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Update on Pheochromocytomas and Paragangliomas

Xiao-Jun Huang and Xi-Yuan Chen*

Department of Respiratory Medicine, Zhejiang Provincial People's Hospital, Hangzhou, China

Abstract

Pheochromocytomas are rare neuroendocrine tumors that originate from chromaffin cells of the adrenal medulla; paragangliomas are tumors originate from extra-adrenal paraganglions, and found in association with sympathetic and parasympathetic nerves. Pheochromocytomas and paragangliomas may cause sympathetic symptoms such as headache, tachycardia, chest pain, paroxysmal hypertension and sweating. If anytime pheochromocytomas and paragangliomas are suspected, a measurement of catecholamine should be taken as well as localization of tumors with imaging examination or functional testing. Pheochromocytomas and paragangliomas are mostly benign tumors, and a small percentage may become malignant and metastasize; hence, early identification leading to complete surgical resection is usually curative and carries a favorable prognosis.

Keywords: Pheochromocytoma • Paraganglioma • Neuroendocrine tumors • Chromaffin cells • Adrenal medulla • Paraganglion • Catecholamine • Parasympathetic system • Sympathetic system • Heritability • Genetic screening • Surgical resection

Abbreviations

CT: Chest Computed Tomography; MR: Magnetic Resonance; PET: Positron Emission Tomography; MEN: Multiple Endocrine Neoplasia; VHL: Von Hippel-Lindau; NF-1: Neurofibromatosis-1; FPGL: Familial Paraganglioma; PET: Positron Emission Tomography; NGS: Next-Generation Sequencing.

Introduction

Pheochromocytomas and paragangliomas are rare tumors reported at a rate of 2–8 cases/million a year [1], and are thought to have a high degree of heritability. Those originating from chromaffin cells are located in 90% cases in adrenal gland and recognized as pheochromocytomas, while in the remaining 10% of cases have an extra-adrenal origin and are termed paragangliomas [2]. Paragangliomas may occur anywhere in the body rich of paraganglions, commonly are located in head, neck, paravertebral sympathetic plexus and abdomen. As catecholamine secreting neuroendocrine tumors, pheochromocytomas and sympathetic paragangliomas may cause varies sympathetic symptoms. In contrast, paragangliomas arising from parasympathetic system are asymptomatic and inactive, and are usually revealed accidentally at Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) as hypervascular mass. Histopathological evaluation is necessary for a definitive diagnosis. Early recognition and a radical surgical treatment are fundamental to obtain clinical recovery [1,3]. Complete surgical resection is the first-line therapy, while, the effect of radiotherapy and chemotherapy are uncertain.

Literature Review

Etiology

Pheochromocytomas and paragangliomas are a rare type of catecholamine secreting neuroendocrine tumors originating during the neural crest cell migration [4]. Tumors in most cases originate from chromaffin cells in adrenal medulla, and are called pheochromocytomas. Those originate from the extra-adrenal paraganglions (rich of chromaffin cells) are termed paragangliomas; they account for about 10% of cases.

Paragangliomas may occur at any body parts rich in paraganglions, and may be either parasympathetic or sympathetic. Paragangliomas arising from parasympathetic systems are usually non-functional and asymptomatic, located mostly in the head, neck, mediastinum, even thyroid and lung as reported [5]. Comparatively, paragangliomas associated with sympathetic system are highly active and symptomatic. Sympathetic paragangliomas can cause symptoms similar to that caused by pheochromocytomas (also called intra-adrenal paragangliomas), such as hypertension, headache, palpitations, sweats and tremor. Approximately 85% arise below the diaphragm, along the paravertebral sympathetic plexus to the pelvis and the abdomen [6].

Epidemiology

Pheochromocytoma/Paraganglioma is a very rare disease, which has been diagnosed 500 to 1000 cases per year in the United States [7]. Although not precisely known, the incidence is roughly estimated 2 to 8 per million population per year [8,9]. Due to diver's clinical presentations and lack of awareness, there are a large number of pheochromocytomas and paragangliomas misdiagnosed. The tumors are mostly sporadic, while 30 to 40% are familial. Sporadic cases are usually diagnosed during the third through fifth decades of life and the sex distribution obviously skewed towards a female predominance with the female to male ratio of 3 to 1. Comparatively, hereditary type is diagnosed earlier in the patients' thirties with the female to male ratio of 1 to 1 [7,10].

