Pheochromocytoma and paraganglioma in children and adolescents

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INTRODUCTION

Pheochromocytoma (PPC) and paraganglioma (PGL) are the tumors that rarely occur in the pediatric population (PPGL). Both originate from chromaffin cells, pheochromocytoma is localized in the adrenal gland, whereas paragangliomas are regarded as the tumors present in other localizations, from head to the pelvis. The clinical image is characterized by the presence of the sustained hypertension, headaches, sweating, palpitations. The symptoms are caused by the catecholamine secretion or are related to tumor mass pressure on different organs. The catecholamines and their metabolites levels in urine collection or plasma are necessary for further evaluation of the diagnosis. In pediatric population the tumors occur in multiple familial syndromes such as Multiple Endocrine type 2, Neurofibromatosis type 1, Von Hippel-Lindau syndrome, Familial Paraganglioma syndrome are related to specific mutations (SDHx, RET, VHL, NF1) leading to the characteristic phenotype. The radiological and nuclear imaging are an important part of the examination. Although CT and MR are reported to have overall good sensitivity for the tumor detection, further analysis with nuclear imaging is recommended for the specified diagnosis. Right now 68GA-DOTATATE is regarded as the tracer of choice, leading to the complex evaluation of diagnosis, treatment and lifetime surveillance (Shah MH et al., 2021). The catecholamine production contributes to the symptoms and clinical image of the PPGL, leading to the occurrence of hypertension, excessive sweating, palpitations, headaches and abdomen pains (Eisenhofer et al., 2022). Around 0.5–1.7% of pediatric hypertension is the implication of the PPGL (Ross et al., 2000; Yen & Lodish, 2021; Barontini et al., 2006). 50-80% of the tumors present in the pediatric population are showing the germline mutations in the known genes, including VHL, RET, SDHx, MAX, NF1, HIF2 presenting the phenotype characteristic for various familial syndromes (Park et al., 2021; Shah et al., 2021; De Tersant et al., 2020). Due to the high incidence of the mutations in pediatric PPGL population, the tumors tend to be more aggressive and metastatic, which should lead to the complex evaluation of diagnosis, treatment and lifetime surveillance (Shah et al., 2021).

CLINICAL IMAGE

The clinical image of pheochromocytoma and paraganglioma depends predominantly on the catecholamine secretion. As the tumors present in the pediatric population are highly related to the germline mutations, leading to the metastatic, multifocal and aggressive disease, the majority of the pediatric patients – 90% show the symptoms of the illness (Kuo et al., 2022). The most common symptom is the sustained hypertension, which, in rare and severe cases can lead to the encephalopathy, cardiomyopathy, hypertensive crisis and cardiac failure (Edmonds et al., 2011; Armstrong et al., 2008). The paroxysmal hypertension is less frequent in children comparing to adults (Kuo et al., 2022; Jain et al., 2020; Edmonds et al., 2011; Ben-Skowronek & Kozaczuk, 2015). It is reported that there is no direct correlation between the catecholamine level and the severity of hypertension (Havekes et al., 2009; Bravo & Tagle, 2003). The triad of symptoms is characteristic in various localizations of the body, from head to the pelvis (Park et al., 2021; Ross et al., 2000). Around 33% of tumors are located in the adrenal glands, and the rest are found in the other body regions (Pamporaki C et al., 2017). The tumors produce and most of them (70%) release catecholamines such as epinephrine and norepinephrine and their metabolites, metanephrines and normetanephrines. Head and neck paragangliomas are mostly biochemically silent, however they can produce dopamine (Shah MH et al., 2021). The catecholamine production contributes to the symptoms and clinical image of the PPGL, leading to the occurrence of hypertension, excessive sweating, palpitations, headaches and abdomen pains (Eisenhofer et al., 2022). Around 0.5–1.7% of pediatric hypertension is the implication of the PPGL (Ross et al., 2000; Yen & Lodish, 2021; Barontini et al., 2006).

