ACTA ABP BIOCHIMICA POLONICA

Vol. 70, No 3/2023
487–493
https://doi.org/10.18388/abp.2020_6955

Review

Pheochromocytoma and paraganglioma in children and adolescents

Teresa Stachowicz-Stencel✉, Natalia Pasikowska and Anna Synakiewicz

Department of Pediatrics, Hematology and Oncology, Medical University of Gdansk, Gdańsk, Poland

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 patients with different mutations and metastatic disease. The treatment of choice is the tumor excision. Also, lately new therapeutic approaches including genetically targeted therapies are under investigation for more complex treatment of tumors with underlying genetic cause or metastatic disease. Long term follow-up after treatment to avoid recurrence or to detect it in early stadium must be performed.

Keywords: children, malignant tumors, paraganglioma, pheochromocytoma, treatment, young adults

Received: 31 July, 2023; revised: 31 August, 2023; accepted: 05 September, 2023; available on-line: 17 September, 2023

✉e-mail: tsten@gumed.edu.pl

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 computed tomography; PGL, paraganglioma; PPC, pheochromocytoma; PZS, Pacak Zhuang syndrome; VHL, von Hippel-Lindau

INTRODUCTION

Pheochromyctoma (PPC) and paragnaglioma (PGL) are rare tumors in the pediatric population. The prevalence is 0.2–0.5 per million of children, which constitutes only for 20% of its general incidence in the population (Ardicli *et al*., 2021; Park *et al*., 2021). They can occur at any age, however the mean age at diagnosis is reported to be 11 years old, with male predominance (Ross *et al*., 2000; Havekes *et al*., 2009). Pheochromocytoma and paraganglioma are the neuroendocrine tumors originating from chromaffin cells which form the adrenal medulla. Tumors located in the adrenal medulla are regarded as pheochromocytomas. The chromaffin cells can also be present extramedullary around sympathetic and parasympathetic ganglia, resulting in the formation of paragnagliomas 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%) relsease 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). 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 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 specialistic 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 neurofibromas and gliomas of optic nerves, pheochromocytoma occurs rarely, nonetheless the patients should be under observation (Edmonds *et al*., 2011; Miller *et al*., 2019). Familial Paraganglioma syndrome is the result of the *SDHx* pathogenic variants, according to Chetty *et al*. it is reported that patients with *SDHA* pathogenic variants do not develop paragangliomas (Chetty *et al*., 2010), however Nölting and others proves that paragangliomas can be present in this pathogenic variant (Nolting S *et al*., 2022; Bausch B *et al*., 2014). In SDHB pathogenic variants the tumors are solitary, in various localizations including abdomen, pelvis, retroperitoneum; less common in mediastinum and head/neck, and they tend to metastasize. Up to 70% of patients with *SDHB* mutations can show metastases. Most commonly metastases can be found in bones, lymph nodes, liver and lungs (Kuo *et al*., 2022). *SDHD* and *SDHC* pathogenic variants carriers show incidence in presence of tumors in the head and neck localization, but *SDHD* pathogenic variant carriers can show multiple tumor presence, whereas SDHC carriers solitary tumor (Chetty *et al*., 2010). The patients with head and neck paragangliomas are mostly asymptomatic, while tumors in other localization show typical symptoms (Işik *et al*. 2006). Multiple Endocrine Neoplasia type 2 syndrome is divided in type 2A and type 2B. Type A is associated with C-cell hyperplasia or medullary thyroid cancer, phechromocytoma and hyperparathyroidism, while type B is associated with higher prevalence of C-cell hyperplasia or medullary thyroid cancer than type A, pheochromocytoma, mucosal neuromas and marfanoid habitus (Van Treijen *et al*., 2022).

