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Understanding the origin of paraganglioma

Compreendendo a origem dos paragangliomas

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ABSTRACT

Introduction: Paragangliomas are rare, slow-growing neuroendocrine tumors, often grouped with pheochromocytomas due to their cellular similarities. They arise from neural crest cells and can be found within the sympathetic or parasympathetic nervous systems, with varied clinical presentations, depending on their location and functionality.

Objective: To prepare a comprehensive review of paragangliomas in the context of neurosurgery.

Method: The review used the PubMed, Scopus and Web of Science databases. Studies on epidemiology, pathophysiology, genetic characteristics and clinical manifestations were included. Inclusion criteria included clinical studies, systematic reviews and case studies published between 2000 and 2023. The analysis focused on the neurosurgical aspects of treatment, associated risks and advances in the diagnosis and management of these neoplasms.

Result: 68 articles that focused on the topic referred to in this review were included.

Conclusion: Although they are predominantly benign, approximately 10% present malignant behavior. Its highly vascularized nature and proximity to critical neurovascular structures present surgical challenges. Genetic testing, especially for SDH gene mutations, plays an important role in directing management and assessing the risk of malignancy.

KEYWORDS: Paragangliomas. Pheochromocytomas. SDH mutations. Neuroendocrine tumors. Genetic syndromes. Neurosurgery. Familial syndromes. Head and neck tumors.

RESUMO

Introdução: Os paragangliomas são tumores neuroendócrinos raros e de crescimento lento, frequentemente agrupados com os feocromocitomas devido às suas semelhanças celulares. Eles surgem a partir de células da crista neural e podem ser encontrados dentro dos sistemas nervosos simpático ou parassimpático, com apresentações clínicas variadas, dependendo da sua localização e funcionalidade.

Objetivo: Elaborar ampla revisão sobre paragangliomas no contexto da neurocirurgia.

Método: A revisão utilizou as bases PubMed, Scopus e Web of Science. Foram incluídos estudos sobre epidemiologia, fisiopatologia, características genéticas e manifestações clínicas. Os critérios de inclusão abrangeram estudos clínicos, revisões sistemáticas e estudos de caso publicados entre 2000 e 2023. A análise foi focada nos aspectos neurocirúrgicos do tratamento, riscos associados e os avanços no diagnóstico e manejo dessas neoplasias.

Resultado: Foram incluídos 68 artigos que focaram o tema referido nesta revisão.

Conclusão: Apesar de serem predominantemente benignos, aproximadamente 10% apresentam comportamento maligno. Sua natureza altamente vascularizada e a proximidade com estruturas neurovasculares críticas apresentam desafios cirúrgicos. O teste genético, especialmente para mutações no gene SDH, desempenha papel importante para o direcionamento do manejo e na avaliação do risco de malignidade.

PALAVRAS-CHAVE: Paragangliomas. Feocromocitomas. Mutações SDH. Tumores neuroendócrinos. Síndromes genéticas. Neurocirurgia. Síndromes familiares. Tumores de cabeça e pescoço.

Central Message

The article addresses paragangliomas, rare neuroendocrine tumors that share characteristics with pheochromocytomas, focusing on their particularities, epidemiology, pathophysiology, genetic analysis and clinical presentation. By exploring molecular and genetic characteristics, the article reveals the importance of differentiating between sporadic and hereditary forms, highlighting specific mutations such as those of the SDH enzyme complex. In addition, it emphasizes the surgical challenges and the classification of these tumors as "ongoing risk" due to their indeterminate behavior.

Perspective

A comprehensive review of paragangliomas in the context of neurosurgery is important, and offers detailed analysis of their biological characteristics, relevance of genetic variants, and their influence on clinical presentation and management. The article also highlights the importance of multidisciplinary approach, including genetic screening for those diagnosed with paraganglioma, especially with mutations associated with higher risk of malignancy or aggressive behavior.