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Abbreviations: CT, computed tomography; F-DOPA, 6,18F-fluoro-L-3,4-dihydroxyphenylalanine; HU, Hounsfield unit; MEN 2, Multiple Endocrine; MR, magnetic resonance; Neoplasia type 2; NF 1, Neurofibromatosis Type 1; PET/CT, pet ct positron emission tomography; PGL, paraganglioma; PPC, pheochromocytoma; PZS, Pacak Zhuang syndrome; VHL, von Hippel-Lindau.
symptoms typical for the pediatric population includes: palpitations (53%), excessive sweating and headaches (39–95%) (Jain et al., 2020; Kuo et al., 2022). Other frequently and less commonly occurring symptoms of the tumor presence include the disturbances in vision, diarrhea, orthostatic hypotension, nausea, flushing, pallor, behavioral and psychiatric changes. The tumor can also be found incidentally in the radiological work-up or due to the mass-related symptoms e.g. abdomen pain, back pain, loss of weight and constipation (Jain et al., 2020; Edmonds et al., 2011). Pheochromocytoma and Paraganglioma can be present in various familial syndrome including Von Hippel-Lindau syndrome, Multiple Endocrine Neoplasia type 2 syndrome, Neurofibromatosis type 1 syndrome and Familial Paraganglioma syndrome, so that once the syndrome is diagnosed or suspected, the patient should be under the specialist care for tumor evaluation (Edmonds et al., 2011; Fargette et al., 2023). The VHL syndrome is characteristic for the occurrence of various tumors, in pediatric population especially PPGLs and hemangioblastomas which can remain silent until presence of serious symptoms as a result of a tumor mass pressure on organs (Rednam et al., 2017; Ben-Skowronek & Kozaczuk, 2015). In neurofibromatosis, the clinical image develops with children’s age and the most common features include cafe-au-lait spots, freckles of auxiliary and inguinal regions, plexiform neuromas and marfanoid habitus (Van Treijen et al., 2019). Familial Paraganglioma syndrome is the result of hereditary susceptibility genes: VHL, SDHX, RET, and NFI, pediatric PPGLs are frequently found to possess a genetic cause. Genes encoding for pseudohyoxia in cluster 1 are organized to cluster 1A with TCA-cycle genes, along with the SDHX genes, and cluster 1B associated with hypoxia signaling, primarily VHL and EPAS1. Cluster 2 is where the other two crucial genetic causes of pediatric PPGL, RET and NFI associated with kinase signaling are located (Crona et al., 2017; Nolting et al., 2022). Genetic abnormalities underlying PPGL are all inherited in autosomal dominant patterns, but with the risk of increased PPGL susceptibility in case of paternal inheritance as a result of pathogenic variants of SDHD (including SDHAF2 and M.AX). Nevertheless, identification of SDHD variants inherited from the mother is implicated for screening of the relatives and further generations. Although genealogical records of PPGL are often present in pediatric patients with PPGL, the lack of genealogical record should not restrain clinicians from referring for genetic counseling and testing, as the feasibility of de novo mutations must be contemplated. With no exception, genetic counseling and evaluation are encouraged in all patients with PPGL.

**Succinate Dehydrogenase Subunit Defects (SDHD)**

PPGLs were reported to harbor mutations in four subunits of SDHD and assembly factor gene SDHAF2. Mutations in SDHB on chromosome 1p36.13 were proved to be responsible for metastatic PPGL. In the study of King and others 71.9% patients who were younger than 20 years had a germline mutation in SDHB (King et al., 2011). The risk of a metastatic disease for SDHB carriers with PPGL is noted about 31–70% (Rijken et al., 2018). Other authors reported that 70% children with PPGL had metastases at a median age of 16. SDHC on chromosome 1q23.3 and SDHA on chromosome 5p15.33 are less common in PPGLs with a percentage of 8.3 and 1.7, respectively (Benn et al., 2018). Nonetheless, the metastatic risk is higher in SDHA in 30–60% but in SDHC it is very low (Nolting et al., 2022; Bausch et al., 2014). SDHC and SDHD are present in

