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Diagnostic and Therapeutic Difficulties in Carotid Body Paragangliomas, Based on Clinical Experience and a Review of the Literature

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Abstract

Background. Paragangliomas are rare neuroendocrine tumors, representing 0.03% of all tumors. Half of them develop in the head and neck, and among these 50% are sporadic cervical tumors.
Objectives. The aim of the study was to carry out an epidemiological and clinical analysis of paraganglioma patients diagnosed and treated at the authors' clinics between 1985 and 2014.
Material and Methods. The medical data of 47 patients were analyzed. All the patients were qualified for surgery. In 43 cases (88%), simple resection of the tumor was performed, including 11 cases (22%) that additionally required vascular suturing, and 5 (10%) that required reconstruction of the internal carotid artery. Carotid vessel repair was performed by shortening the internal carotid artery in 3 cases (6%), using a saphenous vein graft in 2 cases (4%), and by creating an anastomosis between the external carotid artery and the distal portion of the internal carotid artery in one case (2%).
Results. In 40 cases (82%), the course of treatment was uneventful. Three patients (6%) were reoperated because of symptoms of cerebral stroke. Palsy of the hypoglossal nerve occurred in 3 cases (6%), and facial nerve palsy in 2 patients (4%). Six patients (12%) developed postoperative hematomas in the wound. In all the cases, histopathological examinations confirmed carotid paraganglioma.
Conclusions. Cooperation with an otolaryngologist and vascular surgeon during surgery is recommended due to frequent damage to carotid vessels by carotid paragangliomas. Detection of the tumor in the early stages improves surgical treatment outcomes and reduces the number of complications. Regular postoperative check-ups are necessary due to possible occurrences of multiple tumors (**Adv Clin Exp Med 2016, 25, 6, 1173–1177**).

Key words: diagnosis, surgical treatment, chemodectoma, carotid body paraganglioma, carotid body tumor.

Paragangliomas, also known as chemodectomas or carotid body tumors, are rare neuroendocrine tumors. They represent about 0.03% of all neoplasms and appear more frequently in women than men (1.9 : 1) [1–3]. About 50% of paragangliomas develop in the head and neck region, of which approximately 50% originate from the carotid body [4]. The carotid body was first described by von Haller in 1743 [5]. It mainly regulates pH, pO_2 and pCO_2 levels in the blood by registering changes in those parameters and transmitting them though the glossopharyngeal nerve

to the reticular formation [2, 6]. It has been reported that 6% of carotid paragangliomas are malignant [3, 4]. Malignancy is defined by presence of metastases in regional lymph nodes or distant sites, mainly in the lungs or bones [2, 7–9]. About 30% of paragangliomas are caused by mutations in succinate dehydrogenase (SDH) subunit genes: SDHD (the subunit D gene), SDHB (the subunit B gene), SDHC (the subunit C gene) or SDHAF (the subunit A gene) [10]. SDH mutations are associated with familial paragangliomas, previous pheochromocytomas, or the presence of multifocal paragangliomas such as tumors in the neck [11, 12]. In SDH mutation carriers, who are predominantly male, the onset of paraganglioma often occurs before 40 years of age [11, 12]. Tumors related to gene mutations have a high risk of malignancy. The malignancy rate is the highest in the SDHB mutations, reaching about 38% [12].

Bilateral carotid paragangliomas account for 5% of all cases. Familial tumors occur in 33% of the cases, and in those patients multifocal localization is as high as 80% [13]. The tumors are usually located at the bifurcation of the common carotid artery. The first symptoms are painless, mobile, slow growing tumors which may pulsate. In cases where nerve XII and the common carotid artery are infiltrated, hearing loss and tinnitus appear [8, 9]. Other symptoms related to tumor compression on cranial nerves IX, X, XI, and XII include hoarseness, ear pain, difficulty swallowing and Horner's syndrome. Vascular phenomena such as pulsations or murmurs, and symptoms of common carotid artery compression resulting in cerebral ischemia or carotid sinus syndrome with bradycardia and syncope may also occur [2, 6, 8, 9, 14–16]. Rarely, hoarseness appears as the first symptom. This is caused by vocal cord paralysis, as paragangliomas tend to spread to the superior and recurrent laryngeal nerve [2, 6, 9, 15].