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INTRODUCTION

Paragangliomas are rare, slow-growing neuroendocrine tumors. They show little difference with pheochromocytomas, being indistinguishable at the cellular level. It is noteworthy that when it comes to nomenclature, in 2004 the World Health Organization referred to paragangliomas as "extra-adrenal pheochromocytoma", currently the distinction aims to more accurately catalog associated neoplasms, risk of malignancy and genetic tests. Thus, paragangliomas can be defined as neuroendocrine tumors of the extra-adrenal autonomic paraganglia. As a rule, they are derived from embryonic neural crest cells.[1-2]

The presentation of a paraganglioma can be in the sympathetic or parasympathetic nervous system. The former are usually catecholamine secretors, influencing blood pressure autoregulation, manifesting with hypertension, headache, and tachycardia. They are located in paravertebral ganglia of the chest, abdomen and pelvis. In turn, the latter, for the most part, are non-functional and are along the glossopharyngeal and vagal nerves, with a higher incidence in the neck and skull base.[2]

Commonly, due to its slow growth and characteristic histology, it has a typically benign behavior; however, about 10% evolve with clinical characteristics of malignancy; for this reason, they are currently classified as tumors of continuous risk. In addition, being highly vascularized and depending on the implantation site along the vascular-nervous bundle, they represent a surgical challenge when indicated.[3-4] Thus, this article aims to develop a broad review of paragangliomas in the context of neurosurgery.

METHOD

This study used PubMed, Scopus, and Web of Science as the search base. Publications on the epidemiology, pathophysiology, genetic characteristics and clinical manifestations of paragangliomas were included. Inclusion criteria covered clinical studies, systematic reviews, and case studies published between 2000 and 2023. The analysis focused on the neurosurgical aspects of treatment, associated risks, and advances in the diagnosis and management of these neoplasms. Only articles that contained the theme referred to in this review were included.

DISCUSSION

The incidence of paragangliomas is often described together with that of pheochromocytomas due to their common characteristics. Thus, it is still difficult to characterize the specific incidence of paragangliomas. However, it is worth noting that studies agree on their rarity, citing that they correspond to approximately 0.6% of head and neck neoplasms, as well as an incidence of 0.[8] per [100,000] person-years.[1-4]

Paragangliomas were considered for many years to be sporadic; However, more and more studies show the discovery of genetic tendencies with tumors of their own characteristic. To expose this fact, some epidemiological characteristics of sporadic tumors can be highlighted, such as their appearance in middle-aged patients - 40 to 50 years - and a prevalence of 71% in females; A reason for such a presentation is not yet well described. At this point, it can be seen that although they are still considered mostly sporadic, there are recent data on genetic tendencies linked to paragangliomas and hereditary syndromes, where patients with genetic load tend to develop them earlier, up to 10 years before the usual age. In addition,- the prevalence between men and women becomes indifferent.[1-5]

The genetic load has shown increasing significance, with the SDH protein mutation being the most described. Hereditary/familial syndromes have also been reported, with a greater influence on head and neck paragangliomas, representing up to 40% of cases, as well as being one of the reasons for their appearance in children.

Pathophysiology

Paragangliomas originate from cells derived from the neural crest, thus involved in the pluripotentiality, migratory and proliferative capacity of these cells. Thus, although they have been considered benign for many years, the WHO has recently characterized them as tumors of continuous risk, since there is no histological classification system for them, as they are considered to have indeterminate biological potential.[6]

The disparity observed in sporadic paragangliomas vs. paragangliomas with genetic trait is reinforced. It is noted that the first carotid in the body were observed more frequently in individuals exposed to chronic hypoxia, being related to patients who inhabit high altitudes with significantly thinner air, as well as patients with cyanotic congenital heart disease and chronic obstructive pulmonary disease.

