GLOMUS TUMOR OF THE MIDDLE EAR: ETIOLOGY, CLINICAL PRESENTATION, DIAGNOSIS, TREATMENT

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The article considers the etiology, pathogenesis, diagnosis, clinical presentation, treatment of a glomus tumor of the middle ear – tympanal chemodectoma – a rare benign profusely vascularized neoplasm with an invasive growth. It can be localized in the carotid body, the vagus nerve, the temporal bone, very rarely – in the preoptic region, the trachea, the larynx, the nose, the mandible, ciliated ganglia. Tympanal chemodectoma is more common in the area of the jugular vein bulb and on the promontorial wall of the tympanic cavity. Every year, about one million cases of glomus tumor of the middle ear are diagnosed in the world, the mortality rate from which is 6%. The etiology of the glomus tumor is not known. It forms from the vessels and nerves of the glomus bodies located in the adventitia. Clinical manifestations of tympanal chemodectoma are progressive hearing loss, throbbing ear noise, relieved by compression of the common carotid artery; when it passes to the vestibular part, vestibular crises are observed, which end in complete termination of auditory and vestibular functions, as well as neurological symptoms. The latter is very variable from persistent headaches with nausea, vomiting to paresis to paresis and paralysis of the tongue, the soft palate, hoarseness of voice, aphonia, Berne's symptoms (contralateral spastic hemiparesis, homolateral paresis of the soft palate, the tongue, the accessory nerve) and Sicard's symptoms (short-term knife-like pains in the homolateral half of the tongue during yawning, chewing, eating excessively hot or cold food, irradiating in the neck, the ear). Computed tomography of the temporal bones is highly informative in the diagnosis of glomus tumor of the middle ear. In common forms of tympanic paraganglioma with germination into the internal carotid artery, internal jugular vein, the sinuses of the dura mater are higher than the opportunities of magnetic resonance imaging. The main method for the treatment of tympanal paraganglioma is its surgical removal, which is sometimes preceded by embolization of tumor vessels, laser destruction. Radiation therapy is used for both combined and monotherapy. The latter has a symptomatic character and is indicated in old age, weakened general condition of the patient and a widespread tympanal chemodectoma. Timely diagnosis, oncological alertness of the doctor and the patient are important in the treatment.

Keywords: glomus tumor of the middle ear, tympanal chemodectoma, etiology, pathogenesis, clinical presentation, diagnosis, treatment.

A glomus tumor is a rare profusely vascularized neoplasm [1, 2, 3]. Most of them are benign and locally invasive [4]. The clinical course of a glomus tumor can be characterized to a greater extent as malignant, due to its infiltrative growth, destruction of the surrounding bone tissue, and the possibility of intracranial growth [5]. It can be localized in the carotid body, the vagus nerve, the temporal bone, very rarely – in the preoptic region, the trachea, the larynx, the nose, the mandible, ciliated ganglia. The glomus in the temporal bone, localized in the area of the jugular vein bulb, as well as on the promontorial wall of the tympanic cavity, was first described by S. Guild in 1941 [6, 7]. The term "glomus tumor of the middle ear" (GTME) – "tympanal glomus tumor" is applicable only for neoplasms limited to the tympanic cavity and the mastoid process without spreading to the jugular vein bulb [4].

The purpose of the study is to analyze information about the morphology, etiology, pathogenesis, diagnosis, clinical presentation, treatment of glomus tumor of the middle ear.

Materials and methods of research: literary-analytical, generalizing.

Research results

Morphology

The glomus tissue as hyperplasia of glomus bodies was first described by P. Masson in 1924 [8]. Glomus bodies or non-chromaffin paraganglia are normal components of the diffuse neuroendocrine system accompanying cranial nerves and representing chemoreceptor cells [9]. A glomus tumor is a neoplasm of glomus tissue containing an abundance of blood vessels. A specific feature of the vessels in a glomus tumor is that in their walls muscle fibers are replaced by special epithelioid or glomus cells. Basically, the tumor is supplied with blood from the carotid artery system [10]. A microscopic examination of a glomus tumor shows that glomus cells form nests and strands. These structures are located perivascularly and are frequently observed to have an obvious infiltrative growth along choroid fissures, fibrous interlayers. The stromal and parenchymal components can be conditionally distinguished in the tumor. The stromal component is represented by the connective tissue, developed to varying degrees, containing fibrous interlayers, vessels and nerve trunks. The parenchymal part consists of two types of cells: light large (main) and dark, eosinophilic, compact, somewhat smaller (supporting) [11]. Depending on the ratio between the parenchymal and the stromal components, five types of glomus tumors are distinguished: alveolar, adenoma-like, angioma-like, compact and combined [10, 11]. In the alveolar type, there is an alveolar-

