Hypoplasia of internal carotid artery associated with carotid paraganglioma. A case report and review of the literature

ABSTRACT

Background: Hypoplasia of the internal carotid artery is a rare congenital malformation mainly associated with aneurysms and other pathologies but not in association with paraganglioma. The incidence is < 0.01% of all the anomalies of carotid vessels. Although the exact cause is unknown, it is thought to represent a sequel to an insult due to mechanical causes or hemodynamic stress but perhaps also involves aspects of molecular biology of embryonic development.

Clinical case: We describe the case of a 37-year-old female patient with paraganglioma associated with hypoplasia of the internal carotid artery, which was found incidentally during surgery. Previous angiographic studies as well as other analyses were carried out, but we failed to detect hypoplasia of the internal carotid artery. Tumor was removed along with ligation of the external carotid artery due to injury. The hypoplastic internal carotid artery was left intact.

Conclusion: Angiographic studies of the skull base are important as well as hemodynamic analysis in order to not overlook these anomalies. The patient had a satisfactory evolution without sequelae.

Key words: Hypoplasia, internal carotid artery, paraganglioma.

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BACKGROUND

According to Ibarra de Grassa, the first descriptions of incomplete development of the internal carotid artery (ICA) are attributed to Lie (1787) and Hirtl (1836). These are rare congenital anomalies and may be classified as agenesis, aplasia and hypoplasia. From 1968 to 2002, there were only 50 cases reported in the English medical literature, 20 of them bilateral. Most cases were diagnosed with conventional angiographic studies. It was noted that this anomaly is asymptomatic due to the compensation of the circle of Willis. According to a more recent report (2007), 148 cases are found in the medical literature and, of these, only 33 are of concomitant ICA hypoplasia predominantly with aneurysms. In the same investigation, a case linked with glomus of the vagus nerve was reported, but with aplasia of the internal carotid. With respect to the paragangliomas, Luis Kraus Sentíes is credited with the Mexican history of carotid body tumors in 1971 and mentioned that in 1907 Masson coined the term paraganglioma and in 1937 Lubbers first reported a comprehensive description of carotid body tumor. In this same reference it was reported that in Mexico there were 57 cases found between 1976 and 2011, of which only 1.82% were malignant. There were no deaths. According to the Shamblin classification of this series studied, there were 18 grade I tumors (32.72%); 23 grade II (41.83%) and 16 grade III tumors (25.45%). None were associated with hypoplasia of the internal carotid (ICAh) or other described alterations.

CLINICAL CASE

We present the case of a 37-year-old female who arrived at the Oncology Surgery Service without prior significant medical history. She had a left, painless cervical tumor of 3 years evolution with well-defined nodular characteristics and measuring ~3 x 3 cm. Magnetic angioresonance showed a tumor (2 x 2 cm) in the left carotid bifurcation. After signed informed consent was obtained for treatment and after the risks and benefits were explained, the tumor was surgically resected. A left ICAh was found (Figure 1). The external carotid was resected because it was adhered to the tumor (Figure 2). Histopathological report of the tumor was of a non-chromaffin paraganglioma. Postsurgical course was satisfactory and without sequelae.

DISCUSSION

An incidence of < 0.01% of these disorders is described (aplasia, hypoplasia or agenesis) in the carotid vessels. Patients with ICAh frequently suffer from other vascular disorders (malformations, aneurysms, atherosclerosis, arteritis, fibromuscular hyperplasia, dissection, trauma, Moyamoya, etc.) and even cerebral transient ischemic attacks. In this case, hypoplasia was concomitant with paraganglioma although no history for such association was found.

With respect to diagnosis, noninvasive studies are mentioned such as color duplex ultrasound that could reveal carotid hypoplasia, which is confirmed with computed tomography (CT) of the skull base. Other tests recommended are magnetic angioresonance, which detects the occlusion or stenosis of the ICA and can be determined whether it is congenital or acquired hemodynamically. Recognition of this anomaly with imaging techniques has important implications because the considerations listed by Vaghela must be taken into account: 1) to determine a probable association of intracranial aneurysms; 2) to avoid making a mistake in regard to the diagnosis of a high-grade carotid stenosis; 3) to identify intracavernous collaterals before transsphenoidal surgery; 4) to not ignore transellar intracavernous collateral vessels that may be mistakenly diagnosed as pituitary microadenoma and, 5) to adequately plan the carotid endarterectomy according to the dependent cerebral perfusion. Also, CT with simple photon
emission allows confirming adequate cerebral perfusion and preservation of vasomotor activity.\cite{11} As previously mentioned, this hemodynamic analysis was not done in this study.