Hypoxia factor is also reported in the presence of malignancy of paragangliomas and pheochromocytomas. It is theorized that with hypoxia, enzyme losses occur, leading to the accumulation of metabolites, directly inducing malignant phenotypes.[7] Some reported mechanisms cite the physiology of increased red blood cell production, which has already been well described, highlighting the hypoxia-induced binding of factor 1 (HIF1) and vascular endothelial growth factor (VEGF). The first, considered to regulate the expression of hundreds of genes, encompasses those that encode metabolic enzymes, angiogenic factors and cell cycle regulators.[7-9] In addition, a HIF stabilizer has already been described and approved in the treatment of anemia. In addition, HIF2 inhibitors have been developed with promising results in kidney cancers, also considered pseudo-hypoxic tumors.[10,11]

Regarding possible genetic origins, there is a considerable range of studies on molecular variants corresponding to paragangliomas. Before entering into the subdivisions of hereditary syndromes and possible molecular alterations with subsequent origin of paragangliomas, it should be noted that, although studies have considered data together with

pheochromocytomas, recent studies have shown that most paragangliomas in children under 18 years of age have genetic traits, reaching 56% of those affected. On the other hand, when focusing on those found in children under 5 years of age, this percentage increases, reaching 70-85%.[12-14] It is also important to highlight that when compared to adults, pediatric paragangliomas present more like multiple paragangliomas.[12,15]

Even though most paragangliomas continue with sporadic diagnosis, it should be noted that with modern genetic tests a wide range of enzymatic alterations and hereditary syndromes are described as risk factors for their development, described together with pheochromocytomas, as explained in the introduction. Among the alterations, genes encoding some subunits of the enzyme complex, succinate dehydrogenase (SDH), as well as 4 syndromes described, namely, multiple endocrine neoplasia, types 2A and 2B (MEN2); neurofibromatosis type 1 (NF1); von Hippel Lindau disease (VHL) and the Carney-Stratakis dyad, with the pathogenic variants SDHD, SDHB and SDHC, VHL and NF1 explaining most familial paragangliomas.[16]

Although with great pathogenic variability, genetic traits are described in studies with genetic screening, again emphasizing alteration of the SDH subunit, being SDH-D in 9.3%, SDH-B in 4.8%, SDH-C 0.8%, in addition to 2.2% of NF1.[7] It is noteworthy for this article that all 15 patients who presented skull and neck base paragangliomas or secretory paragangliomas also had a pathogenic variant of the germline. These data are similar to published genetic screenings, where 30% of patients with pheochromocytoma/paraganglioma had familial syndrome or susceptibility gene, with VHL in 9%, SDHD in 7.1%, SDHB in 5.5%, RET in 5.3% and NF1 in 2.9%.[7]

As mentioned above, most studies do not differentiate pheochromocytomas from paragangliomas due to their similarity at the cellular level However, when separated by a study with genetic screening, a significant difference was observed in terms of presentation, where pathogenic variants were found in 83% of those with paragangliomas, in contrast to 57% of those with pheochromocytoma.[8,9] Patients with multiple tumors also stand out -20% of 24.83%.[17]

Genetic analysis of SDH factor

Among the variants of the SDH enzyme complex, paraganglioma syndromes 1, 2, 3, 4 and 5 (PGL1, PGL2, PGL3, PGL4 and PGL5, respectively) stand out with greater precision. According to the error in the subunit, one can identify individual characteristics of the syndromes that follow.[1]

PGL1

It is associated with the SDHD variant at the 11q23 genetic locus, being the most common type of familial syndromes. In addition, SDHD is a gene with a putative maternal imprint, that is, it is limited to paternal genetic inheritance. It should be remembered here that paternal pathogenic variants are considered highly penetrating in middle age, reaching 50% precisely in the period of prevalence of paragangliomas.[7,10,11]

When it comes to head and neck paragangliomas, interesting data emerge from the 236 patients in a Dutch study, where, of all patients, up to 83% were carriers of a pathogenic variant SDHD, and a single founding pathogenic variant, p.Asp92Tyr, accounted for 72% of skull base and neck paragangliomas.[16] Another study in Sweden shows that in the face of phenotype we have both paragangliomas and pheochromocytomas; however, paragangliomas accounted for up to 93%.[7] In addition, it is observed that paragangliomas were mostly parasympathetic, up to 84%, and many of them multiple, up to 56%, although rarely malignant 4%.

