophthalmic artery was evident on the same side and reached the orbit through the superior orbital fissure. Histological examination of both internal carotid artery (ICA) walls documented a significantly decreased thickness of the tunica media and adventitia on the side of the anomalous ophthalmic artery, with a significantly different content of collagen types I and III. The literature review documented an association of aneurysms and anomalous ophthalmic arteries. To the best of our knowledge, this is the first anatomical report that includes a radiological and arterial wall analysis of a persistent ventral ophthalmic artery. The latter provides histological data that support the clinical evidence of a higher association of aneurysms with anomalous origins of the ophthalmic artery.

Keywords Anatomy · Aneurysm pathogenesis · Ophthalmic artery

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Abbreviations

ICA	Internal carotid artery
C3	C3 tract of the internal carotid artery
C4	C4 tract of the internal carotid artery
ECA	External carotid artery
MDCT	Multidetector computed tomography
CBCT	Cone beam computed tomography
OphA	Ophthalmic artery
DOA	Dorsal ophthalmic artery
VOA	Ventral ophthalmic artery
MMA	Middle meningeal artery
MOA	Meningo-ophthalmic artery
MLA	Meningolacrimal artery
ACA	Anterior cerebral artery
ACoA	Anterior communicating artery
A1	A1 tract of the anterior cerebral artery
A3	A3 tract of the anterior cerebral artery
MCA	Middle cerebral artery

M1	M1 tract of the middle cerebral artery
PCoA	Posterior communicating artery
SOF	Superior orbital fissure

Introduction

The ophthalmic artery (OphA) is usually the first subarachnoid branch of the internal carotid artery (ICA) and has a variable course in relation to the optic nerve [17]. The prevalence of anomalous origins of the OphA is reported to be around 2–4 % of cases [21, 60]. Although rare, these variants have critical clinical implications in the preoperative and operative treatment of different surgical diseases.

During the endonasal endoscopic dissection of a fresh-frozen head, we documented the anomalous origin of an ophthalmic artery, which was located superiorly to the optic nerve and originated from the anterior cerebral artery. The specimen was then studied in detail, collecting radiological, anatomical, and histological data.

The findings are herein presented, together with a review of the embryogenesis and of anomalous origins of the ophthalmic artery and its associated pathologies.

Material and methods

Specimen and dissections

The dissection was carried out on a fresh-frozen specimen head, whose arterial system had been injected with a catalyzed silicon rubber. The specimen was studied both through a transnasal endoscopic dissection and a transfrontal sinus, endoscope-assisted approach to the suprasellar region. The dissections were performed with an endoscopic HD camera with 0, 45, and 70° optics (Karl Storz®, Tuttlingen, Germany). A dedicated optic navigation system (NDI Polaris® Vicra®, Waterloo, Canada) was used throughout the dissections. Vessels diameters were directly measured with a millimeter paper.

Radiological analysis

The specimen had undergone a multidetector computed tomography (MDCT) and a cone beam CT (CBCT - NewTom 5G, Image Works, Verona, Italy). MDCT scan was used for neuronavigation. CBCT was used to analyze the vascular anatomy in detail from a radiological perspective, as the catalyzed silicon rubber used to inject the arteries is hyperdense on CT. The vessels calibers were measured using the CBCT, loaded on a freeware DICOM viewer (OsiriX®, Bernex, Switzerland).

Histological study

Both ICAs, comprising parasellar, paraclinoid, and intracranial tracts, were removed. Histomorphological, histomorphometric, immunohistochemical, and double immunofluorescence analyses were performed on these arterial walls.

Histomorphological and histomorphometric analyses

The samples were fixed in 10 % neutral buffered formalin, p 6.9, for 72 h and embedded in paraffin according to standard procedures. Eight-micrometer-thick sections were cut by microtome (Microm HM 325, Thermo Scientific, Walldorf, Germany) and collected on poly-L-lysine-coated glass slides; the sections were taken transversally to the vessel longitudinal axis. Sections were deparaffinized in xylene, rehydrated in descending concentrations of ethanol, and prepared with hematoxylin-eosin and Masson-Goldner staining for morphometric evaluation (thickness of tunica intima, tunica media, and tunica adventitia) and Sirius red staining for collagen fiber evaluation.

Hematoxylin-eosin staining and Masson-Goldner trichrome staining

The sections were processed according to the standard protocols. In order to evaluate vessel histomorphological aspects and compare the two carotid samples by quantifying the three vessel layers thickness (tunica intima, media, and adventitia); five digitally fixed images (standardized arbitrary area) for each section (50 serial sections/sample) were blindly evaluated by two investigators, using an optical light microscope (Olympus BX50, Olympus, Hamburg, Germany) at a final magnification of ×200. Quantitative analysis of the three-layer thickness was performed using a digital color video camera equipped with an image analysis program (Image Pro-Plus, Milan, Italy).

Sirius red staining

The sections were processed according to the standard protocol. All sections were then analyzed using a light microscope (Olympus BX50, Olympus, Hamburg, Germany) equipped with U-POT polarizer (Olympus, Hamburg, Germany) to assess the organization of collagen fibers. Under polarized light microscopy, the dense collagen fibers were stained orange-red, whereas the thin collagen fibers appeared green. In both samples, for each digitally fixed image (five images for section), five standardized arbitrary areas for tunica media, and one for tunica adventitia were taken. The collagen content was evaluated at a final magnification of ×400 by two investigators unaware of the sample side. The measurements were made as

the percentage of positive area/standard area using an image analyzer (Image Pro-Plus, Milan, Italy).