BIOCHEMICAL TESTING

As the pheochromocytomas and paragangliomas can secrete catecholamines and their metabolites eg. methanephrines and normethanephrines, 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-metoxythyramine 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 pseudohypoxia 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 undermining 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 *MAX*). 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

head and neck PGLs (Read *et al*., 2021). In accordance with the international guidelines for PPGLs 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 metastases 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 PPGL 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 PPGL 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 PGL in the adolescence. Post-zygotic somatic mutation in the gene encoding for the transcription factor HIF-2 ALFA (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). PGLs 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 undermining factor of neurofibromatosis type 1 is mutation in the *NF1* gene that encodes for neurofibromin 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 (Plouin *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-Sharefi *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 (Moriaitis *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 (Carrasquillo *et al*., 2021). Adenomas on CT show the attenuation value of around 10 HU, while pheochromocytomas around 50–60 HU (Carrasquillo *et al*., 2021; Fsrrugia *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 be easily administered to the patient as no preparation is needed before the examination (unless the anesthesia in pediatric population is necessary, then 6 hours prior to examination food/fluids uptake is forbidden) (Rees *et al*., 2023). It is used in paraganglioma diagnostic work up in

adult population as it is reported that patients with sporadic and *SDHx*-related paraganglioma 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*., 2018). 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 susceptability 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/PGGL 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).

131/123 I-MIBG

A guanethidine analog, the compound is structurally similar to norepinephrine, binds with norepinephrine 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-arrhtyhmics, 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 PPC/PPGL, 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 predominantly and historically used to diagnose parkinsonian's syndromes 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/PGGL and metastatic pheochromocytoma, though sensitivity for metastatic paraganglioma is low, 68GA-DOTATATE outperforms F-DOPA in the general detection rate of PCC/PGGL(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 (Taïeb *et al*., 2018).

TREATMENT

Before the surgery is performed the crucial role plays the cooperation of the endocrinologist, oncologist, surgeon, cardiologist and anasthesiologist. 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 indivudual assesment of patient including tumor loclization, 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-antagnoist should be administered, if this treatment is insufficient the calcium antagonists can be used as the additional drugs. It is imporatant 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 anasthesiological assesment before and during surgery. Open laparotomy is reserved for the patients with huge tumors orr difficult to approach paragangliomas. During surgeries there is a huge risk of hypertensive crisis, myocardial ischemia, stroke, etc. (Schutler *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 *SDHA*-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, NF1, 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, CSDE 1*) 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-

astatic PPGls. (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 hypertension, palpitations, 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 treatment 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 the urine collection as well as radiological imaging tests in case of clinical symptoms or catecholamine increase. For patients with certain mutations (*SDHD* and *VHL*) where there is a risk of recurrence, there is a need for frequent and long-term monitoring.

REFERENCES

Al-Sharefi A, Javaid U, Perros P, Ealing J, Truran P, Nag S, Kamaruddin S, Abouglila K, Cains F, Lewis L, James RA (2019) Clinical presentation and outcomes of phaeochromocytomas/paragangliomas in neurofibromatosis type 1. *Eur Endocrinol* **15**: 95–100. https://doi.org/10.17925/EE.2019.15.2.95

Alzofon N, Koc K, Panwell K, Pozdeyev N, Marshall CB, Albuja-Cruz M, Raeburn CD, Nathanson KL, Cohen DL, Wierman ME, Kiseljak-Vassiliades K, Fishbein L (2021) Mastermind Like transcriptional coactivator 3 (MAML3) drives neuroendocrine tumor progression. *Mol Cancer Res* **19**: 1476–1485. https://doi.org/10.1158/1541-7786.MCR-20-0992

Amar L, Pacak K, Steichen O, Akker SA, Aylwin SJB, Baudin E, Buffet A, Burnichon N, Clifton-Bligh RJ, Dahia PLM, Fassnacht M, Grossman AB, Herman P, Hicks RJ, Januszewicz A, Jimenez C, Kunst HPM, Lewis D, Mannelli M, Naruse M, Robledo M, Taïeb D, Taylor DR, Timmers HJLM, Treglia G, Tufton N, Young WF, Lenders JWM, Gimenez-Roqueplo AP, Lussey-Lepoutre C (2021) International consensus on initial screening and follow-up of asymptomatic SDHx mutation carriers. *Nat Rev Endocrinol* **17**: 435–444. https://doi.org/10.1038/s41574-021-00492-3