PGL2

It is associated with the SDH2 complex assembly variant at the genetic locus 11q12.[2,] reported only in 2 European families, with only parasympathetic paragangliomas being observed, being multiple in its majority.[7,17,18]

PGL3

It is associated with the SDHC variant in the locus genetic 1q21. It demonstrates rarity and predominance in parasympathetic paragangliomas.

PGL4

It is associated with the SDHB variant at the genetic locus 1p36.1-35, being the second most common type of familial paraganglioma. Genetic modifications of SDHB are also reported with renal cell carcinoma. The phenotype also includes pheochromocytomas; however, the majority, up to 78%, corresponds to paragangliomas, of which the majority of the sympathetic system is multiple. Penetrance usually represents 25% at 50 years of age, and 10% of those investigated demonstrated a family history. When talking about mutations related to SDHB, the secretion of catecholamines, including norepinephrine and some cases dopamine, is a typical characteristic. Some important features about SDHB-related paragangliomas are that these tumors appear earlier, around age 28, and dopamine secretion is related to a worse prognosis; variants of SDHB have a higher rate of malignancy. Thus, when there is a diagnosis of paraganglioma with variant of SDHB, the investigation of metastatic disease is indicated.[10,19-22]

PGL5

It is associated with the SDHA variant, with 3 nonsense pathogenic variants reported (p.Arg585Trp, p.Arg589Trp, and p.Arg31X). The mean age was 40 years, and the phenotype varies between pheochromocytoma and paraganglioma. Finally, variants were found in healthy control patients, inferring low penetrance in patients with SDHA.[23,24] Considering the data on germline variants of the SDH above, genetic screening is recommended in all patients diagnosed with paraganglioma.

Analysis of other genetic alterations

In addition to PGL due to SDH variations, some

hereditary syndromes that course with the paraganglioma or pheochromocytoma phenotype are: MEN2, NF1, VHL and the Carney-Stratakis dyad. Recently, the MAX protein variant was also discovered.

MEN2

Paragangliomas are rarely observed, being more related to pheochromocytomas, including bilateral ones. It can also be subdivided into MEN2A and MEN2B according to the variant of the RET proto-oncogene. MEN2A is characterized by medullary thyroid cancer, pheochromocytoma/paraganglioma, and primary parathyroid hyperplasia. MEN2B is characterized by medullary thyroid cancer, pheochromocytoma/paraganglioma, but without hyperparathyroidism.[7]

NF1

NF1 is a tumor suppressor gene on chromosome 17q11.1 that characterizes neurofibromatosis type 1, with a range of clinical findings including pheochromocytomas/paragangliomas. It is important to report that pathogenic variants of NF1 are often acquired and not inherited, generating a mosaic phenotype. As a rule, paragangliomas are rare in this alteration and, when present are located in periadrenal areas.[7,25]

VHL

The VHL gene is a tumor suppressor gene on chromosome 3p25-26, its products regulate hypoxia-inducible factor (HIF) oxygen dependence. Between 10-34% of von Hippel-Lindau patients develop pheochromocytoma/noradrenergic paraganglioma.[7,17] The risk of developing the tumor is higher in families with type 2 disease than type 1; in addition, it should be noted that in the families of VHL type 2, pathogenic variants Y112H were diagnosed in the elderly, and the tumors were more likely to secrete vanillmandelic acid (VMA), and less likely to secrete norepinephrine. In addition to being more multifocal, they had lower rates of surgical cure (76% vs. 100%), as well as a higher rate of malignancy (20% vs. 5%) and a worse prognosis.[26]

Dyad Carney – Stratakis

An autosomal dominant disease with incomplete penetrance27, it is of primary significance because it characterizes gastrointestinal stromal tumors (GISTs) and paragangliomas, often attributed to the germline pathogenic variant of SDHB, SDHC, or SDHD.[28,29]

MAX

It is a gene located on chromosome 14q23.[3.] Some patients with pheochromocytoma/paraganglioma without other pathogenic variants have been identified with germline pathogenic variants in MAX.[30]

Presentations

Although the phenotype encompasses pheochromocytoma and paraganglioma, regarding paragangliomas, and their presentations, some peculiarities can be mentioned with some classifications as follows: sympathetic or parasympathetic, solitary or multiple, sporadic or hereditary, benign or malignant.