**BIOCHEMICAL TESTING**

As the pheochromocytomas and paragangliomas can secrete catecholamines and their metabolites e.g. methanephines and normethanephines, the laboratory 24-hours urine or plasma collection need to be undertaken to evaluate the diagnosis. Before the beginning of the laboratory tests, the patient should be prepared for the sample taking, which means going off the drugs and dietary products that would impact the catecholamine production or that would influence the methods of its detection. The products that must be avoided are bananas, cheese, nuts, tomatoes, alcohol, disulfiram, metronidazole, paracetamol, amoxicillin, methenamine, urapidil, L-dopa and others (Corcuff et al., 2017; Shah et al., 2021). As well the stress should be avoided before the sample taking and the blood tests should be undertaken while patient is laying as it is reported that sitting position can alter the level of blood metanephrines (Lenders & Eisenhofer, 2017; Seamon & Yamaguchi, 2021). It is reported that measurements taken from the plasma samples show higher sensitivity than from the urine collection (Lenders & Eisenhofer, 2017). The results of plasma level metanephrines 2 times more than the upper normal limit is considered to result in PPGL diagnosis (Lenders & Eisenhofer, 2017, Eisenhofer et al., 2023). Shah MH et al. consider the diagnosis while the metanephrines level is 3 times upper than the cut-off value (Shah et al., 2021). The SDHB pathogenic variant carriers can show lack of elevation of catecholamines, while increased level of 3-methoxytyramine can be useful to assess the metastatic disease (Lenders & Eisenhofer, 2017).

**GENETICS**

Owing to germline mutation in one of the subsequent susceptibility genes: VHL, SDHX, RET, and NFI, pediatric PPGLs are frequently found to possess a genetic cause. Genes encoding for pseudohyoxia in cluster 1 are organized to cluster 1A with TCA-cycle genes, along with the SDHX genes, and cluster 1B associated with hypoxia signaling, primarily VHL and EPAS1. Cluster 2 is where the other two crucial genetic causes of pediatric PPGL, RET and NFI associated with kinase signaling are located (Crona et al., 2017; Nolting et al., 2022). Genetic abnormalities underlying PPGL are all inherited in autosomal dominant patterns, but with the risk of increased PPGL susceptibility in case of paternal inheritance as a result of pathogenic variants of SDHD (including SDHAF2 and M.AX). Nevertheless, identification of SDHD variants inherited from the mother is implicated for screening of the relatives and further generations. Although genealogical records of PPGL are often present in pediatric patients with PPGL, the lack of genealogical record should not restrain clinicians from referring for genetic counseling and testing, as the feasibility of de novo mutations must be contemplated. With no exception, genetic counseling and evaluation are encouraged in all patients with PPGL.
head and neck PGLs (Read et al., 2021). In accordance with the international guidelines for PPGILs in asymptomatic SDHA, SDHB, SDHC and paternally-inherited SDHD variants screening should be conducted (Amar et al., 2021). Pediatric patients with SDHB carriers screening is worth doing at the age of 6–10 years old and at 10–15 years old in cases of other mutations. The tumor size plays an essential role in the prognosis. Patients with tumor’s diameter less than 5 cm developed metasteses within 7 years post the primary treatment, while patients with larger tumors show metastatic spread within 2 years. (Jochmanova et al., 2020). It has been reported that mutations in SDHD on chromosome 11q23.1 show higher penetrance than in SDHB and autosomal dominant inheritance pattern is modified by maternal imprinting, hence the disease is frequently inherited from the paternal allele (Bayley et al., 2020).

**Von Hippel-Lindau Syndrome (VHL)**

VHL syndrome is a consequence of pathogenic variants in VHL located on chromosome 3p25.3. Owing to the loss of tumor suppressor gene function that encoded for an E3 ubiquitin ligase decaying HIF-2a, VHL, a cluster 1B gene, is linked to noradrenergic biochemical phenotype. About 10-25% individuals with VHL develop PPC, with sympathetic and parasympathetic PGLs occurring less commonly, bearing metastatic risk of 5–8%. It has been proved that VHL is the cause of PGLs in children and it develops at the age of 11–12. Every fifth patients will possess de novo mutation. What is worth noticing is that the rate of de novo mutation has been found to be significantly higher in PGIL patients representing an overall rate of 60% and 50% for the pediatric group; the sample size was accredited by the researchers. (Cascon et al., 2013; Rednam et al., 2017). The earliest onset of PGIL occurs in patients between the age of 11–12 on average.