Ardicli B, User IR, Ciftci AÖ, Akyuz C, Kutluk MT, Gonc N, Ozon ZA, Alikasifoglu A, Oguz B, Haliloğlu M, Orhan D, Tanyel FC, Karnak I, Ekinci S (2021) Approach to pheochromocytoma and paraganglioma in children and adolescents: A retrospective clinical study from a tertiary care center. *J Pediatr Urol* **17**: 400.e1–400.e7. https://doi.org/10.1016/j.jpurol.2021.01.043

Armstrong R, Sridhar M, Greenhalgh KL, Howell L, Jones C, Landes C, McPartland JL, Moores C, Losty PD, Didi M (2008) Phaeochromocytoma in children. *Arch Dis Child* **93**: 899–904. https://doi.org/10.1136/adc.2008.139121

Barontini M, Levin G, Sanso G (2006) Characteristics of pheochromocytoma in a 4- to 20-year-old population. *Ann N Y Acad Sci* **1073**: 30–37. https://doi.org/10.1196/annals.1353.003

Bausch B, Wellner U, Bausch D, Schiavi F, Barontini M, Sanso G, Walz MK, Peczkowska M, Weryha G, Dall'igna P, Cecchetto G, Bisogno G, Moeller LC, Bockenhauer D, Patocs A, Rácz K, Zabolotnyi D, Yaremchuk S, Dzivite-Krisane I, Castinetti F, Taieb D, Malinoc A, von Dobschuetz E, Roessler J, Schmid KW, Opocher G, Eng C, Neumann HP (2014) Long-term prognosis of patients with pediatric pheochromocytoma. *Endocr Relat Cancer* **21**: 17–25. https://doi.org/10.1530/ERC-13-0415

Bayley JP, Bausch B, Rijken JA, van Hulsteijn LT, Jansen JC, Ascher D, Pires DEV, Hes FJ, Hensen EF, Corssmit EPM, Devilee P, Neumann HPH (2020) Variant type is associated with disease characteristics in SDHB, SDHC and SDHD-linked phaeochromocytoma–paraganglioma. *J Med Genet* **57**: 96–103. https://doi.org/10.1136/jmedgenet-2019-106214

Bechmann N, Moskopp ML, Ullrich M, Calsina B, Wallace PW, Richter S, Friedemann M, Langton K, Fliedner SMJ, Timmers HJLM, Nölting S, Beuschlein F, Fassnacht M, Prejbisz A, Pacak K, Ghayee HK, Bornstein SR, Dieterich P, Pietzsch J, Wielockx B, Robledo M, Qin N, Eisenhofer G (2020) HIF2α supports pro-metastatic behavior in pheochromocytomas/paragangliomas. *Endocr Relat Cancer* **27**: 625–640. https://doi.org/10.1530/ERC-20-0205

Benn DE, Zhu Y, Andrews KA, Wilding M, Duncan EL, Dwight T, Tothill RW, Burgess J, Crook A, Gill AJ, Hicks RJ, Kim E, Luxford C, Marfan H, Richardson AL, Robinson B, Schlosberg A, Susman R, Tacon L, Trainer A, Tucker K, Maher ER, Field M, Clifton-Bligh RJ (2018) Bayesian approach to determining penetrance of pathogenic SDH variants. *J Med Genet* **55**: 729–734. https://doi.org/10.1136/jmedgenet-2018-105427

Ben-Skowronek I, Kozaczuk S (2015) Von Hippel-Lindau Syndrome. *Horm Res Paediatr* **84**: 145–152. https://doi.org/10.1159/000431323

Bravo EL, Tagle R (2003) Pheochromocytoma: state-of-the-art and future prospects. *Endocr Rev* **24**: 539–553. https://doi.org/10.1210/er.2002-0013