Paralymph node paragangliomas are usually located along the glossopharyngeal and vagus nerves, with a higher incidence in the neck and skull base. Up to 60% of carotid body tumors are in the neck and skull base. In these cases, most are non-functional, presenting symptoms usually due to the mass effect.[31]

Sympathetic paragangliomas are located along the sympathetic chain from the base of the skull to the bladder and prostate. Most are functional with hypersecretion of catecholamines. Up to 75% of tumors appear in the abdomen, with a predilection for the junction of the vena cava with the left renal vein, or in the aortic bifurcation. Up to 10% of tumors appear in the chest. They can also arise in the thyroid, adjacent to the thoracic spine, and in the cauda equina. 32-37

Approximately 26% of paragangliomas are thought to be multiple and 1/3 are associated with hereditary syndrome, as mentioned above. Also, it is observed that 15-20% of tumors with hypersecretion are extra-adrenal. Finally, multiple tumors appear to be much more frequent in hereditary cases than sporadic ones: 17% to 85% vs. 1.2%.[38]

Malignancy is seen in 20% of extra-adrenal secretory paragangliomas. When found at the base of the skull and neck, they are usually benign. As mentioned in PGL4, SDHB variants are usually malignant and have a worse prognosis. 39-41

The findings usually correspond to one of the following cases: mass effect, hypersecretion of catecholamines, incidental asymptomatic or asymptomatic in a carrier of a pathogenic variant.[1,31,42]

Diagnosis

Due to their catecholamine-secreting characteristic, all paragangliomas should be tested for hypersecretion in 24-h urine or serum collection, even in those without clinical suspicion. That said, the diagnosis of secretory paraganglioma is made through measurements of urinary or plasma fractionated metanephrines and catecholamines.

Secretors

In general, there is still no consensus in the literature on the best test for diagnosing paraganglioma. As a rule, except for MEN2-related tumors that secrete epinephrine, most tumors are norepinephrine-secreting.

For tumor location, the biochemical test should be followed by radiological evaluation, CT or MRI, investigating according to the predilection of the tumor location mentioned in "presentation". It should be noted that MRI can distinguish paragangliomas from other masses, and CT misses up to 1/4 of the tumors related to MEN2 syndrome. After these processes, a cross-sectional image of the thorax/head and neck is justified in the face of previous images with negative results. It is followed with radioisotope imaging if it remains negative. It is noteworthy that radioisotope imaging is also justified as a screening for metastatic disease in patients with high probabilities of malignant tumors.

Conventional PET imaging is considered to have a high degree of sensitivity, being an interesting choice both in primary tumors and in metastases.[43,44] With the emergence of somatostatin analogues and positron-emitting radiomarkers, it is possible to combine with CT-integrated PET; 2 examples are gallium Ga-68 DOTATATE and gallium Ga-68 DOTATOC, which can improve the detection and staging of neuroendocrine tumors, including paraganglioma.[45-47]

It should be noted that for surgical planning, or even clinical decision, fine-needle biopsy is contraindicated for any type of catecholamine-secreting tumor; therefore, it is contraindicated for the vast majority of paragangliomas.[48]

Non-secretors

Of the paragangliomas that course with mass effect, the following cases will be highlighted:

1) Tumors of the carotid body: As a rule, they are painless masses, with a rubbery appearance, being more mobile horizontally than vertically, characterizing Fontaine's sign. They show a gradual increase. It can also present as a pulsatile mass and with carotid murmur. They displace the posterolateral common carotid bifurcation of the internal carotid.[49]

