REVIEW ARTICLE

PHEOCHROMOCYTOMA AND PARAGANGLIOMA IN CHILDREN AND ADOLESCENTS

Guzy chromochłonne i przyzwojaki u dzieci i młodzieży

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Abstract

Pheochromocytomas and paragangliomas are rare neuroendocrine tumours that are an important cause of secondary hypertension. Pheochromocytomas and paragangliomas manifest with a varied clinical picture, including life-threatening hypertensive crises. Persistent, sustained hypertension, the incidence of which far exceeds paroxysmal hypertension, is the predominant clinical manifestation. In the paediatric population, 70–80% of tumours have a genetic background. Hereditary pheochromocytomas and paragangliomas are manifested by early tumour development, bilaterality, multifocality, mainly extra-adrenal localization, and an increased risk of recurrence. Measurement of free metanephrines (MNs) in plasma is considered the gold diagnostic standard due to its high sensitivity and reliable reference values in children. Nuclear medicine plays a key role in the diagnosis of pheochromocytomas and paragangliomas, with high sensitivity and specificity. They are used to assess regional extent, multifocality, and the presence of metastases. Surgical resection preceded by appropriate preoperative preparation is the primary therapeutic approach. Genetic testing and implementation of genetic counselling are recommended in all paediatric patients with confirmed pheochromocytomas and paragangliomas. Scientific evidence and clinical studies on pheochromocytomas and paragangliomas in the paediatric population are limited. The diagnostic and therapeutic process is challenging, often requiring a multidisciplinary approach. The purpose of this paper was to present the clinical picture, genetic background, diagnosis, and treatment of pheochromocytomas and paragangliomas in children and adolescents.

Streszczenie

Guzy chromochłonne i przyzwojaki to rzadkie nowotwory neuroendokrynne, będące istotną przyczyną wtórnego nadciśnienia tętniczego. Manifestują się zróżnicowanym obrazem klinicznym, obejmującym zagrażające życiu przełomy nadciśnieniowe. Dominującym objawem klinicznym jest utrzymujące się utrwalone nadciśnienie tętnicze, którego częstość występowania znacznie przewyższa nadciśnienie napadowe. W populacji pediatrycznej 70–80% nowotworów ma podłoże genetyczne. Dziedziczne guzy chromochłonne i przyzwojaki objawiają się wczesnym rozwojem guza, obustronnym występowaniem, wieloogniskowością, lokalizacją głównie pozanadnerczową oraz zwiększonym ryzykiem wznowy. Pomiar stężenia wolnych metoksykatecholamin w osoczu jest uznawany za złoty standard diagnostyczny ze względu na jego wysoką czułość i wiarygodne wartości referencyjne u dzieci. Badania z zakresu medycyny nuklearnej odgrywają kluczową rolę w diagnostyce tych nowotworów, cechując się wysoką czułością i swoistością. Są one stosowane w ocenie zasięgu regionalnego, wieloogniskowości oraz obecności przerzutów. Podstawową metodą terapeutyczną jest resekcja chirurgiczna, poprzedzona odpowiednim przygotowaniem okołooperacyjnym. U wszystkich pacjentów pediatrycznych z potwierdzonym rozpoznaniem rekomenduje się przeprowadzenie badań genetycznych i wdrożenie poradnictwa genetycznego. Dowody naukowe oraz badania kliniczne dotyczące guzów chromochłonnych i przyzwojaków w populacji dziecięcej są ograniczone. Proces diagnostyki i leczenia stanowi wyzwanie, często wymagając wielospecjalistycznego podejścia. Celem pracy jest przedstawienie obrazu klinicznego, podłoża genetycznego, diagnostyki oraz leczenia guzów chromochłonnych i przyzwojaków u dzieci i młodzieży.

Keywords: children; arterial hypertension; pheochromocytoma; paraganglioma; catecholaminesy

Słowa kluczowe: dzieci; nadciśnienie tętnicze; guz chromochłonny; przyzwojak; katecholaminy

DOI 10.53301/lw/208535

Received: 24.06.2025

Accepted: 23.07.2025

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Introduction

Pheochromocytoma (PCC) is a neuroendocrine tumour originating from the chromaffin cells of the adrenal medulla and characterized by overproduction of at least one catecholamine, such as adrenaline, noradrenaline, and dopamine. Paraganglioma (PGL) is also a tumour arising from chromaffin cells, but it develops in extra-adrenal locations, most commonly within the thoracic, abdominal and pelvic sympathetic ganglia. PGLs may also originate from parasympathetic paraganglia of the head, neck, and mediastinum. Parasympathetic PGLs typically do not produce catecholamines. According to current guidelines from scientific societies, pheochromocytomas (PCC) and paragangliomas (PGL) are collectively classified as PPGLs [1].

PPGLs can lead to secondary hypertension (HT) in children. Although primary HT, increasingly linked to lifestyle factors and the rising prevalence of obesity, is increasingly commonly diagnosed in the paediatric population, secondary causes of HT should always be thoroughly evaluated and excluded in every child.

Data on PPGLs in children and adolescents remain limited. As a result, some clinical recommendations continue to rely on experience derived from adult patients, even though paediatric PPGLs have a distinct phenotype [2]. Due to the hereditary nature of these tumours, bilateral, multifocal, and extra-adrenal lesions are more likely to occur in children than in adults [3]. This paper is a literature review presenting the differences in clinical presentation, diagnostic approach, and management of paediatric PPGLs, with particular emphasis on the most recent guidelines.