Carrasquillo JA, Chen CC, Jha A, Ling A, Lin FI, Pryma DA, Pacak K (2021) Imaging of pheochromocytoma and paraganglioma. *J Nucl Med* **62**: 1033–1042. https://doi.org/10.2967/jnumed.120.259689

Cascón A, Inglada-Pérez L, Comino-Méndez I, de Cubas AA, Letón R, Mora J, Marazuela M, Galofré JC, Quesada-Charneco M, Robledo M (2013) Genetics of pheochromocytoma and paraganglioma in Spanish pediatric patients. *Endocr Relat Cancer* **20**: L1–L6. https://doi.org/10.1530/ERC-12-0339

Chetty R (2010) Familial paraganglioma syndromes. *J Clini Pathol* **63**: 488–491. https://doi.org/10.1136/jcp.2010.076257

Corcuff JB, Chardon L, El Hajji Ridah I, Brossaud J (2017) Urinary sampling for 5HIAA and metanephrines determination: revisiting the recommendations. *Endocr Connect* **6**: R87–R98. https://doi.org/10.1530/EC-17-0071

Crona J, Lamarca A, Ghosal S, Welin S, Skogseid B, Pacak K (2019) Genotype–phenotype correlations in pheochromocytoma and paraganglioma: a systematic review and individual patient meta-analysis. *Endocr Relat Cancer* **26**: 539–550. https://doi.org/10.1530/ERC-19-0024

Crona J, Taïeb D, Pacak K (2017) New perspectives on pheochromocytoma and paraganglioma: toward a molecular classification. *Endocr Rev* **38**: 489–515. https://doi.org/10.1210/er.2017-00062

Darcourt J, Schiazza A, Sapin N, Dufour M, Ouvrier MJ, Benisvy D, Fontana X, Koulibaly P (2014) 18F-FDOPA PET for the diagnosis of parkinsonian syndromes. *Q J Nucl Med Mol Imaging* **58**: 355–365. PMID: 25366711

Därr R, Nambuba J, Del Rivero J, Janssen I, Merino M, Todorovic M, Balint B, Jochmanova I, Prchal JT, Lechan RM, Tischler AS, Popovic V, Miljic D, Adams KT, Prall FR, Ling A, Golomb MR, Ferguson M, Nilubol N, Chen CC, Chew E, Taïeb D, Stratakis CA, Fojo T, Yang C, Kebebew E, Zhuang Z, Pacak K (2016) Novel insights into the polycythemia–paraganglioma–somatostatinoma syndrome. *Endocr Relat Cancer* **23**: 899–908. https://doi.org/10.1530/ERC-16-0231

Edmonds S, Fein DM, Gurtman A (2011) Pheochromocytoma. *Pediatr Rev* **32**: 308–310. https://doi.org/10.1542/pir.32-7-308

Eisenhofer G, Lenders JW, Siegert G, Bornstein SR, Friberg P, Milosevic D, Mannelli M, Linehan WM, Adams K, Timmers HJ, Pacak K (2012) Plasma methoxytyramine: A novel biomarker of metastatic pheochromocytoma and paraganglioma in relation to established risk factors of tumour size, location and SDHB mutation status. *Eur J Cancer* **48**: 1739–1749. https://doi.org/10.1016/j.ejca.2011.07.016

Eisenhofer G, Pamporaki C, Lenders JWM (2023) Biochemical Assessment of Pheochromocytoma and Paraganglioma. *Endocr Rev* **44**: 862–909. https://doi.org/10.1210/endrev/bnad011

Eisenhofer G, Peitzsch M, Bechmann N, Huebner A (2022) Biochemical diagnosis of catecholamine-producing tumors of childhood: neuroblastoma, pheochromocytoma and paraganglioma. *Front Endocrinol (Lausanne)* **13**: 901760 https://doi.org/10.3389/fendo.2022.901760