**EPAS1 Gain-of-Function Syndrome**

Pacak Zhuang syndrome (PZS) characterized by polycythemia, PPGL, and duodenal somatostatinoma is the noteworthy exception for the generally established rule of germline susceptibility; it was initially discerned in two female patients with congenital polycythemia and PPGL in the adolescence. Post-zygotic somatic mutation in the gene encoding for the transcription factor HIF-2a (the EPAS1 gene located on chromosome 2p21) can lead to PZS which is hardly ever related to germline inheritance (Zhuang et al., 2012; Lorenzo et al., 2013). PGILs were occurring repeatedly in all patients and almost 30% of them had metastatic disease, which was indicated in a study of 7 patients with PZS (Darr et al., 2016). Hence, those cases are a profound driving factor in favor of somatic, as well as germline, genetic testing when patient tumor tissue is inaccessible. Not only may it provide information about the etiological factors, but also it may improve omnipresent understanding of related formidable clinical characteristics and risk of “multiplicity, recurrence, and malignancy”.

**Neurofibromatosis Type 1**

The underlining factor of neurofibromatosis type 1 is mutation in the NF1 gene that encodes for neurofibrin placed on chromosome 17q11.2. NF1, a tumor suppressor in cluster 2, inhibits the RAS-MAPK signaling pathway. National Institutes of Health established the clinical diagnostic criteria for NF1 (Gutmann et al., 2017). Interestingly, up to 50% patients with NF 1 arise de novo, which is why the absence of a family history should not preclude NF1 from the differential diagnosis in the presence of suggestive clinical findings. Pheochromocytomas occur in patients with NF1 in 0.1 to 5.7%, yet in 3.3 to 13% on autopsy (Ploquin et al., 2001). Kepenekian and others (Kepenekian et al., 2016) identified pheochromocytoma in 7.7% adult patients with NF1 presenting no symptoms. The adrenal disease presents most commonly unilaterally (in 78–84%), with bilateral disease reported in 9.6 to 16.6% of patients with pheochromocytoma (Al-Shareef et al., 2019). Metastatic PCC was mainly noted in adults in 11.5% (Jiang et al., 2020). Fortunately PPGL in children with NF1 is less frequent (1–3%) (Pamporaki et al., 2017).

**Multiple Endocrine Neoplasia Type 2 (MEN-2)**

MEN-2A is associated with pheochromocytoma in 57% and other diseases such as medullary thyroid cancer or hyperparathyroidism. MEN-2B is only in 5% of MEN-2 and is linked to pheochromocytoma in 50% and aggressive medullary thyroid cancer, mucosal neuromas and a marfanoid habitus (Moriaiti et al., 2014). The risk of metastases in pheochromocytoma is less than 5% (Nolting et al., 2022).

**RADIOLOGICAL AND NUCLEAR DIAGNOSTIC WORK UP**

**Computed Tomography (CT) and Magnetic Resonance**

Although the computer tomography is an easily accessible diagnostic method, with no specific preparation needed before the examination and short time of the imaging test, it is not considered as the best diagnostic method for children’s PPGL tumors detection, as it leads to the radiation absorption. In children, MR is preferred for the initial diagnostic pathway as it is a safer method. Both methods are good in imaging tumors, including incidentalomas and differentiating them between benign tumors like adenoma or PPGLs (Carraquillo et al., 2021). Adenomas on CT show the attenuation value of 10 HU, while pheochromocytomas around 50–60 HU (Carraquillo et al., 2021; Fstrugia et al. 2019). The MR examination is important, as it can show the vascularization of the big tumors which is necessary to be determined before further evaluation (Farrugia & Charalampopoulos, 2019). Nevertheless, Havekes et al. report that as much as MR sensitivity is high for tumor detection, its specificity for the PPGLs is not enough and further nuclear imaging is recommended (Havekes et al., 2009).