Differential diagnoses of head and neck paragangliomas include enlarged neck lymph nodes, lateral neck cysts, pathological changes in the parotid gland and carotid aneurysm [2, 6]. Carotid body hyperplasia must also be considered; it can develop due to chronic hypoxia and is described mainly in patients living at high altitudes [6, 9]. Diagnoses of paragangliomas are based on imaging. The examination of choice is computed tomography angiography. If a diagnosis of paraganglioma is suspected, a biopsy is contraindicated due to the high risk of hemorrhage [9, 15]. The recommended treatment is surgical intervention or stereotactic radiosurgery. The choice of treatment modality depends on many factors: the location of the tumor, the stage of the disease, the patient's age and health condition, as well as his or her preferences.

Material and Methods

The study group was made up of patients with carotid paragangliomas who were treated at Wroclaw Medical University's Department of Otolaryngology, Head and Neck Surgery and Department of General, Vascular and Transplant Surgery, and at the Surgery Department of the 4th Military Teaching Hospital in Wroclaw (Poland) between 1985 and 2014. During this period of time, 47 patients were operated on and 49 paragangliomas were diagnosed (including 2 cases of bilateral carotid paraganglioma). The patients' medical data were retrospectively analyzed. The study group included 28 men (60%) and 19 women (40%). Bilateral tumor occurred in 2 patients: 1 woman and 1 man (4%). The average age of the patients was 45 years (ranging from 34 to 56). All the patients denied any neoplastic disease in family members. All the patients presented neck tumors (100%). Other complaints were as follows: hoarseness in 14 patients (30%), swallowing difficulties in 10 (21%), discomfort in the neck area in 10 (21%) and tinnitus in 13 (28%). All the patients underwent duplex ultrasound examinations, and in 20 (43%) computed tomography angiography of the neck was also performed. In 36 patients (77%) the diagnosis was made correctly before surgery, while in the remaining 11 (23%), the tumors were diagnosed as enlarged lymph nodes and qualified for open biopsy. After discovering tumors located at the bifurcation of the common carotid artery during the biopsy, surgery was postponed and the patients were transferred to the authors' departments. The tumors were labeled according to Shamblin's classification from 1971, based on the involvement of carotid vessels [1–9]. In the study group, 16 tumors (33%) were Shamblin class I, 26 (53%) were class II and seven (14%) were class III.

Results

All the patients were qualified for surgery. The operations were performed under general anesthesia. After positioning the patient with the head extended and rotated to the opposite side, the incision was made along the anterior border of the sternocleidomastoid muscle. Before tumor removal, the carotid vessels and both vagal and glossopharyngeal nerves were secured. Dissection started from the external carotid artery. Typically, the branches supplying the tumor were ligated in order to reduce intraoperative bleeding. At the final stage, the internal carotid artery was dissected. After total tumor excision, the length of the internal carotid artery was assessed, because

it may have been displaced and elongated by tumor growth. In such cases, turning the head may cause the artery to fold and thus impair blood flow, increasing the risk of cerebral ischemia.

In the study group, 43 simple resections (88%) of the tumor were performed; however, 11 of those cases (22%) required vascular sutures in the area of common carotid artery bifurcation due to damage to the wall of the internal carotid artery. In 5 cases (10%), internal carotid artery repair was carried out along with tumor excision, due to folding of the vessel when the head was turned. Three cases (6%) required resection of the internal carotid artery because of its involvement; in 2 of these cases (4%), the vessel was replaced by a saphenous vein graft; and in 1 (2%), due to lack of an appropriate vein, the repair operation was performed by creating anastomosis between the external carotid artery and the distal portion of the internal carotid artery.

Out of 49 operations performed in 47 patients, 40 cases (82%) had an uncomplicated postoperative period. Three patients (6%) were reoperated due to symptoms of cerebral ischemia; in 2 of them, the symptoms resolved completely, while one died because of a massive stroke, probably provoked by chronic thrombus. Three patients (6%) developed paralysis of the hypoglossal nerve and 2 (4%) developed facial nerve paralysis. In 6 patients (12%), hematomas occurred in the postoperative wound, including 2 of the patients reoperated due to bleeding. In all the patients, the lymph nodes and internal organs were free from metastases. Histopathologic examinations confirmed that all the tumors were paragangliomas.