Fang F, Ding L, He Q, Liu M (2020) Preoperative management of pheochromocytoma and paraganglioma. *Front Endocrinol (Lausanne)* **11**: 586795. https://doi.org/10.3389/fendo.2020.586795

Fargette C, Shulkin B, Jha A, Pacak K, Taïeb D (2023) Clinical utility of nuclear imaging in the evaluation of pediatric adrenal neoplasms. *Front Oncol* **12**: 1081783. https://doi.org/10.3389/fonc.2022.1081783

Farrugia FA, Charalampopoulos A (2019) Pheochromocytoma. *Endocr Regul* **53**: 191–212. https://doi.org/10.2478/enr-2019-0020

Havekes B, Romijn JA, Eisenhofer G, Adams K, Pacak K (2009) Update on pediatric pheochromocytoma. *Pediatr Nephrol* **24**: 943–950. https://doi.org/10.1007/s00467-008-0888-9

Işik AC, Erem C, Imamoğlu M, Cinel A, Sari A, Maral G (2006) Familial paraganglioma. *Eur Arch Otorhinolaryngol* **263**: 23–31. https://doi.org/10.1007/s00405-004-0885-y

Jacobson AF, Travin MI (2015) Impact of medications on mIBG uptake, with specific attention to the heart: Comprehensive review of the literature. *J Nucl Cardiol* **22**: 980–993. https://doi.org/10.1007/s12350-015-0170-z

Jain A, Baracco R, Kapur G (2020a) Pheochromocytoma and paraganglioma – an update on diagnosis, evaluation, and management. *Pediatr Nephrol* **35**: 581–594. https://doi.org/10.1007/s00467-018-4181-2

Jaiswal SK, Sarathi V, Malhotra G, Verma P, Hira P, Badhe P, Memon SS, Barnabas R, Patil VA, Anurag, Lila R, Shah NS, Bandgar T (2021) The utility of ^{68}ga-dotatate pet/ct in localizing primary/metastatic pheochromocytoma and paraganglioma: Asian Indian experience. *Indian J Endocrinol* **25**: 410–417. https://doi.org/10.4103/ijem.ijem_307_21

Janssen I, Chen CC, Taieb D, Patronas NJ, Millo CM, Adams KT, Nambuba J, Herscovitch P, Sadowski SM, Fojo AT, Buchmann I, Kebebew E, Pacak K (2016) ^{68}Ga-DOTATATE PET/CT in the Localization of head and neck paragangliomas compared with other functional imaging modalities and CT/MRI. *J Nucl Med* **57**: 186–191. https://doi.org/10.2967/jnumed.115.161018

Jha A, Ling A, Millo C, Gupta G, Viana B, Lin FI, Herscovitch P, Adams KT, Taïeb D, Metwalli AR, Linehan WM, Brofferio A, Stratakis CA, Kebebew E, Lodish M, Civelek AC, Pacak K (2018) Superiority of 68Ga-DOTATATE over 18F-FDG and anatomic imaging in the detection of succinate dehydrogenase mutation (SDHx)-related pheochromocytoma and paraganglioma in the pediatric population. *Eur J Nucl Med Mol Imaging* **45**: 787–797. https://doi.org/10.1007/s00259-017-3896-9

Jhawar S, Arakawa Y, Kumar S, Varghese D, Kim YS, Roper N, Elloumi F, Pommier Y, Pacak K, Del Rivero J (2022) New insights on the genetics of pheochromocytoma and paraganglioma and its clinical implications. *Cancers* **14**: 594. https://doi.org/10.3390/cancers14030594

Jiang J, Zhang J, Pang Y, Bechmann N, Li M, Monteagudo M, Calsina B, Gimenez-Roqueplo AP, Nölting S, Beuschlein F, Fassnacht M, Deutschbein T, Timmers HJLM, Åkerström T, Crona J, Quinkler M, Fliedner SMJ, Liu Y, Guo J, Li X, Guo W, Hou Y, Wang C, Zhang L, Xiao Q, Liu L, Gao X, Burnichon N, Robledo M, Eisenhofer G (2020) Sino-European differences in the genetic landscape and clinical presentation of pheochromocytoma and paraganglioma. *J Clin Endocrinol Metab* **105**: 3295–3307. https://doi.org/10.1210/clinem/dgaa502