With respect to the initial embryological development, the following is mentioned: blood cells and system of arteries and veins originating from the mesoderm and formed in two ways: vasculogenesis from the blood islets and by angiogenesis from the already existing vessels. This begins during the third week of embryonic development. The islets created by the mesodermal cells are induced to form hemangioblasts, which are precursors of blood vessels and blood cells.\cite{12} Due to the advances in molecular biology, molecules that direct and/or modulate growth have been discovered such as fibroblast growth factor (FGF-2) that promotes the blood islets to generate hemangioblasts. Vascular endothelial growth factor (VEGF) secreted by the mesodermal cells induces hemangioblasts to form vessels and blood cells. Subsequently, these hemangioblasts are differentiated into angioblasts, which are precursors of blood vessels. This same VEGF produces the formation of endothelial cells. This process of vasculogenesis establishes a vascular bed so that with angiogenesis the dorsal aorta and the cardinal veins are generated until the adult pattern is established. Vascular maturation and remodeling are regulated by other growth factors, among them platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF-\(\beta\)). Also, determination of arteries, veins and lymph nodes takes place shortly after induction of angioblasts. Sonic hedgehog, a substance secreted by the notochord, stimulates the surrounding mesenchyme to express VEGF which, in turn, activates the notch pathway (a transmembrane receptor pathway) that determines the development of the arteries through the expression of EPHRIN B2 (ephrins are ligands that bind to EPH receptors on a pathway signaled by tyrosine kinase).\cite{12} Added to this, in the formation of the arteries the expression of EPHRIN B2
suppresses the venous fate of the cells. The Notch signaling pathway also regulates the expression of EPHB4, and although its mode of action is not well defined, it is known that it is a specific gene that encodes for the formation of new veins. Likewise, it appears that PROXI, a transcription factor containing a homeodomain, is the main gene of the differentiation of the lymphatic vessels. The vessels do not follow a random growth pattern but appears to be determined by orientation factors similar to those used in the nervous system. As noted, embryonic developmental factors are still being discovered so that in the future there will be a greater understanding of the origin of its anomalies.12

It is mentioned in the medical literature that although the exact cause of these developmental anomalies has not been determined, the three variations of lesions that occur in these neck vessels represent a sequelae of damage in embryonic development. Mechanical causes have also been found or of hemodynamic stress in embryonic placement in utero, including the effects related with the exaggerated folding towards one side and constriction of the amniotic bands; however, bilateral absence of carotid vessels has not yet been considered. There is controversy regarding the origin of the common and external carotid arteries, from the third aortic arch derived from the dorsal aorta. Some researchers argue that the ICA also stems from the third aortic arch (~4-5 mm in length of the embryo and at 6 weeks of development), although it continues to be claimed that the shared origin of the common carotid artery and the external carotid artery are not yet defined. Other investigations suggest that the ICA and the external carotid artery arise together from the third aortic arch. In this manner, absence of the ICA and the ipsilateral absence of the external carotid artery go “hand in hand”. With respect to the circle of Willis, it is known that it forms during the stage of 7–24 mm embryonic development and that there would be compensatory collateralization in that portion, depending on what type of arterial disruption occurs (aplasia, hypoplasia).13 Six collateral circulation pathways have been described together with the absence of the ICA: types A, B, and C, unilateral types (A and B) and bilaterals (C). Absence of the ICA is associated with hypertrophy of the anterior communicating artery (AComA) and of the posterior communicating artery (AcomP) (type A) and with permeable anterior communicating artery (type B) vertebrobasilar carotid anastomosis (type C). Type D represents intracavernous communications to the ipsilateral carotid siphon from the contralateral intracavernous portion of the ICA when there is unilateral agenesis of the segment of this artery. In type E, the anterior cerebral arteries are compensated by hypoplastic ICA, and in type F the compensatory anastomoses are from the internal maxillary artery, branches of the external carotid artery and the system supplied by the distal ICA called rete mirabile.

In the case we described here the compensatory vascular anatomy was not determined.14 Although the patient was studied from the perspective of the tumor mass, images did not show hypoplasia of the ICA; therefore, it was not suspected or visualized preoperatively.