Discussion

Carotid paragangliomas are rare tumors that are mostly described in the literature as single case reports [17]. They are mainly unilateral. Fruhmann et al. reported 37 patients with unilateral and 10 with bilateral tumors, while Gad et al. studied 42 paraganglioma patients including only two bilateral cases [13, 18]. In the present study, 45 patients presented unilateral tumors, and two bilateral tumors. In the study by Gad et al., the average age of the patients was 45 years, which was similar to the average age in the current study [18]. According to Fruhmann et al., 20% of patients with paraganglioma carried an SDH gene mutation [13]. Genetic testing for SDHD, SDHB, SDHC and SDHAF, as well as VHL, RET and NF1, is recommended for paraganglioma patients under 40 years of age. SDH carriers require continued follow-up due to the higher risk of the development of multiple tumors [19, 20]. In paragangliomas, the risk of metastatic disease remains low [1]. Smith et al. estimate the risk of malignancy at less than 10% [18, 21].

Paragangliomas cause diagnostic and management difficulties. There is a lack of guidelines in the literature for the diagnosis and treatment of paraganglioma. Tumor diagnoses are based on imaging examinations such as Doppler duplex ultrasound, computed tomography angiography and magnetic resonance angiography [18]. Ultrasound examination is used for screening because it is non-invasive and widely available. Computed tomography and magnetic resonance help to evaluate the degree of the tumor. Angiography allows assessment of the vessels supplying the tumor and preoperative embolization [22–24].

Paragangliomas are challenging for surgeons due to their localization. Despite the lack of recommendations for treatment in the literature, radical resection is performed to prevent malignant transformation. Infiltration and damage to the arterial wall ranges from 20 to 25% [25, 26]. Luna-Ortiz et al. have modified Shamblin's classification, labelling all class II tumors and those infiltrating vessels as Shamblin class III [27].

The clinical value of preoperative embolization remains controversial [28]. It can be considered in large tumors; however, it might increase the risk of transient ischemic attack and ischemic stroke. According to Qin et al. and Makeieff et al., embolization increases the possible complications during surgery [29, 30]. Netterville et al. state that the procedure can start the inflammatory process in the treated area and therefore increase the risk of damage to the carotid arteries during tumor excision [31]. Kakkos et al. recommend embolization in tumors involving the carotid arteries and Shamblin class III lesions extending to the base of the skull [28]. In the present study group, embolization was not performed, and in the authors' opinion, it does not improve the prognosis.

Radiotherapy can decrease the size of the tumor or stop its growth; therefore, it is recommended for patients with many diseases who are at risk during general anesthesia. In a study by Gilbo et al., out of 156 paraganglioma patients treated with radiotherapy, only 5 tumors showed a decrease in size, but a lack of tumor growth after 5 years was observed in 99% of the patients [7]. Surgical treatment is recommended for younger people because radiotherapy increases the risk of cancer development in the long term. Gilbo et al. also reported other radiotherapy complications, such as dry mouth, hearing loss and balance disorders [7].

Endarterectomy is the gold standard for paraganglioma. The incision is made parallel and anterior to the sternocleidomastoid. Carotid vessel

reconstruction is considered optional [13]. Typical intraoperational complications include stroke and dysfunction or paralysis of cranial nerves IX–XII and VII [3, 6–20]. The complication rate is relatively high: Makeieff et al. reported 14%, and Gad et al. 17%. Fruhmann et al. reported cranial nerve paralysis in 20% of the patients, which was similar to the findings in the present study, in which this complication happened in 18% of the patients [13, 18, 30]. Standard paraganglioma operations can be performed with the use of water knife surgery. The stream of water allows for easier dissection of tissues, nerves and vessels, which is especially important in the area of the carotid artery bifurcation. The use of a water knife reduces intraoperational bleeding and the rate of vascular damage.

After surgery, paraganglioma patients require follow-up and regular imaging examinations. For patients with sporadic carotid body tumors, Fruhmann et al. recommend regular check-ups and ultrasound examinations of the neck, while for patients with genetic mutations, they recommend ultrasound examinations and resonance imaging angiography of the neck, head, chest, abdomen and pelvis [13]. In elderly patients in bad health, observation is the only possible approach [7].

The authors concluded that cooperation with an otolaryngologist and vascular surgeon during surgery is recommended due to frequent damage to carotid vessels by carotid paragangliomas. Detection of the tumor in an early stage improves surgical treatment outcomes and reduces the number of complications. Regular postoperative check-ups are necessary due to the possible occurrence of multiple tumors.

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