Jochmanova I, Abcede AMT, Guerrero RJS, Malong CLP, Wesley R, Huynh T, Gonzales MK, Wolf KI, Jha A, Knue M, Prodanov T, Nilubol N, Mercado-Asis LB, Stratakis CA, Pacak K (2020) Clinical characteristics and outcomes of SDHB-related pheochromocytoma and paraganglioma in children and adolescents. *J Cancer Res Clin Oncol* **146**: 1051–1063. https://doi.org/10.1007/s00432-020-03138-5

Képénékian L, Mognetti T, Lifante JC, Giraudet AL, Houzard C, Pinson S, Borson-Chazot F, Combemale P (2016) Interest of systematic screening of pheochromocytoma in patients with neurofibromatosis type 1. *Eur J Endocrinol* **175**: 335–344. https://doi.org/10.1530/EJE-16-0233

King KS, Prodanov T, Kantorovich V, Fojo T, Hewitt JK, Zacharin M, Wesley R, Lodish M, Raygada M, Gimenez-Roqueplo AP, McCormack S, Eisenhofer G, Milosevic D, Kebebew E, Stratakis CA, Pacak K (2011) Metastatic pheochromocytoma/paraganglioma related to primary tumor development in childhood or adolescence: significant link to *SDHB* mutations. *J Clin Onco* **29**: 4137–4142. https://doi.org/10.1200/JCO.2011.34.6353

Kumar S, Lila AR, Memon SS, Sarathi V, Patil VA, Menon S, Mittal N, Prakash G, Malhotra G, Shah NS, Bandgar TR (2021) Metastatic cluster 2-related pheochromocytoma/paraganglioma: a single-center experience and systematic review. *Endocr Connect* **10**: 1463–1476. https://doi.org/10.1530/EC-21-0455

Kuo, M. J. M., Nazari, M. A., Jha, A., & Pacak, K. (2022) Pediatric Metastatic Pheochromocytoma and Paraganglioma: Clinical Presentation and Diagnosis, Genetics, and Therapeutic Approaches. *Frontiers in Endocrinology*, *13*. https://doi.org/10.3389/fendo.2022.936178

Lee YT, Tan YJ, Oon CE (2018) Molecular targeted therapy: Treating cancer with specificity. *Eur J Pharmacol* **834**: 188–196. https://doi.org/10.1016/j.ejphar.2018.07.034

Lenders JWM, Eisenhofer G (2017) Update on modern management of pheochromocytoma and paraganglioma. *Endocrinol Metab (Seoul)* **32**: 152. https://doi.org/10.3803/EnM.2017.32.2.152

Lorenzo FR, Yang C, Ng Tang Fui M, Vankayalapati H, Zhuang Z, Huynh T, Grossmann M, Pacak K, Prchal JT (2013) A novel EPAS1/HIF2A germline mutation in a congenital polycythemia with paraganglioma. *J Mol Med (Berl)* **91**: 507–512. https://doi.org/10.1007/s00109-012-0967-z

Mak IYF, Hayes AR, Khoo B, Grossman A (2019) Peptide receptor radionuclide therapy as a novel treatment for metastatic and invasive phaeochromocytoma and paraganglioma. *Neuroendocrinology* **109**: 287–298. https://doi.org/10.1159/000499497

Miller DT, Freedenberg D, Schorry E, Ullrich NJ, Viskochil D, Korf BR; COUNCIL ON GENETICS; AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS (2019) Health Supervision for children with neurofibromatosis type 1. *Pediatrics* **143**: e20190660. https://doi.org/10.1542/peds.2019-0660