Immunohistochemical analysis

Carotid tissue sections were processed for immunohistochemical analysis to detect collagen I- and collagen III-positive fibers into the vessel slices. The sections were processed according to the standard protocol. Mouse monoclonal antibody to collagen type I (1:50 - COL-1, Abcam, Cambridge, UK – ab6308) and rabbit polyclonal antibody to collagen type III (1:250 – Abcam, Cambridge, UK – ab7778) were used. A section incubated without the primary antibody served as a negative control. Quantitative analysis of immunopositivity was performed to calculate the percentage of collagen I- and collagen III-positive fibers. The analysis was performed blindly using an optical light microscope (Olympus) at a final magnification of ×200. Digitally fixed images of slices were analyzed using an image analyzer (Image Pro-Plus, Milan, Italy). The measurements were made as the percentage of stained area in five random fields for each section.

Double immunofluorescence analysis

The carotid sections were processed according to the standard protocols. Mouse monoclonal antibody to collagen type I (1:50 - COL-1, Abcam, Cambridge, UK – ab6308) mixed with rabbit polyclonal antibody to collagen type III (1:250 – Abcam, Cambridge, UK – ab7778) were used. After incubation in the primary antibody, the sections were sequentially incubated with appropriate fluorescent secondary antibodies diluted 1:200 in PBS (anti-mouse Alexa-Fluor 588, green fluorescent dye and anti-rabbit Alexa-Fluor 555, red fluorescent dye, Invitrogen, Carlsbad, CA, USA). The co-localization on carotid vessel sections was evaluated on digitally images acquired with laser scanning confocal microscopy (LSM 510, Zeiss, Oberkochen, Germany). Immunopositivity analysis was performed to calculate the percentage of collagen I- and collagen III-positive area/standard area.

Statistical analysis

Histomorphometric, immunohistochemical, and double immunofluorescence data were represented by the mean ± standard error (SEM). Appropriate analyses of variance, corrected with the Bonferroni method, were performed using statistical analysis software (Origin7 - OriginLab Corporation®, Northampton; USA); $p < 0.05$ was considered to be significant.

Corrosion casting analysis

A portion of the specimen, encompassing the right face skull and part of the frontal, sphenoidal, temporal, and occipital bones, was taken in order to perform a corrosion casting. The injected specimen was placed into a water bath (40 °C, 8 h) for tempering and then immersed in a 25 % sodium hydroxide solution at a constant temperature of 40 °C for maceration. The specimen was removed every 2/3 h and gently rinsed in water to remove the excess material and allow the fluid to penetrate additional tissue. The complete tissue dissolution was obtained after 8 h. After washing with 5 % formic acid solution for 5 min, the specimen was immersed in solutions with increasing concentrations of alcohol to minimize vascular network surface tension during drying. The specimen was then dried at room temperature and the vascular anatomy analyzed in detail.

Literature review

The literature review on anomalous origins of the ophthalmic artery was performed using multiple searches on PubMed, cross-referencing the following keywords: "ophthalmic," "artery," "origin," "anomal*," "variation," and "variab*." Relevant articles were selected also through reference analysis. Reported associated pathologies were also recorded.

Anatomical report

During the academic year 2013–2014, performing an endoscopic study of the skull base in the Section of Anatomy and Physiopathology, Department of Clinical and Experimental Sciences, University of Brescia, Italy, a right OphA arising from the A1 tract of the anterior cerebral artery (A1) was encountered (Fig. 1). The donor was an 81-year-old Caucasian male.

Surgical and radiological anatomy

The right ophthalmic artery (OphA) arose from the inferior surface of A1, approximately 5 mm distally to the ICA bifurcation. The diameter of the artery was less than 1 mm (direct, endoscopic measurement; 0.746 mm by radiological measurement). In the subarachnoid tract, the artery passed just over the optic nerve, released some branches for it, and crossed a small branch for the optic nerve, coming from the right recurrent artery of Heubner; finally, it reached the falciform ligament passing under it and moving medially; consequently, the artery began its intracanalicular tract just medial to the optic nerve (Fig. 1). A normal OphA was evident on the left side (Fig. 1).