With respect to the paragangliomas, these are rare tumors (neoplasms) with an incidence of ~0.2-0.5 cases/100,000 population, representing 0.03% of all neoplasms.15 These tumors display low growth and originate from the neural crest (paralymphatic or chemoreceptor system). They adopt a cellular pattern referred to as Zellballen and may secrete serotonin, gastrin, somatostatin and bombesin, besides which there are sustentacular cells positive to S-100 protein. The gene related with these tumors is located on chromosome 11 and demonstrates abnormalities of chromosomes 5 and 7 and oncogenes C_MYC, bel2, C-erbB2, C-erbB3 and C-jun, whose deregulation contributes to tumor development.14 Other genetic considerations mentioned in the literature are the discovery
of the PGL1 gene of the SDHD mutation (three identified, PGL1, PGL2 and PGL3) that codifies the small cybS subunits. This allows investigators to directly examine different hypotheses such as the function of cybS on the perception of oxygen and common tumor pathogenesis and genomic participation on the disease.5

In general these tumors are benign, although they may present local metastasis in up to 5% of cases. Multiple forms may be seen in 4% of cases and hereditary characteristics in up 10%. These can be in the carotid corpuscle, bifurcation, vagal nerve, path of cranial nerve X, adventitia of the jugular vein or its foramen, as well as in the tympanic glomus in the path of the nerve of Arnolds and Jacobson and other locations such as in the mediastinum, aortic arch, etc. These tumors are irrigated by the external carotid artery and occasionally by the ICA and the vertebral artery.15 Embryologically, paragangliomas have their origin in the neuroectoderm and function as chemoreceptors sensitive to the direct changes in arterial pressures of oxygen and of carbon dioxide (pCO₂). In addition, although indirectly, they are sensitive to modifications in pH and temperature and induce changes in reflexes during vasomotor and respiratory activity.16

With regard to treatment, if the tumor is of the carotid body as was this case, it is recommended to use the Shamblin classification as a basis to plan the surgical treatment as described below.

Modified Shamblin classification according to the stages of tumors in the carotid body

Type I. Tumor < 4 cm that does not surround the carotid vessels and without difficulty to excise Type II. Tumor > 4 cm that partially surrounds the carotid vessels and whose resection is more challenging.

Type IIIa. Tumor > 4 cm that narrowly surrounds the vessels and is difficult to resect.

Type IIIb. May be I, II or III with infiltration to any carotid vessel, indistinct in size and requiring vascular sacrifice or vessel replacement; intramural invasion should be clinically and/or histologically confirmed

This study mentions that there may be mixed or intermediate grades I–II that infiltrate the carotid and prevent resection without sacrificing the vessels, and that there may be grades III that do not infiltrate and their resection implies greater risk, although they do not involve the carotids. For this reason another grading classification is suggested.15

Surgical resection is carried out for the following reasons: a) some tumors are malignant; b) no reliable screening mechanism exists for cytological monitoring of tumor progression; c) no evidence exists that correction of hypoxemia, if possible, induces tumor regression; d) risk of vascular injury is acceptable in skilled hands; and e) all tumors may all begin as asymptomatic.17

There have been ~33 cases of ICA hypoplasia in the international literature and an additional 50 cases in the Anglo-Saxon literature,3,4 but none concomitant with a paraganglioma as in this patient. There is no defined clinical picture associated with this malformation. It is a casual finding made during cervical examination, but in general diagnosis is confirmed with arteriography with digital subtraction and finally with magnetic angioresonance and duplex ultrasound. ICA hypoplasia has been linked with other diseases, occasionally affecting the neurological status as in the case of infarcts of the bilateral anterior cerebral artery territory. This patient, on the contrary, recovered satisfactorily without hemodynamic or neurological repercussions possibly due to the chronic evolution of the disease and to the compensation of the circle of Willis, which prevented neurological sequelae as reported in the literature by Yamaguchi et al.18

In some studies it is mentioned that it is difficult
to visualize the lesion of ICA agenesis and even to treat it surgically or to manipulate it, as in this case, by endovascular procedures such as the placement of an endoprosthesis in the cervical vessels. It also suggested to avoid ischemia and the use of a balloon during surgery.\textsuperscript{3,17}

The paraganglioma that affected this patient was classified as Shamblin type II and was not difficult to resect, although it was necessary to ligate the external carotid artery to which it was adhered as recommended in difficult cases.\textsuperscript{17}

In conclusion, paraganglioma with ICA hypoplasia is rare. The latter is caused by defects in embryonic development in the carotid vessels that is manifested during later ages; however, it is important to carry out a better analysis of the angiographic and/or hemodynamic studies so as not to overlook anomalies of the concomitant vessels and evaluate the circulation of the circle of Willis, as in this case. This patient had a good evolution compensated by the collateral circulation and without postoperative neurological deficit.

REFERENCES