**Somatostatin receptor-based PET/CT**

68GA-DOTATATE (68Ga-DOTA(0)-Tyr(3)-octreotate)

A radiotracer composed of hormone peptide and 68Ga positron emitter, targeting the somatostatin receptors. It has a 68-minutes half-life period and can accumulate in every tissue providing the entire body scan. It is used in PPGL/PCC detection due to the high level of somatostatin receptors expression in PCC/PPGL (Rees et al., 2023; Jaiswal et al., 2021). The Substance can also it may improve omnipresent understanding of related formidable clinical characteristics and risk of “multiplicity, recurrence, and malignancy”.

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adult population as it is reported that patients with sporadic and SDHx-related paragangliomas indicate higher number of lesions found by Ga-DOTATATE PET CT compared to F-FDG PET CT and CECT/MRI (Jaiswal et al., 2021; Jha et al., 2012). Jaiswal and others reported that it has a better sensitivity for both primary and metastatic lesions, as well as for VHL-associated lesions not detected by CECT in pediatric population (Jaiswal et al., 2021). Also it has a higher susceptibility for head and neck paragangliomas, which are difficult to be found as they are not biochemically active (Carrasquillo et al., 2021; Yen & Lodish, 2021). 68GA-DOTATATE is a tracer of choice in any situation stated above (Janssen et al., 2016).

CU-DOTATATE

Another target for somatostatin receptors, with a higher half-life period and similar sensitivity to 68GA-DOTATATE, however not yet approved in the paediatric population (Rees et al., 2023; Yen & Lodish, 2021).

18FDG PET/CT (18fluorodeoxyglucose)

Before the diagnostic work up patient should not be given glucose or any fluid containing glucose intravenously for 6 hours prior to the examination, no food should be administered orally as it interferes with the radiotracer and can lead to false positive results (Rees et al., 2023). The F-FDG is better in detecting metastatic PCC/PGL than MIBG, but has a lower sensitivity than 68GA-DOTATATE, for benign tumors its sensitivity is similar/lower than MIBG (Carrasquillo et al., 2021; Jaiswal et al., 2021). 18FDG PET/CT has a higher detection for the tumors with SDHx pathogenic variant comparing to the SDHx negative tumors, however still lower than 68GA-DOTATATE (Carrasquillo et al., 2021).

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A guanethidine analog, the compound is structurally similar to noradrenaline, binds with noradrenaline transporters and accumulates in adrenergic tissues (Carrasquillo et al., 2021; Rufini et al., 2008). Prior to the examination, the uptake of potassium iodate is mandatory for thyroid blockade, also interfering medications including anti-arrhythmic, beta-, adrenergic-, calcium-blockers, vasoconstrictors and others should be gone off before the diagnostic work up (Rees et al., 2023; Jacobson & Travin, 2015). The I-MIBG has a significantly high detection rate for non metastatic PCC/PGLG, the overall rate is higher for pheochromocytoma rather than paraganglioma. The detection of tumors with SDHx pathogenic variant is low, in general the rate of hereditary tumors discovery is low by I-MIBG (Carrasquillo et al., 2021).

F-DOPA (6-18F-fluoro-L-3,4-dihydroxyphenylalanine)

The amino acid radio tracer which was predominately and historically used to diagnose parkinsonian’s syndrome as it evaluates the dopamine synthesis (Carrasquillo et al., 2021; Darcourt et al., 2014). No preparation is needed before the tracer administration as no drugs have been claimed to disturb the radioimaging with F-DOPA (Carrasquillo et al., 2021). The tracer has a high detection rate for benign PCC/PGL and metastatic pheochromocytoma, though sensitivity for metastatic paraganglioma is low, 68GA-DOTATATE outperforms F-DOPA in the general detection rate of PCC/PGL (Carrasquillo et al., 2021). It is reported that MYC-associated factor X (MAX) pheochromocytomas show high level of F-DOPA uptake and should be considered a tracer of choice in those particular cases (Taieb et al., 2018).