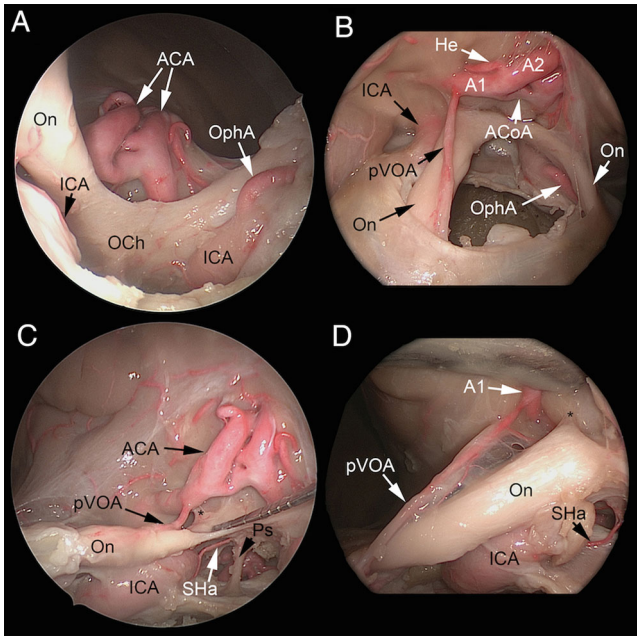

Fig. 1 Endoscopic view of the anomalous ophthalmic artery (OphA), a persistent ventral ophthalmic artery (pVOA), from a nasal (**a**, **c**) and transcranial, transfrontal sinus perspective (**b**, **d**). **a** Endonasal view of the optic chiasm (OCh) and nerves with a 70° endoscope pointing upward, through the right nasal cavity; the left OphA is visible at its origin from the ICA, while a common OphA is not present on the contralateral side. **b** Transcranial perspective with a down-turned 70° optic, showing how the pVOA passes under the falciform ligament, medially to the optic nerve (On). **c** Endonasal view (the planum has been removed (**a**, **b**)) with a 0° optic through the left nasal cavity and along the planum sphenoidalis, partially removed; the right persistent VOA arises from the A1 tract, while only a superior hypophyseal artery (SHa) originates in the first intracranial tract of the right ICA. It is also possible to foresee a small branch for the right optic nerve, from the recurrent artery of Heubner (*asterisk*). **d** Transcranial perspective with a right-turned 70° optic, documenting the small branches to the optic nerve by the pVOA. The *asterisks* indicate the branch for the right optic nerve, from the recurrent artery of Heubner. *A1* A1 tract of the anterior cerebral artery, *A2* A2 tract of the anterior cerebral artery, *ACA* anterior cerebral artery, *ACoA* anterior communicating artery, *He* recurrent artery of Heubner, *ICA* internal carotid artery, *OCh* optic chiasm, *On* optic nerve, *OphA* ophthalmic artery, *pVOA* persistent ventral ophthalmic artery, *Ps* pituitary stalk, *SHa* superior hypophyseal artery, *Asterisk* branch for the optic nerve, coming from the recurrent artery of Heubner

Considering that the right OphA appeared too small to feed the entire right orbit, we accurately checked the CBCT and discovered that, on the same side of the anomalous OphA, a meningo-ophthalmic artery was present (Figs. 2 and 3), establishing an intraorbital anastomosis between the ICA and external carotid artery (ECA) arterial systems. This artery had a diameter of more than 1.5 mm (direct, macroscopic measurement; 1721 mm by radiological measurement) and reached the orbit through the superior orbital fissure (Figs. 2 and 3). After entering the orbit, the artery released a small recurrent meningeal artery, which vascularized the dura mater surrounding the superior orbital fissure laterally.

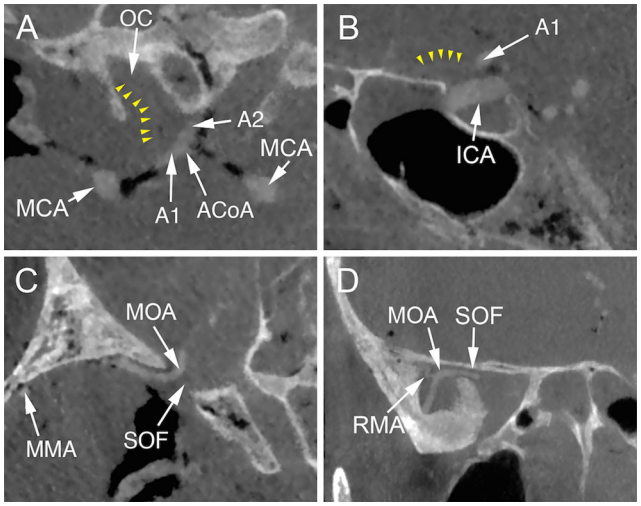

Fig. 2 Cone beam computed tomography of the specimen, which shows the persistent ventral ophthalmic artery, arising from the right A1 and reaching the optic canal (OC), as well as the meningo-ophthalmic artery (MOA) entering the right superior orbital fissure (SOF). **a**, **b** Axial and sagittal images documenting the pVOA (*yellow arrowheads*), arising from the right A1 and reaching the OC. **c**, **d** Axial and coronal maximum intensity projection (MIP) documenting the MO entering the orbit through the SOF. *A1* A1 tract of the anterior cerebral artery, *A2* A2 tract of the anterior cerebral artery, *ACoA* anterior communicating artery, *MCA* middle cerebral artery, *MOA* meningo-ophthalmic artery, *MMA* middle meningeal artery, *OC* optic canal, *RMA* recurrent meningeal artery, *SOF* superior orbital fissure, *yellow arrowheads* persistent ventral ophthalmic artery

Histological study

Histomorphological results

Hematoxylin-eosin and Masson-Goldner trichrome staining of both ICA walls revealed intimal hyperplasia with early to intermediate stadium of atherogenesis in both samples. A large quantity of collagen fibers revealed vascular fibrosis in the tunica media. No evident differences were found between the two samples in regard to intimal or tunica media alterations (Fig. 4).

Thickness analysis

Histomorphometric analysis documented that both tunica media and adventitia of the right ICA showed a significantly decreased thickness as compared to the left one; no differences were found in the two intimal layers (Table 1 and Fig. 4).

Total collagen content analysis

Polarized light microscopy revealed a significantly different collagen content in both right tunica media and adventitia as compared to the left (Table 1 and Fig. 4).