trabecular arrangement of the tumor, groups of glomus cells are delimited by thin connective tissue septa and are closely adjacent to sinusoidal vessels. The alveolar type mainly consists of large light polygonal cells forming a symplast. In the adenoma-like variant, cells form structures resembling a glandular tissue due to the single-layer arrangement of cells on the connective tissue matrix with the formation of alveolar-like structures. In its structure the adenoma-like type morphologically resembles a carcinoid, the leading component in the tumor is vascular. A large number of vessels which are mostly thin-walled, of sinusoidal type, and a small number of perivascularly located glomus cells are noted. The angioma-like type should be differentiated from vascular tumors, where glomus cells can mimic the cavernous component. The compact type is characterized by a dense arrangement of glomus cells, by predominance of smaller dark cells over light and polygonal ones. The combined type is characterized by the sites of different structures, characteristic of the above-mentioned histological types [11].

Historical data

Neoplasms from glomus tissue in different time periods had the following names: a tumor resembling a carotid body – carotidbody-like tumors (H. Rosenwasser, 1945), a glomus tumor (T. Winship, 1948), non-chromaffin paraganglioma (R. Lattes, 1949), chemodectoma (R. Mulligan, 1950), a receptoma (Zettergren, 1952), as well as an extra-adrenal glomus tumor. Taking into account this tumor's special features, a number of authors consider it appropriate to adhere to the terminology glomus tumor (chemodectoma) [7]. It belongs to the neoplasms of the endocrine system and is capable of producing biogenic amines, although inactive forms are also observed. There is also an opinion that the glomus tumor has a common origin with the adrenal medulla, the source of which in ontogenesis are sympathetic cells of the nervous system. Similarly to the structures of the adrenal glands, 1-3% of chemodectomas produce catecholamines, express them based on signals from chemical or neuronal substances and may be falsely invasive [11, 12, 13]. There are also tumors secreting a variety of biogenic amines, both belonging to the parasympathetic or sympathetic part of the nervous system, and not related to any of them [7].

Epidemiology

Glomus tumors of the middle ear are rare tumors of the middle ear, which occurs in 1:300,000 of the population, it takes the second place after neurinoma of the vestibular cochlear nerve [1, 2, 3]. During a year, there are about one million cases of glomus tumors of the middle ear in the world, the mortality rate from which is 6% [3]. According to a number of authors, glomus tumor of the middle ear is more often diagnosed at the age of 40-60 years, but it can also occur at a young age; in women it is 3 times more common than in men; with the same frequency it is observed on the right and left sides, less often it is bilateral [3]. Its size ranges from 5 mm to 5-6 cm in diameter. Tympanal chemodectomas are malignized in 16-24% [14], and recur in 29% after their eradication [3, 11].

Etiology and pathogenesis.

The etiology of glomus tumor of the middle ear is not known to date [14, 15]. It is assumed that the etiological moment is restructuring of the body's hormonal system. At a young age, pregnancy can be a factor causing tumor growth. At the age of 20-30 years, hormone-active forms are more common [2, 3, 14].

Some studies link the formation of glomus tumors with chronic hypoxia, in which glomus hypertrophy is observed in response to prolonged oxygen deficiency in congenital heart defects [16].

There is a genetic predisposition to this disease, transmitted by an autosomal dominant type and accounting for 1-2% of all patients. In the presence of this pathology in the next of kin, the risk of developing a neoplasm is 30%. This form of glomus tumor of the middle ear is more often observed to have a bilateral involvement. Currently, a number of genes have been identified whose mutations lead to an increased risk of developing paragangliomas [2, 15]. This work was based on mapping the human genome and examining families with hereditary forms of glomus tumor. Gene mutations resulted in mitochondrial dysfunction, which caused disturbances in intracellular oxygen metabolism and angiogenesis, inhibition of apoptosis of compromised cells [15]. The analysis of chemodectomas' genome revealed a significant difference between hereditary and sporadic tumors in the presence and absence of chromosome 11q23, respectively. If this chromosome is present, hereditary glomus tumor transmission has been established. If it is not present, the tumor appears sporadically, like any other neoplasm. Thus, early identification of 11q23 can serve as an indicator of the hereditary oncogenesis factor for glomus tumor [17].