Moraitis AG, Martucci VL, Pacak K (2014) Genetics, diagnosis, and management of medullary thyroid carcinoma and pheochromocytoma/paraganglioma. *Endocr Pract* **20**: 176–187. https://doi.org/10.4158/EP13268.RA

Nölting S, Bechmann N, Taieb D, Beuschlein F, Fassnacht M, Kroiss M, Eisenhofer G, Grossman A, Pacak K (2022) Personalized management of pheochromocytoma and paraganglioma. *Endocr Rev* **43**: 199–239. https://doi.org/10.1210/endrev/bnab019

Nölting S, Grossman A, Pacak K (2019) Metastatic phaeochromocytoma: spinning towards more promising treatment options. *Exp Clin Endocrinol Diabetes* **127**: 117–128. https://doi.org/10.1055/a-0715-1888

Pamporaki C, Hamplova B, Peitzsch M, Prejbisz A, Beuschlein F, Timmers HJLM, Fassnacht M, Klink B, Lodish M, Stratakis CA, Huebner A, Fliedner S, Robledo M, Sinnott RO, Januszewicz A, Pacak K, Eisenhofer G (2017) Characteristics of pediatric *vs* adult pheochromocytomas and paragangliomas. *J Clin Endocrinol Metab* **102**: 1122–1132. https://doi.org/10.1210/jc.2016-3829

Park H, Kim MS, Lee J, Kim JH, Jeong BC, Lee S, Lee SK, Cho SY, Jin DK (2021) Clinical presentation and treatment outcomes of children and adolescents with pheochromocytoma and paraganglioma in a single center in Korea. *Front Endocrinol (Lausanne)* **11**: 610746. https://doi.org/10.3389/fendo.2020.610746

Patel D, Phay JE, Yen TWF, Dickson PV, Wang TS, Garcia R, Yang AD, Solórzano CC, Kim LT (2020) Update on pheochromocytoma and paraganglioma from the SSO endocrine/head and neck disease-site work group. Part 1 of 2: Advances in pathogenesis and diagnosis of pheochromocytoma and paraganglioma. *Ann Surg Oncol* **27**: 1329–1337. https://doi.org/10.1245/s10434-020-08220-3

Plouin PF, Duclos JM, Soppelsa F, Boublil G, Chatellier G (2001) Factors associated with perioperative morbidity and mortality in patients with pheochromocytoma: analysis of 165 operations at a single center. *J Clin Endocrinol Metab* **86**: 1480–1486. https://doi.org/10.1210/jcem.86.4.7392

Quee TC, Bergeron MJ, Amsel R, Chan EC (1986) A staining method for monitoring subgingival bacteria associated with periodontal disease. *J Periodontal Res* **21**: 722–727. https://doi.org/10.1111/j.1600-0765.1986.tb01510.x

Read AD, Bentley RE, Archer SL, Dunham-Snary KJ (2021) Mitochondrial iron–sulfur clusters: Structure, function, and an emerging role in vascular biology. *Redox Biol* **47**: 102164. https://doi.org/10.1016/j.redox.2021.102164

Rednam SP, Erez A, Druker H, Janeway KA, Kamihara J, Kohlmann WK, Nathanson KL, States LJ, Tomlinson GE, Villani A, Voss SD, Schiffman JD, Wasserman JD (2017) Von Hippel–Lindau and hereditary pheochromocytoma/paraganglioma syndromes: clinical features, genetics, and surveillance recommendations in childhood. *Clin Cancer Res* **23**: e68–e75. https://doi.org/10.1158/1078-0432.CCR-17-0547

Rees MA, Morin CE, Behr GG, Davis JC, Lai H, Morani AC, Parisi MT, Saigal G, Singh S, Yedururi S, Towbin AJ, Shulkin BL (2023) Imaging of pediatric adrenal tumors: A COG Diagnostic Imaging Committee/SPR Oncology Committee White Paper. *Pediatr Blood Cancer* **70** (Suppl 4): e2997. https://doi.org/10.1002/pbc.29973