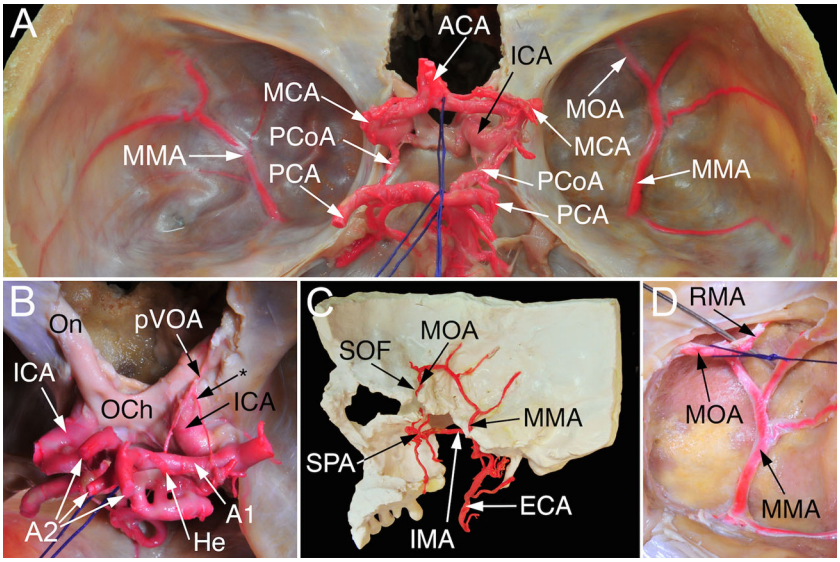

Fig. 3 Macroscopic, superior view (**a**, **b**, and **d**) and lateral view after corrosion casting of the specimen (**c**). **a** Macroscopic view from above of both middle cranial fossae. On the right side, the meningo-ophthalmic artery (MOA) is visible through the dura mater, while on the left side, a common middle meningeal artery (MMA) is present. **b** Macroscopic view from above of the pVOA and of the branch from the recurrent artery of Heubner (*asterisk*); the planum sphenoidalis has been removed. **c** Lateral view of the specimen after corrosion casting. The middle meningeal artery origin is evident together with the MO entering the SOF. **d** The left MMA and MO are isolated. A recurrent meningeal artery (RMA) is evident on this side. *A1* A1 tract of the anterior cerebral artery, *A2* A2 tract of the anterior cerebral artery, *ACA* anterior cerebral artery, *ACoA* anterior communicating artery, *ECA* external carotid artery, *He* recurrent artery of Heubner, *ICA* internal carotid artery, *IMA* internal maxillary artery, *MCA* middle cerebral artery, *MOA* meningo-ophthalmic artery, *MMA* middle meningeal artery, *OCh* optic chiasm, *On* optic nerve, *PCA* posterior cerebral artery, *PCoA* posterior communicating artery, *pVOA* persistent ventral ophthalmic artery, *RMA* recurrent meningeal artery, *SOF* superior orbital fissure, *SPA* sphenopalatine artery, *Asterisk* branch for the optic nerve, coming from the recurrent artery of Heubner

Double immunofluorescence analysis

Fluorescence microscopy analysis documented that collagen type III content was significantly lower in the right tunica adventitia than the left one; the difference was not statistically significant in the tunica media (Table 1). Collagen type I content was lower in the right tunica media than in the left one; the difference was not statistically different in the right adventitia (Table 1 and Fig. 4).

Literature review

The reported prevalence of abnormal origins of the ophthalmic artery is generally between 1.89 [21] and 3.1 % [60] (Table 2), although some authors have reported significantly different data (Table 2).

Reported anomalous origins from ICA and its branches include:

- Origin within the cavernous sinus, with a frequency from 0.42 to 14.1 % [35]. It is regarded as due to a persistent DOA [7, 35, 50, 58, 60, 61, 64] (see "Discussion" section for further details and Fig. 5).
- Origin from the C3 tract of the internal carotid artery (C3) with an interdural course at the carotid dural ring [26] in 6.7 [20] to 26.6 % [35].
- Origin from the choroidal segment of the C4 tract of the internal carotid artery (C4) [47] or, in general, from a non ophthalmic, C4 segment, in 0.18 % of cases [21].
- Origin as double arteries, with an additional, caudal artery that has an intracavernous origin and passes through the superior orbital fissure (SOF) [23, 42, 43, 52, 59, 64].
- Origin from ICA bifurcation [12].
- Origin from A1 [1, 3, 15, 19, 22, 29, 49], in 0.12 % of cases [21]. In one case, the pre-communicating anterior cerebral artery (ACA) is unique and passes between the optic nerves while giving rise to the anomalous OphA [13].
- Origin from the middle cerebral artery (MCA) with unilateral or bilateral ICA absence [8, 34].