Clinical presentation

The clinical presentation of pheochromocytomas and paragangliomas is due to sympathetic overload or direct mass effect. Although the clinical presentation is variable, it is classically characterized by a triad of headache, palpitations, and profuse sweating [10]. Pheochromocytomas and sympathetic paragangliomas, as catecholamine (mainly norepinephrine) secreting neuroendocrine tumors, may cause sympathetic symptoms as follows: headache, tachycardia, dry mouth, constipation, face flushing, diaphoresis, episodic syncope, chest pain, paroxysmal hypertension, dilated pupils. Besides, hoarseness, cranial nerve paralysis, dysphagia are mostly due to the mass effect. Moreover, panic symptoms, fidgetiness, blurry vision, lightheadedness, mood disturbances, high blood sugar, generalized fatigue and weight loss may also commonly present [11,12].

Evaluation

In the diagnosis of pheochromocytomas and paragangliomas, it is necessary to validate the excessive production of catecholamines. The measurement of plasma fractionated metanephrines is the most favorable test as it has a high sensitivity of 97% and a specificity of 93% [13]. Moreover,

***Address for Correspondence:** Xi-Yuan Chen, Department of Respiratory Medicine, Zhejiang Provincial People's Hospital, Hangzhou, China, Tel: +0086-571-85893509; E-mail: tshcz-508@163.com or huangxiaojun858@sohu.com*

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checking plasma or 24 hr urine catecholamine is helpful in diagnosis [10]. It is important that the patient should been taken off from certain medications such as tricyclic antidepressants, antipsychotics, levodopa, and norepinephrine reuptake inhibitors, before the test, since these medications can result in a false-positive result. Moreover, stressful clinical conditions can also contribute to false-positive test results [10].Parasympathetic paragangliomas can present as non-functional tumors without catecholamine secretion.

CT and MRI are the important imaging examination methods of diagnosis of pheochromocytomas and paragangliomas. Some pheochromocytomas and paragangliomas show no evident clinical symptoms, and are usually detected incidentally at CT scanning or MRI as highly vascular masses. Those present typical features at CT scan [2,3] isodensity or slightly lower density, homogeneous and intense enhancement, except for necrotic areas with scarce enhancement. It was previously thought that intravenous contrast media may induce hypertension in patients with pheochromocytomas and functional paragangliomas, however it has been proved nowadays to be safe in patients without treatment with α or β blockers [14]. MRI has a high sensitivity close to 100%, which is superior to CT scanning. T1W1 shows isodensity and low signal. T2W1 shows medium, high, or uneven mixed signal. DW1 shows high signal. MRI can also show the rare salt-appearance of the tumor that reflects hemorrhage. A positron emission tomography (PET)/CT can be used in identifying occult pheochromocytomas and paragangliomas and assessing distant metastasis.

Pathology

Surgical biopsy of the lesion is the gold standard to confirm the diagnosis, but it does not differentiate between pheochromocytomas and paragangliomas; they are almost identical in histologically. Diagnosis based on preoperative biopsies/fine-needle aspiration can be challenging, since pheochromocytoma/paragangliomas are hypervascular and easily bleeding. Moreover, a complete pathological examination evaluating tumor morphology and structure is necessary [3], especially for differential diagnosis from neuroendocrine tumors [15,16].

Macroscopically, pheochromocytomas and paragangliomas are firm, yellow-reddish in colour, can be completely or incompletely capsulated. Microscopically, they present irregular clusters of irregular nuclei arranged in a trabecular pattern or a nesting pattern within a highly vascular tissue. Sympathetic cells may have hyaline globules in h&e stain. Immunohistochemical test is particularly important. Positivity for CgA, CD56 and Sy is typically found in pheochromocytomas and paragangliomas, while negativity for cytokeratins and epithelial membrane antigens is an important differentiating factor from carcinoid tumors [16].Pleomorphism, nuclear atypia, mitotic figures, necrosis, and local/vascular invasion is common in pheochromocytomas and paragangliomas but not indicative of malignancy [17].