Clinical presentation

Symptoms of manifestation of glomus tumor of the middle ear depend on the spread of

the process in the tympanic cavity and neighboring organs. Classification of tympanal chemodectomas is based on their localization, the degree of invasion into adjacent organs. Clinically, two classifications of glomus tumors are used – that of Jackson – Glasscock [18] and U. Fish, D. Mattox modified by M. Sanna [19, 20], which are presented in Tables 1 and 2.

According to a number of authors, localization and extension of the process correspond to a certain histological type of tumor structure. Type A, which is observed in 18.2%, is characterized by an adenoma-like or compact form of the tumor structure. Type B tumors occurring in 63.6% are characterized by adenoma-like, angioma-like and combined types of neoplasm. In 18.2% of patients with type C glomus tumor, a combined structure prevailed [21].

Clinically, a glomus tumor of the middle ear is characterized by a slow course with the development of otiatric, neurological, cervical, intracranial and terminal syndromes [2, 18, 22].

Otiatric syndrome in a glomus tumor of the middle ear is manifested by throbbing blowing noise in one ear, synchronous with the pulse rate and disappearing when compressing the common carotid artery, progressive unilateral conductive and later combined hearing loss, otorrhea. When extending into the inner ear, there are complaints of vestibular crises, culminating in termination of vestibular and auditory functions [2, 18].

Table 1

Classification of glomus tumor by Jackson – Glasscock (1982)

Type (prevalence)	Localization	
	Glomus tumor of the middle ear	Glomus tumor of the jugular foramen
I	A small tumor of the tympanic cavity, limited by the promontory	A small tumor involving the bulb of the jugular vein, the tympanic cavity and the mastoid process
II	The tumor completely fills the tympanic cavity	The tumor spreads through the internal auditory canal; intracranial expansion is possible.
III	The tumor fills the tympanic cavity and spreads into the mastoid process	The tumor expands to the petrous apex; intracranial expansion is possible
IV	The tumor fills the tympanic cavity and spreads into the mastoid process or fills the external auditory canal through the tympanic membrane, spreads anteriorly to the internal carotid artery	The tumor spreads through the petrous apex to the vault of the skull base fornix or into the infratemporal fossa; intracranial expansion is possible

Table 2

Classification of glomus tumor of the temporal bone by U. Fisch, D. Mattox (1988) modified by M. Sanna (2013)

Type	Localization
A	A tumor within the promontory
C	The tumor extends into the hypothympanum, but does not destroy the jugular fossa and does not spread to the infra-labyrinthine space
B1	The tumor partially destroys the lower wall of the tympanic cavity, but does not reach the jugular bulb
B2	The tumor extends to the mastoid process
C	Tumor with damage to the infra-labyrinthine space and expansion to the petrous apex
C1	The tumor extends up to the carotid foramen, but does not involve the carotid artery
C2	The tumor involves the vertical portion of the carotid canal
C3	The tumor involves vertical and horizontal portions of the carotid canal, but does not reach the lacerated foramen
C4	The tumor spreads up to the cavernous sinus
D	Tumor with intracranial extension
De1	Tumors extending into the cranial cavity up to 2 cm (epidurally)
De2	Tumors extending into the cranial cavity up to 2 cm (epidurally)
Di1	Tumors extending into the cranial cavity up to 2 cm (intradurally)
Di2	Tumors extending into the cranial cavity for more than 2 cm (intradurally)