Anomalous origin from other vessels:

- Origin from middle meningeal artery (MMA) [4–6, 14, 16–18, 24, 25, 30, 31, 37, 38, 40, 52, 56, 62, 63], in 0.08 [6] to 4 % [2] of cases. Some authors [11, 16, 44, 53, 56] demonstrated, using external carotid angiography, the filling of the ophthalmic artery from the middle meningeal artery via the meningolacrimal artery. Louw et al. [33] reported a case of meningolacrimal artery associated

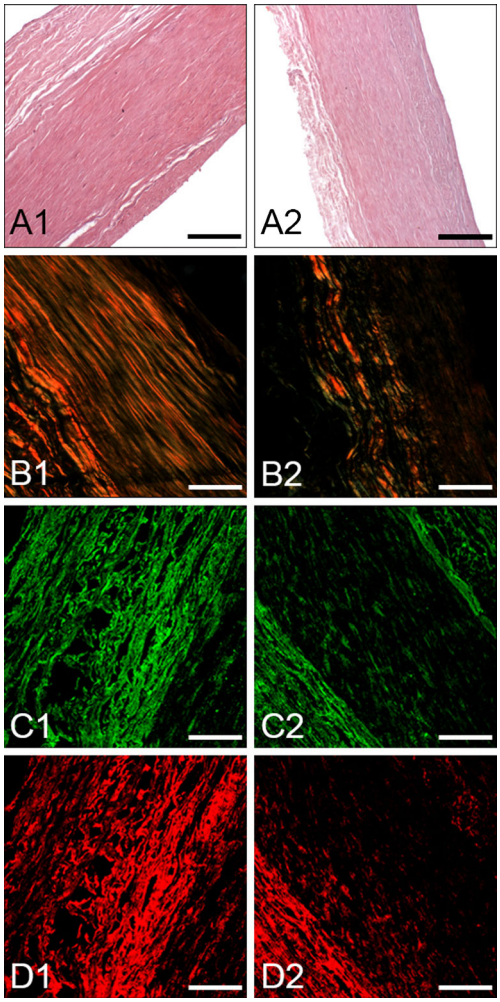

Fig. 4 Microscopic fields with different coloration techniques of left (*1*) and right (*2*) ICA wall. **a** Hematoxylin-eosin staining showing smaller media and adventitia thickness of the right ICA wall (**a**2) (*bar* = 160 μm). **b** Polarized Sirius Red staining showing a less overall collagen content on the right side (**b**2) (*bar* = 80 μm). **c**, **d** Double immunofluorescence staining showing decreased collagen I and collagen III content on the right side (**c**2 and **d**2, respectively) (*bar* = 80 μm)

Table 1 Summary of histological analysis results

ICA analysis		Left	Right
Thickness (μm ± SEM)	Tunica intima	73.91 ± 2.87	68.90 ± 3.88
	Tunica media	200,08 ± 5,08	164,02 ± 4,65*
	Tunica adventitia	178,20 ± 6,92	131,88 ± 5,48*
Collagen content (% ± SEM)	Tunica media	10,55 ± 1,29	3,82 ± 0,52*
	Tunica adventitia	30,33 ± 1,33	20,97 ± 1,36*
Collagen type I (% ± SEM)	Tunica media	3,56 ± 0,38	2,32 ± 0,44*
	Tunica adventitia	22,23 ± 3,11	20,91 ± 2,67
Collagen type III (% ± SEM)	Tunica media	7,84 ± 6,89	6,23 ± 1,16
	Tunica adventitia	36,18 ± 4,61	21,16 ± 2,21*

ICA internal carotid artery, *SEM* standard error of the mean

*Statistically significant ($p < 0.05$; see text for further details)

with a normal ophthalmic artery, which gave origin only to the central retinal artery.
- Origin from the basilar artery [55].
- Origin from posterior communicating artery (PCoA) [39, 41, 51].

Cerebral aneurysms are the most commonly reported pathology that has been associated with a variant origin of OphA (Table 2). Other vascular [4, 5, 7, 8, 11–13, 19, 23, 34, 36, 37, 39, 41, 51, 54, 55, 60, 62, 63] and non-vascular anomalies [11, 15, 16, 29, 40, 43, 47, 50] have also been reported (Table 2).

Discussion

In 96 % of cases the OphA arises from the ICA [3]: in particular, in 83 % of cases from the C4 tract, after the internal carotid artery emerges from the cavernous sinus [27], i.e., from the ICA "ophthalmic segment." In the remaining cases, the most frequent origin is from the cavernous ICA, with an extradural and, more rarely, an interdural course [26].

The embryology of the ophthalmic artery is relatively complex, but the current theory explains almost all described anomalous origins. In principle, OphA variants originate through the abnormal development of anastomotic networks [32].

Two primitive vessels, the ventral ophthalmic artery (VOA) and the dorsal ophthalmic artery (DOA), are involved in the formation of the ophthalmic artery (Fig. 5). The theory by Padget [46], who supposed that both arteries originate from the ICA and pass through the optic canal, has been perfected by Lasjaunias [27, 28], who has suggested that the DOA originates from the cavernous segment of the ICA and passes through the superior orbital fissure, while the VOA originates from the anterior cerebral artery and passes through the optic canal (Fig. 5a). During the embryogenetic process, two anastomoses are formed, one intraorbital between DOA and VOA and the other one between the C4 segment of ICA and VOA. After that, the proximal parts of DOA and VOA regress and the remnant of proximal DOA becomes the inferolateral trunk [28] (Fig. 5b). According to this theory, the present case is explained by a VOA that maintains its embryonic origin from A1 (Fig. 5c).