2) Julgulotimpanic paragangliomas: Also slow-growing, they culminate in conductive hearing loss, or pulsatile tinnitus. In addition, there may be deficits of the lower cranial nerves, with greater impairment of the easy nerve. Also, during the physical examination, a bluish pulsating mass may be visible behind the tympanic membrane.[49]

3) Vagal paragangliomas: It can occur at any point of the cervical vagus nerve, usually appear in the inferior nodosum ganglion. They displace the internal and external carotid artery anteriorly and cause erosion and enlargement of the jugular foramen. Thus, there can be several symptoms, including facial drooping, cranial nerve deficits or even Horner's syndrome.[50]

It is worth remembering that paragangliomas in the dura mater can course with neurological compression.

Considering diagnostic tests, ultrasonography or cross-sectional CT or MRI images are included in the initial evaluation of skull base and neck paragangliomas. In a carotid body tumor, US demonstrates a solid, well-defined, hypoechoic tumor with enlargement of the carotid bifurcation.[51,52]

On CT, the classic findings of paraganglioma demonstrate a homogeneous mass with non-contrast-enhanced Hounsfield units in the range of 40 to 50, in addition to cystic changes, necrosis, and internal calcifications in many cases.[1] That said, CT is the best initial imaging test when julgulotimpanic paraganglioma is suspected, due to its better method of evaluating the destruction of the temporal bone in its extension. It contributes to the Fisch classification at the stage, although the studies do not present consensus on staging systems, they are important in the choice of surgical approach.

Regarding the use of contrast, it should be noted that all patients must have a negative biochemical result for hypersecretion of catecholamines or undergo alpha blockade before receiving ionic contrast, in order to avoid catecholamine crisis. The use of nonionic contrast is considered safe.[53,54]

Regarding gadolinium MRI, it provides a greater definition of the relationship between paragangliomas and adjacent vascular structures, and is recommended in some guidelines.[55] It is considered complementary to CT in julgulotalamic patients, with the objective of detecting dural infiltration and intradural tumor growth. In addition, it is also the test of choice in children and pregnant women or in those allergic to CT contrast.

Paragangliomas in children

Considering the limitation of experiments and studies on paragangliomas in children, the data are mixed with the adult literature. However, it is feasible to discuss this topic with some recent data.

Again, the cellular similarity between the paraganglioma and pheochromocytoma phenotypes is mentioned, which, when considered together, represent 0.^{3} cases per million per year, with approximately 20% of these diagnoses in childhood. When the research in hypertensive children is isolated, the incidence varies from 0.^{8} to 1.7%. Another worrying fact occurs when compared to adults; smaller patients are more likely to have malignant and multicentric tumors, in addition to greater link with genetic factors. Even if up to 2/3 have no family history of disease, up to 56% have germline pathogenic variants of the genesRET, VHL, SDHD, SDHB, SDHC, SDHAF2 or SDHA, as well as TMEM127 or MAX.

Regarding malignancy, a causal factor is not yet well established. However, 2 studies reported that almost 50% of the children had malignant/metastatic disease[56,57], compared to approximately 30% in adults.[56,57] The increased rate of malignancy among children was debated in one study, being explained by their higher rate of pathogenic cluster 1 variants, especially SDHB and VHL.[57]

CONCLUSION

Paragangliomas have a complex combination of genetic and environmental factors that influence their presentation and prognosis. Early identification of genetic mutations can guide clinical management, especially in cases with a higher risk of malignancy. Advances in the understanding of pathophysiology, including the role of HIF, may result in new therapeutic approaches. In the neurosurgical context, adequate planning for the resection of highly vascularized tumors remains a challenge, reinforcing the importance of a multidisciplinary approach.

Authors' contributions

Luiz Henrique Perszel: Formal analysis, Methodology
Viviane Aline Buffon: Conceptualization, Investigação
Milton Manrique Rastelli Junior: Data curation, Writing – original draft
Giovana Nascimento Antocheviez: Conceptualization, Investigação
Ricardo Silva dos Santos: Project administration
Joel Lavinsky: Data curation, Writing – original draft
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