Rijken JA, Niemeijer ND, Jonker MA, Eijkelenkamp K, Jansen JC, van Berkel A, Timmers HJLM, Kunst HPM, Bisschop PHLT, Kerstens MN, Dreijerink KMA, van Dooren MF, van der Horst-Schrivers ANA, Hes FJ, Leemans CR, Corssmit EPM, Hensen EF (2018) The penetrance of paraganglioma and pheochromocytoma in *SDHB* germline mutation carriers. *Clin Genet* **93**: 60–66. https://doi.org/10.1111/cge.13055

Ross JH (2000) Pheochromocytoma. Special considerations in children. *Urol Clin North Am* **27**: 393–402. https://doi.org/10.1016/S0094-0143(05)70088-4

Rufini V, Treglia G, Perotti G, Giordano A (2013) The evolution in the use of MIBG scintigraphy in pheochromocytomas and paragangliomas. *Hormones (Athens)* **12**: 58–68. https://doi.org/10.1007/BF03401287

Schüttler J, Westhofen P, Kania U, Ihmsen H, Kammerecker S, Hirner A (1995) Quantitative assessment of catecholamine secretion as a rational principle of anesthesia management in pheochromocytoma surgery]. *Anasthesiol Intensivmed Notfallmed Schmerzther* **30**: 341–349 (in German). https://doi.org/10.1055/s-2007-996507

Seamon ML, Yamaguchi I (2021) Hypertension in pheochromocytoma and paraganglioma: evaluation and management in pediatric patients. *Curr Hypertens Rep* **23**: 32. https://doi.org/10.1007/s11906-021-01150-9

Shah MH, Goldner WS, Benson AB, Bergsland E, Blaszkowsky LS, Brock P, Chan J, Das S, Dickson PV, Fanta P, Giordano T, Halfdanarson TR, Halperin D, He J, Heaney A, Heslin MJ, Kandeel F, Kardan A, Khan SA, Kuvshinoff BW, Lieu C, Miller K, Pillarisetty VG, Reidy D, Salgado SA, Shaheen S, Soares HP, Soulen MC, Strosberg JR, Sussman CR, Trikalinos NA, Uboha NA, Vijayvergia N, Wong T, Lynn B, Hochstetler C (2021) Neuroendocrine and Adrenal Tumors, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* **19**: 839–868. https://doi.org/10.6004/jnccn.2021.0032

Taïeb D, Jha A, Guerin C, Pang Y, Adams KT, Chen CC, Romanet P, Roche P, Essamet W, Ling A, Quezado MM, Castinetti F, Sebag F, Pacak K (2018) 18F-FDOPA PET/CT Imaging of MAX-Re-

lated Pheochromocytoma. *J Clin Endocrinol Metab* **103**: 1574–1582. https://doi.org/10.1210/jc.2017-02324

van Treijen MJC, de Vries LH, Hertog D, Vriens MR, Verrijn Stuart AA, van Nesselrooij BPM, Valk GD (2022) *Multiple Endocrine Neoplasia Type 2*. In Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hofland J, Kalra S, Kaltsas G, Kapoor N, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, New M, Purnell J, Sahay R, Shah AS, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, eds. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–. PMID: 29465928.

Wang K, Crona J, Beuschlein F, Grossman AB, Pacak K, Nölting S (2022) Targeted therapies in pheochromocytoma and paraganglioma. *J Clin Endocrinol Metab* **107**: 2963–2972. https://doi.org/10.1210/clinem/dgac471

Yen K, Lodish M (2021) Pheochromocytomas and paragangliomas. *Curr Opin Pediatr* **33**: 430–435. https://doi.org/10.1097/MOP.0000000000001029

Zhuang Z, Yang C, Lorenzo F, Merino M, Fojo T, Kebebew E, Popovic V, Stratakis CA, Prchal JT, Pacak K (2012) Somatic *HIF2A* gain-of-function mutations in paraganglioma with polycythemia. *N Engl J Med* **367**: 922–930. https://doi.org/10.1056/NEJMoa1205119