During embryogenesis, collateral connections develop between the VOA and DOA and adjacent vessels, including the middle meningeal artery (MMA). In general, there is a hemodynamic balance between the internal (ICA) and the external carotid (ECA) systems; thus, the dominant blood supply to the orbit can be provided by either of them [48]. Therefore, it is possible to find, in cases where the ophthalmic artery is embryologically dominant, an ophthalmic origin of the middle meningeal artery from the recurrent meningeal branch of the ophthalmic artery (0.5 % of cases) [10, 45]. In the present case, the hypothesis of hemodynamic balance [10, 45] between the ECA and ICA systems is supported by the finding,

Table 2 Summary of ophthalmic artery variants and their described associated pathological conditions

Origin	Prevalence (author)	Case report	Associated lesion	Side of variant OphA (toward the lesion)
C3 (intracavernous)	0.42 % (Uchino) 1.6 % (Indo) 7.5 % (Hayreh) 7.6 % (Horiuchi) 8 % (Renn) 18,3 % (Lang) 41 % (Matsumura)	Indo [21]	C4 aneurysm	Ipsilateral
		Tanaka [58]	C3 (paraclinoid) aneurysm	Ipsilateral
		Fiore [7]	ACoA aneurysm C4 aneurysm Fibromuscular dysplasia	Ipsilateral (aneurysms) Contralateral (dysplasia)
		Horiuchi [20]	C3 (Paraclinoid) aneurysm	Ipsilateral
		Mazighi [36]	Multiple intracranial aneurysms (paraophthalmic, basilar tip, PCoA, ACoA, MCA)	Bilateral
		Pretterklieber [50]	Pterygospinosus muscle	Bilateral
C3 and C4 (double)	Rare (Rhoton)	Ogawa [43]	Meningioma (tuberculum sellae)	–
		Namba [42]	MCA aneurysm	–
		Uchino [59, 60]	MCA infarct	Contralateral
		Kam [23]	PCoA aneurysm	Ipsilateral
C3 with interdural course at the carotid dural ring	6.7 % (Horiuchi)	Kyoshima [26]	C3 (paraclinoid) aneurysm	–
		Horiuchi [20]	ICA aneurysm	Ipsilateral
C4–Ch/–Co	0.2 % (Indo)	Parlato [47]	Meningioma (tuberculum sellae)	–
A1 (ACA)	0.1 % (Indo)	Picard [49]	–	–
		Hassler [15]	Craniobasal arachnoid cyst	–
		Islak [22]	C3 aneurysm	–
		Li [29]	Meningioma	–
		Bervini [3]	C3 (paraclinoid) aneurysm	Ipsilateral
		Honma [19]	ACoA aneurysm	–
		Baltsavias [1]	C4 aneurysm	Ipsilateral
		Hannequin [13]	Unique pre-communicating ACA	–
MCA		Fisher [8]	Absence of ICA	Bilateral
		Lowrey [34]	Absence of ICA	Ipsilateral
Bifurcation between ACA and MCA		Hamada [12]	C4 Aneurysm	Bilateral
MMA	0.08 % (Dilenge) 1.45 % (Uchino) 3.5 % (Hayreh) 4 % (Bergman)	Weinberg [63]	Amaurosis Fugax with ECA emboli	Ipsilateral
		Nakagawa [40]	Meningioma	–
		Hayashi [16]	Meningioma (3 cases: 2 petroclival, 1 sphenoidal greater wing)	–
		Watanabe [62]	Carotid-cavernous fistula	Bilateral
		Morandi [37]	Occlusion of small CRA arising from ICA	Ipsilateral
		Grossman [11]	Intracranial AVM	Ipsilateral
		Grossman [11]	Meningioma (Petrous Ridge)	Ipsilateral
		Harvey [14]	–	–
		Hiura [18]	–	–
		Chanmugam [5]	Subclavian artery from descending aorta (behind esophagus)	Contralateral
		Brucher [4]	MCA and vertebral artery cerebrovascular insufficiency	Contralateral
		Dilenge [6]	–	–
		Liu [30]	–	–
		Konishi [25]	–	–
BA		Schumacher [55]	AVM of superior eyelid and forehead	Ipsilateral

Table 2 (continued)

Origin	Prevalence (author)	Case report	Associated lesion	Side of variant OphA (toward the lesion)
		Sade [54]	MCA ectasia	Contralateral
PCoA		Nakata [41]	Absence of ICA	Ipsilateral
		Naeini [39]	Absence of ICA	Ipsilateral
		Priman [51]	ICA anomaly	Ipsilateral

A1 (*ACA*) A1 tract of the anterior cerebral artery, *ACA* anterior cerebral artery, *AVM* arteriovenous malformation, *BA* basilar artery, *C3* cavernous tract of the internal carotid artery, *C4-Ch* choroidal segment of the intracranial tract of the internal carotid artery, *C4-co* communicating segment of the intracranial tract of the internal carotid artery, *CRA* central retinal artery, *ICA* internal carotid artery, *MCA* middle cerebral artery, *MMA* middle meningeal artery, *PCoA* posterior communicating artery

on the same side of a small OphA, of a meningolacrimal artery larger than it (Figs. 2 and 3). The recurrent meningeal artery is in hemodynamic balance with the anteromedial branch of the inferolateral trunk. The anteromedial branch is the vessel that gives arterial supply to the orbit in case of persistent dorsal ophthalmic artery (DOA) [27].