TREATMENT

Before the surgery is performed the crucial role plays the cooperation of the endocrinologist, oncologist, surgeon, cardiologist and anesthesiologist. The surgical resection is the mainstay of the treatment of patient with diagnosed PPGL. The type of surgery (laparoscopy vs open access) depends on the individual assessment of patient including tumor localization, age of the patient and clinical stage of the disease. Before the surgery is performed the patient needs the hypertension evaluation e.g normalizing blood pressure, heart rate and preventing patient from excess of catecholamine secretion. Two-three weeks before surgery antihypertensive drug such as non-selective (phenoxybenzamine) α-antagonist should be administered, if this treatment is insufficient the calcium antagonists can be used as the additional drugs. It is important for the patient to be well hydrated. In case of tachycardia, after the α-blocker administration, the cardioselective β-blocker is recommended (Fang et al., 2020). The preparation for surgery in pediatric patients takes about longer as a result of lower starting dose of medications to avoid complications and increased sympathetic activity in children than in adults (Amrish et al., 2020). Laparoscopic excision is recommended, however the surgery type depends of the anesthesiological assessment before and during surgery. Open laparotomy is reserved for the patients with huge tumors or difficult to approach paragangliomas. During surgeries there is a huge risk of hypertensive crisis, myocardial ischemia, stroke, etc. (Schuler et al., 1995). Previously the mortality risk was high, nowadays it is reduced to less than 2% (Ploutin et al., 2001).

It was proved that about 70–80% of patients with PPGL have a germline or somatic mutation, so genetic testing ought to be performed in each patient with that diagnosis to guide their management and improve their clinical outcome (Jiang et al., 2020; Ochmanova et al., 2018). According to the literature germline mutations are known in 30–35% of patients and somatic mutations were found in 50% of patients (Jhwar et al., 2022). While treating patients with PPGL, the metastatic disease is still a challenge and there is no way to completely cure the disease. It is documented that about 10% to 15% of all patients with pheochromocytoma and 35–40% with paraganglioma, develop metastases (Eisenhofer et al., 2012; Patel et al., 2020). Metastasizing depends on the type of the pathogenic variant. In patients with SDHB and SDH-A-mutant PPGL, there is a high risk of metastases, about 75% (Bechmann et al., 2020; Crona et al., 2019). On the other hand, cluster 2 pathogenic variants disrupt the kinase signaling pathway and lead to their overactivation (RET, BRAF, NRAS, HRAS, MAX, NGFR) and are associated with low metastatic risk of 3–10% (Bechmann et al., 2020, Kumar et al., 2021). Cluster 3 pathogenic variants affect the Wnt signaling pathway (MAML3, CSDE1) and are rare but very aggressive with poor prognosis. Overall 5-year mortality rates is 37% but 10-year mortality rate is 29% (Alzofin et al., 2021; Nolting et al., 2022).

In this situation, novel therapeutic approaches are needed (Nolting et al., 2022; Nolting et al., 2019). Lately a lot of genetically guided therapies were investigated and used some molecular treatment in patients with met-
astastic PPGIs. (Wang et al., 2022; Lee et al., 2018; Mak et al., 2019).

CONCLUSION

Pheochromocytoma and paraganglioma in pediatric patients are rare, but should always be considered with tumor mass detected or when typical symptoms such as palpitations, syncope, sweating or headaches are happening. Genetic testing should be performed in every patient with this diagnosis, as it helps in the initial diagnostic pathway, targeted treatment, prognosis of the disease and follow up for early detection of recurrence of the disease. The main target is the radical excision of the tumor.

Patients with a hormonally active tumor are at risk of complications such as internal instabilities and pressure fluctuations. Long follow-up of a patient with PPGL is essential to avoid recurrence. It is important to monitor blood pressure and the level of catecholamines in essential hypertensive patients. Long follow-up of a patient with PPGL is necessary due to the high risk of recurrence. It helps in the initial diagnosis and follow up for early detection of recurrence of the disease. Genetic testing should be performed in every patient with this diagnosis, as it helps in the initial diagnostic pathway, targeted treatment, prognosis of the disease and follow up for early detection of recurrence of the disease.

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