The neurologic syndrome of tympanal paraganglioma is manifested by signs of increased intracranial pressure (papilledemas, persistent headaches, nausea, vomiting). This syndrome can also be caused by malignant invasion into the posterior cranial fossa with the damage to the IX, X, XI cranial nerves, causing paresis or paralysis of the tongue on the corresponding side, articulation disorder, open rhinolalia and liquid food entering the nose (soft palate paralysis), swallowing disorder, hoarseness of voice, aphonia. In case of further progression of the process, the tumor invades into the area of the lateral cerebellomedullary cistern with the damage to the facial, vestibular-cochlear and trigeminal nerves. When expanding in the brain, glomus tumor of the middle ear develops with Berne and Sicard's syndromes. Berne syndrome develops with the damage to the pyramidal tract in the medulla oblongata, which manifests by contralateral spastic hemiparesis, homolateral palate and swallowing musculature paralysis with sensitivity disorders in the posterior third of the tongue, as well as by homolateral accessory nerve paralysis with paresis or paralysis of the sternocleidomastoid and trapezius muscles. The latter results in difficulty in turning and tilting the head to the healthy side, lowering the shoulder on the affected side, deviation of the lower angle of the scapula from the spine outward and upward with difficulty in shrugging the shoulders. Sicard's syndrome is manifested by neuralgia of the glossopharyngeal nerve with short-term (about 2 min) sudden knife-like pains in the half of the soft palate (on the affected side) when yawning, speaking loudly, chewing, ingesting excessively hard, hot, cold food, which radiates into the tongue, the jaws, the neck and the ear [18, 22].

By its manifestations the cervical syndrome resembles an aneurysm of a large cervical vessel in its manifestations and is caused by the presence of a pulsating tumor in the lateral neck region [2, 22].

The intracranial syndrome, which develops when glomus tumor of the middle ear expands intracranially, is characterized by a severe course due to an increase in the intracranial pressure, damage to the III-XII cranial nerves [2, 18].

Terminal paraganglioma syndrome ends in a fatal outcome [2, 18, 22].

Diagnostics

Diagnosis of a glomus tumor of the middle ear is difficult only at the initial stages of the disease. In the early diagnosis it is important to assess the sequence of symptoms: throbbing tympanophonia and conductive hearing loss [23], as well as a characteristic otoscopic picture – turbidity and swelling of the tympanic membrane with the absence of exudate in the tympanic cavity during diagnostic paracentesis of the tympanic membrane [2, 18, 22]. Dysphagia, dysphonia, otorrhea, paresis of the facial nerve are also noted. Otoscopically, there is a characteristic translucence of the tumor through the tympanic membrane into the lower parts of the tympanic cavity [22, 23, 24].

The standards for diagnosing the diseases accompanied by tympanophonia include an objective examination and an audiological examination. Audiometry enables to only identify the degree of hearing impairment, conductive hearing loss, which can be observed in many pathological conditions. Tympanometry in a glomus tumor of the middle ear reveals the type B tympanogram – restriction of the tympanic membrane's mobility. It is not possible to identify the contents of the middle ear otoscopically and tympanometrically [25].

The most effective methods of radiation diagnostics of a glomus tumor of the middle ear were computed tomography and magnetic resonance imaging. These studies are intercomplementary. Computed tomography is to the fullest degree informative in terms of assessing the state of the bone anatomy in this zone – the walls of the tympanic cavity, the carotid canal, the jugular fossa, the posterior wall of the pyramid, the bone labyrinth, the mastoid process. Magnetic resonance imaging assesses the degree of tumor invasion into adjacent structures (sigmoid sinus, internal carotid artery, jugular vein bulb) [26]. Optical coherence tomography in the presence of exudate in the tympanic cavity provides a non-invasive assessing the rheological properties of exudate, it is highly informative in the differential diagnosis of glomus tumor of the middle ear and secretory otitis media [25].

Supplementary methods for examining a tympanic paraganglioma include angiography, scintigraphy, immunography. Only a comprehensive diagnosics can determine the prevalence, relapse, continued growth, metastases, and the choice of treatment tactics for glomus tumor of the middle ear [2, 24, 27]. Histological or histochemical examination of the surgical material is used to confirm the diagnosis [24].

Treatment

The "gold standard" for treating glomus tumors of the middle ear, especially small ones, in the early stages is their surgical removal [27]. Another method for the treatment of a glomus tumor is radiation therapy. Treatment methods

can be used both in isolation and in combination. Surgical removal of glomus tumor of the middle ear can be combined with preoperative embolization [28]. Each treatment plan for glomus tumor of the middle ear is based on the data of a comprehensive diagnostic examination, the age of the patient, the type of tumor, the patient's general condition. The problem is to determine whether the tumor will cause significant complications during the rest of life or death [14, 24]. Surgical treatment of tympanal paraganglioma is carried out in the otorhinolaryngological department. Due to technical opportunities, currently the problems of resectability of glomus tumor of the middle ear have given way to the problems of functional results and the quality of postoperative life. Restoration of significant defects along with restoration of reduced cranial nerves' function, is necessary to minimize the main risk which is the reason for criticism of surgical interventions [18, 24]. In a multifocal lesion, the most life-threatening formations are removed first. The following recommendations are determined by the neurological consequences. Bilateral glomus tumors are particularly complex. If one of them is removed and the patient has no neurological disorders, then the operation on the opposite side is planned only in six months [14, 24].