The arterial configuration herein described is comparable both to the ones reported as an OphA arising from A1 [1, 3, 15, 19, 22, 29, 49] and the ones described as the presence of a meningolacrimal artery or OphA arising from MMA [4–6, 11, 14, 16–18, 24, 25, 30, 31, 37, 38, 40, 44, 52, 53, 56, 62, 63]. It represents a rare combination of variations, which might have been present even in some of the described cases, as in 17 of them the anatomy of both A1 and MMA was explored [4, 5, 11, 14, 16–18, 22, 29, 30, 33, 37, 44, 48, 56, 57, 60], while in 10 of them, it was not studied [1, 3, 13, 15, 19–21, 35, 50, 62]. In particular, in some of the described cases, the anomalous ophthalmic artery was not evident on the angiographic study, while it was on surgical exploration [15, 19]. Islak et al. angiographically demonstrated the absence of the meningolacrimal artery (MLA) in a case of persistent VOA [22]. Moreover, there are cases in which the association of a MLA and a normal OphA (Central Retinal Artery branch) has been described [5, 11, 18, 33, 37, 48], whereas Uchino et al. verified the presence of both a persistent DOA and a MLA [60]. On the contrary, Hayreh and Dass reported the origin of the central retinal artery from the MMA in 10 cases [17]; although only few authors demonstrated its presence [14, 30, 44, 56], while in other cases, the same vascular pattern is only angiographically suspected [4, 16, 62].

Clinical implications

Some authors have underlined the implications of OphA anomalous origins. Rosen et al. reported two cases of blindness among a hundred superselective MMA embolizations for skull base meningioma, attributing the complication to the anomalous origin of OphA from MMA [53]. Similarly, Onerci et al. described a case of blindness after internal maxillary artery embolization for juvenile nasopharyngeal angiofibroma [44].

Shima et al. describe a case of postoperative blindness in a patient treated for two aneurysms (A3 tract of the anterior cerebral artery (A3) and M1 tract of the middle cerebral artery (M1)), whose MMA was ligated to manage the M1 aneurysm with a pterional approach; they further describe two other cases of aneurysms successfully clipped with a pterional approach taking care not to damage the OphA arising from MMA [56]. Hayashi et al., describing the management of three cases of skull base meningioma with an OphA arising from MMA, suggest a transpetrosal or a subfrontal approach rather than a pterional one, in order to avoid an ischemic damage of the orbital content [16].

Correlation with aneurysms and possible pathogenesis

Although the clinical implications of OphA variants are far to be completely comprehended, some correlations with lesions or malformations have been reported, together with different hypothetical mechanisms to explain these findings.

The apparently strongest correlation is between an anomalous OphA (originating from C3, C4 co/ch, ICA bifurcation or A1) and the presence of an ICA anterior wall aneurysm: many case reports with this correlation [1, 3, 7, 12, 20–22, 26, 58] have been reported (Table 2). Recently, Indo and collaborators [21] have documented that ICA aneurysms are approximately 50 times more frequent in patients with an anomalous origin of the OphA than in those with normal OphAs [21] (Table 2). Furthermore, Mazighi found vascular anomalies in 88 % of patients with multiple intracranial aneurysms [36], 3.5 % being represented by a persistent DOA. The correlation with ICA aneurysms reported by Indo et al. could be explained by at least three hypothesis: the first postulates that the arterial wall is weaker because of the non-migration of the VOA inferiorly, according with the Padget's model [46], or the absence of an anastomosis between the VOA and C4 tract of ICA, according with Lasjaunias' model [28]; a second hypothesis is that both the arterial wall and the embryogenesis