Heritability

About 30% to 40% of pheochromocytomas and paragangliomas are familial, usually inherited as an autosomal dominant trait, and may be associated with genetic syndromes like multiple endocrine neoplasia (MEN 1 and MEN 2), Von Hippel-Lindau (VHL), Neurofibromatosis-1 (NF-1), and familial paraganglioma (FPGL) [18], as well as some catecholamine secreting syndromes such as Sturge-Weber syndrome, tuberous sclerosis complex, ataxia-telangiectasia syndrome, and Carney Trilogy [19,20]. An understanding of these syndromes may help to raise awareness of pheochromocytomas and paragangliomas systematically. Additionally, as many as 24% of sporadic cases have also been identified as genetic abnormalities.

Pheochromocytomas and paragangliomas are recognized to have the highest degree of heritability of any endocrine tumor type [21]. To date, approximately 30 genes known to be related to pheochromocytomas and paragangliomas and the exploration of new genes is far from over [22] and the number is rising with the use of next-generation sequencing (NGS). Mutations such as *SDHA, SDHD, SDHB, MDH2, HIF2A, RET, NF1, VHL, MAX, TMEM127*, and *MEN 2A*, and *2B*, have been associated with pheochromocytomas and paragangliomas [18]. Genetic screening is useful to identify carriers of the pathogenic mutations of pheochromocytomas and paragangliomas. Patients can be offered genetic testings once the diagnosis and treatment have concluded [10]. Although pheochromocytomas and paragangliomas are regarded the same in almost every aspect, their location and hereditary background are different. Pheochromocytomas originate from the adrenal medulla are thought to be caused by the mutation of *RET, VHL, MAX, NF1*, and *TMEM127*, while paragangliomas originate from extra-adrenal paraganglions are more likely to be caused by the mutation of *SDHx, MDH2* and *HIF2A* [23]. Therefore, applying appropriate genetic screening according to the location of the tumor can be cost-saving and effective, regards the high cost of NGS.

Treatment

Complete surgical resection is the first-line treatment for solitary pheochromocytomas and paragangliomas [15,24]. For all patients with elevated norepinephrine or metabolism, the updated recommendation is to offer preoperative pharmaceutical "blockade" regardless of symptoms [25]. Based on tumor behavior, it is also necessary to control blood pressure before the surgery as well as to prevent an intraoperative hypertensive crisis [10].

Some authors proposed that paragangliomas is sensitive to radiation therapy, with high local control rates and few complications [26-28] especially in head-and-neck paragangliomas, complete surgical resection may be challenging and an individualized approach with surgical resection or radiation therapy is needed. However, some authors suggest the tumors are relatively resistant to chemotherapy and radiotherapy [3,24,29]. The use of the chemotherapy regimen is not unanimously approved. Sorafenib use has been reported in some metastasis cases [30,31]. Precision therapeutics is the next crucial step. Although progress has developed slowly, there are several drugs targeting a broad range of features unique to pheochromocytomas and paragangliomas are in different developmental stages [32].

Differential diagnoses

Possible differential diagnoses are as following [33] Hyper adrenergic spells, Thyrotoxicosis, Pancreatic tumors, Mast cell disease, Renovascular disease, Labile essential hypertension, Diencephalic epilepsy, Somatization disorder, Paroxysmal cardiac arrhythmia, Carcinoid syndrome, Recurrent idiopathic anaphylaxis, Anxiety and panic attacks, Vancomycin related red man syndrome, Autonomic neuropathy, Migraine headache, Stroke.

Prognosis

Pheochromocytomas and paragangliomas are mostly benign and slow-growing. The malignant rate ranges from 14% to 17% [34]. Unlike most tumors, there are no characteristics in histological, molecular, or genetic markers that can clearly distinguish between benign and malignant pheochromocytomas and paragangliomas. Distant metastasis is the only indicator of malignancy [17]. According to the recommendation by WHO in 2017, paragangliomas should be classified as metastatic or non-metastatic instead of malignant or benign [35,36].

Conclusion

Finally, the prognosis is usually favorable if the tumor can have completely resection. Based on literature, recurrence and metastases may happen even after a long time. A mean incidence of recurrence of paragangliomas of 15 ± 7% at 5 years and 23 ± 9% at 10 years after surgery has been reported. Because of that, a life-long follow-up after surgical resection is mandatory. Annual follow-up catecholamines testing, especially in functional tumors, and imaging studies are recommended.

Conflict of Interest

The authors have no conflict of interest to declare.

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