The complexity and traumatic nature of surgical access, a high risk of complications, including massive intraoperative bleeding, were an obstacle to radical removal of the tumor. Surgical treatment is sometimes preceded by embolization of tumor vessels. These features contributed to the introduction of laser methods of exposing the tympanal paraganglioma, characterized by high technology and efficiency, making it possible to carry out precision action on the tumor, reducing the possibility of complications and significantly reducing bleeding. Laser surgery is particularly indicated for glomus tumors of type A and B localization according to the classification of U. Fisch, D. Mattox (1998) modified by M. Sanna (2013) [29]. New photoangiolytic lasers were developed which differed from cutting $_{CO2}$ lasers, the former are represented by a fluid pulsed laser (PDL with a wavelength of 585 nm), powered by potassium-titanyl-phosphate with a wavelength of 532 nm and 445 nm (KTP). The use of the above-mentioned lasers through flexible fiberglass in flexible endoscopes expands the opportunities of this method in the surgical treatment of vascularized tumors. A combined use of a cutting laser and a photoangiolytic laser operating on liquid pulses and potassium-titanyl-phosphate are often used when dissecting the glomus tumor of the middle ear. The most advantageous property of photoangiolytic lasers is coagulation of superficial and subepithelial blood vessels without destroying the surface epithelium and perivascular tissues. Photoangiolytic lasers make it possible to apply laser pulses contactless through thin fiberglass (300-400 microns) [30].

An alternative method is radiation therapy (γ-knife) – a minimally invasive inexpensive method of conservative treatment of glomus tumor of the middle ear with a low level of complications. Radiation therapy occupies a prominent place in the treatment of glomus tumors of the middle ear [22]. The latter in the form of monotherapy forces the patient to coexist with the tumor. The data obtained do not allow us to talk about "control" over the disease due to -relative rarity of these tumors, long-term (15-20 years) natural development [26]. According to a number of authors, radiation therapy can slow down or even stop the growth of a glomus tumor. Radiological treatment is indicated for advanced tumors, elderly people and patients with contraindications for extensive surgery. The concept of "elderly" is best defined by physiological indicators; the age is approximately from 65 to 70 years [3]. In asymptomatic cases, when a palliative type of treatment is chosen, the glomus tumor is carefully observed, a dynamic X-ray examination is performed. Extensive damage to the cranial nerves changes the treatment plan due to -extreme danger of laryngeal denervation and interruption of afferent pharynx innervation, which is a serious impact on the quality of life with the need for permanent tracheostomy, intubation and/or artificial nutrition. In this case, palliative therapy is indicated for the treatment of residual phenomena [14, 18, 22].

Thus, the treatment of glomus tumor of the middle ear can be palliative or radical: radiation therapy is considered palliative (symptomatic), the main method of treatment is surgical.

Conclusions

1. Glomus tumor of the middle ear is a benign neoplasm with a high degree of vascularization due to the peculiarities of locally invasive growth and localization: proximity of vital neurovascular formations, possibility of spreading into the cranial cavity requires a multidisciplinary approach in diagnosis and treatment with the participation of an otorhinolaryngologist, a radiologist, a neurosurgeon, a vascular surgeon.

2. Currently, the radical method for treating middle ear chemodectoma is the surgical one.

3. The most important in the treatment of a glomus tumor of the middle ear is its early detection, timely referral and treatment in specialized hospitals, which requires oncological alertness of primary care doctors, expansion of sanitary and educational work among the population.

4. Pulsating ear noise is one of the early manifestations of a glomus tumor of the middle ear, which should always alert the doctor.

5. Early identification of 11q23 chromosome can serve as an indicator of the hereditary factor for glomus tumor oncogenesis, which must be taken into account for the early diagnosis of the disease.

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