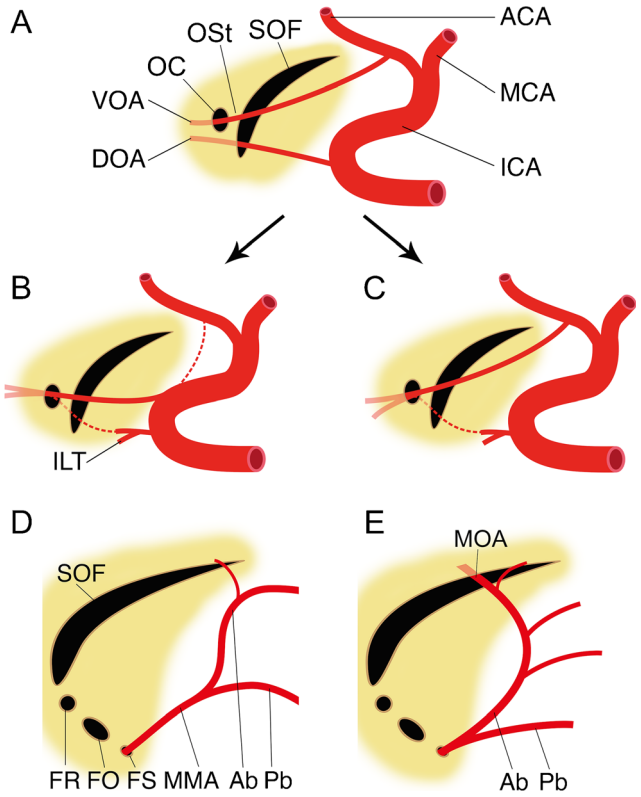

Fig. 5 Illustration of the OphA embryogenesis, with the hypothetical formation mechanism of the presented case. **a** Embryologic vascular pattern, characterized by the VOA, arising from ACA and passing through the optic canal (OC), and the DOA, arising from cavernous ICA (C3 tract) and passing through the superior orbital fissure (SOF). VOA and DOA are consequently separated by the optic strut (OSt). **b** Usual evolution of the primitive pattern, in which an intracranial anastomosis is established between VOA and intracranial ICA (oph-C4 tract), while an intraorbital anastomosis is established between VOA and DOA. The pre-anastomotic tract of VOA regresses completely, while the pre-anastomotic tract of the DOA regresses partially, representing the SOF branch of the inferolateral tract (ILT). **c** Present anomalous OphA development hypothesis: the intracranial anastomosis between VOA and paraclinoid ICA is not established, resulting in a persistent VOA, as in the reported case. The pre-anastomotic tract of the DOA regresses as usual. **d** Normal anatomy of the middle meningeal artery (MMA), with an anterior (Ab) and a posterior branch (Pb). A little artery branches from the Ab to reach the SOF dura. **e** Anatomical variation of the middle meningeal artery; the Ab ends with a meningo-ophthalmic artery (MOA), which passes through the SOF, reaching the orbital content. *Ab* anterior branch of the middle meningeal artery, *ACA* anterior cerebral artery, *DOA* dorsal ophthalmic artery, *FO* foramen ovale, *FR* foramen rotundum, *FS* foramen spinosum, *ICA* internal carotid artery, *ILT* inferolateral trunk, *MCA* middle cerebral artery, *MOA* meningo-ophthalmic artery, *MMA* middle meningeal artery, *OC* optic canal, *OSt* optic strut, *Pb* posterior branch of the middle meningeal artery, *SOF* superior orbital fissure, *VOA* ventral ophthalmic artery

modifications are epiphenomena of a molecular alteration, without a direct and histological correlation between them; a third hypothesis, as stated by Uchino et al. [61], is that this correlation is the result of a selection bias in statistical studies.

Studies that support the two theories based on a biological substrate are present in literature. In fact, the formation of true aneurysms, according to observations from experimental models, appears to be caused by a mismatch in the tensile strength of the artery wall and the hemodynamic stress to which it is exposed [9]. According to Frosen et al., this interpretation is in line with the observations from patients with hypertension and mechanical weakness of the cerebral artery wall, who are predisposed to aneurysm formation.

In our case, the histological ICA analyses have documented that collagen content of the anomalous ICA was significantly lesser compared to the contralateral one (Table 1; Fig. 4); this might be a cause of mechanical weakness that could predispose the artery to aneurysm formation.

Conclusions

This anatomical study represents a unique case of combination of rare variants: the meningo-ophthalmic artery and the persistent VOA. This study is the first to show anatomic images of a persistent VOA together with histologic slides and corrosion casting; an anatomo-radiological comparison was possible thanks to the hyperdensity of the silicon injected in the arterial system.

Our histological study revealed a decreased thickness and collagen content of the ICA that was ipsilateral to the anomalous OphA; this might at least partially explain the statistical correlation between variants of OphA origin and ICA aneurysms, which has been described in previous clinical studies.

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Comments

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The authors should be commemorated for their excellent description of an unusual case of anomalous origin of the ophthalmic artery. Their passion for the scientific detail is demonstrated by the use of several tools not only to visualize but to gain insights into histology and flow dynamics. This could serve as a role model for anatomical education, to be prepared during dissection and eventually apply tools to further elaborate on the findings. Their preparedness gives the reader the unique opportunity to participate.

As pointed out, the course of the ophthalmic artery varies and it is of crucial importance for the neurosurgeon to know about these possible aberrations to intraoperatively judge further management. In the presented case, the anomalous opthalmic artery might have contributed to the intraorbital blood flow to a lesser extent than usual and could have been compromised without causing visual deficit. This is in contrary to the cited publications where the anomalous course of the ophthalmic artery was the sole contributor to optic nerve blood flow.

The association of anatomical variants of intracranial arteries and formation of aneurysm is a well-known fact; with this report, the authors provide evidence that the anomaly is not only restricted to the visible aberration of its anatomical course, but that the adjacent vascular network does show texture changes in their vessel walls leading to possible aneurysm formation. The clinical experience especially in medial ICA aneurysms taught us that often the pathology extends far beyond the actual aneurysm.

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Belotti et al. deal in this well-written article with a very important topic for microsurgery in the parasellar region: anatomical variations of the ophthalmic artery. The authors detected during anatomical dissection of a fresh-frozen, silicon-injected head of a 81-year-old Caucasian donor, the anomalous origin of the ophtalmic artery from the anterior cerebral artery. They elaborated this observation meticulously from a transnasal and transcranial perspective and performed a radiologic analysis and extensive histological study of the specimen's internal carotid arteries as well as a corrosion casting analysis.

Two aspects are of particular surgical interest, in my opinion: First, the intraorbital anastomosis with the meningoophtalmic artery, emphasizing the potential role of the middle meningeal artery in vascularizing optic nerve and retina; second, the apparent correlation between anomalous ophthalmic arteries and ICA aneurysms. Both issues are of clinical importance when dealing with vascular or neoplastic pathologies in the parasellar region.

This paper is an excellent example on how important is a meticulous preoperative and intraoperative assessment of individual anatomy. Variations have to be recognized and respected in order to attain optimal surgical results. Belotti et al. demonstrate once again relevance and up-to-dateness of anatomical studies in modern neurosurgery.