Epidemiology

PPGLs are rare tumours. Their incidence is estimated at 0.4–9.5 cases per million people per year in adults and 1–2 cases per million per year in children [4]. Among hypertensive adults, PPGLs account for approximately 0.2–0.6% of cases, whereas they occur in about 0.5–1.7% of HT children [5]. In the general population, pheochromocytomas are more common than paragangliomas, accounting for approximately 80–85% vs 15–20%, respectively. Extra-adrenal tumour locations predominate in children, occurring in roughly 66% of cases. The incidence of previously undiagnosed PPGLs identified in autopsy studies is estimated at 0.05–0.1% [6].

Genetic background

PPGLs have a strong genetic basis, with one of the highest heritability rates among all cancers [7]. Approximately 40% of all cases arise from germline mutations. In the paediatric population, this proportion is significantly higher and is estimated to reach 70–80%. Hereditary PPGLs are characterized by early onset, bilaterality (20–40%), multifocality (30–70%), and an increased risk of recurrence (30%) [8].

To date, eight genes responsible for syndromic PPGL have been described: *RET*, *VHL*, *NF1*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, and *SDHD*. These are autosomal dominant genes. Furthermore, more than 20 susceptibility genes have been identified, including *FH*, *MAX*, *MDH2*, *SLC25A11*, *DLST*, *DNMT3A*, *TMEM127*, *HIF2A*, *EPAS1*, *EGLN1*, *EGLN2*, *IDH1*, *IDH2*, *IDH3B*, *CSDE1*, *FGFR1*, *PHD1*, *PHD2*, *GOT2*, *HRAS*, *MERTK*, *MET*, *KIF1B*, *H3F3A*, *BRAF*, *SUCLG2*, *H3-3A*, *MAML3*, *WNT4*, *DVL3*, *CHGA*, *ATRX*, *IRP1* [7, 9].

The most frequently described pathogenic variants are those affecting the *SDH* genes (*SDHA*, *SDHB*, *SDHC*, *SDHD*, and *SDHAF2*), which encode subunits of the mitochondrial succinate dehydrogenase complex involved in cellular energy production [9]. Germline mutations within these genes account for approximately 20% of all PPGL cases and may also predispose to other types of tumours [2].

PPGL is frequently associated with hereditary syndromes such as multiple endocrine neoplasia type 2 (MEN2A and MEN2B), von Hippel–Lindau syndrome (VHL), neurofibromatosis type 1 (NF1), and, less commonly, Carney triad and Carney–Stratakis syndrome. Clinical manifestations linked to mutations in genes predisposing to PPGL are summarized in Table 1. It is important to note that clinical presentation may vary considerably even among family members carrying the same mutation due to variable expression.

Most PPGLs are benign in the general population. In children, however, available data suggest that between 2.4% and 85.7% of tumours may exhibit malignant behaviour, which is largely attributed to the strong genetic background of the disease [2]. Pathogenic *SDHB* variants are the most frequently reported genetic alterations associated with malignant PPGL. Additionally, mutations in *FH* and *SLC25A11* have also been linked to an increased risk of malignancy [10, 11].

The historically used "10% rule" in PPGL, where it was thought that 10% of tumours are hereditary, malignant, bilateral, or extra-adrenal, is no longer applicable in current clinical practice [6].

Clinical picture

Symptoms of PPGL arise primarily from catecholamine overproduction and from the pressure exerted by the tumour on adjacent structures (the so-called mass effect). These manifestations may be episodic, reflecting the paroxysmal pattern of catecholamine release typical of these tumours. These episodes may occur spontaneously or be triggered by a variety of factors, including physical exertion, abdominal muscle tension, large meals, alcohol, stress, and certain medications such as glucocorticoids, dopaminergic receptor antagonists, norepinephrine reuptake inhibitors tricyclic antidepressants, monoamine oxidase inhibitors, sympathomimetics, peptide hormones, anaesthetics, β-blockers, and opioids [12].

Table 2 shows the prevalence of clinical manifestations of PPGL in children.

The mean age at diagnosis in the paediatric population ranges from 11 to 13 years [6, 13].

Persistent HT is the most common symptom (93%), significantly more frequent than paroxysmal HT (7%) [6]. The typical triad of paediatric symptoms includes palpi-

Table 1. Hereditary paraganglioma-pheochromocytoma syndromes [2, 6, 7, 9, 12]

Gene	Syndrome	Clinical manifestations
RET	Multiple endocrine neoplasia type 2	MEN2A: pheochromocytoma, medullary thyroid carcinoma, primary hyperparathyroidism, cutaneous lichen amyloidosis MEN2B: pheochromocytoma, medullary thyroid carcinoma, mucocutaneous neuromas, intestinal ganglioneuromatosis
VHL	Von Hippel-Lindau syndrome	pheochromocytoma, hemangioblastoma (of the cerebellum, brainstem, spinal cord), retinal haemangiomas, clear cell renal cell carcinoma, renal cysts, neuroendocrine tumours and cystadenomas of the pancreas, endolymphatic sac tumours, epididymal cystadenomas, cystadenomas of the broad ligament of the uterus
NF1	Neurofibromatosis type 1	PPGL, neurofibromas, multiple cafe-au-lait spots, freckles in the armpits and groin, Lisch nodules of the iris, skeletal malformations, CNS gliomas, macrocephaly, cognitive deficits, GIST
SDHA, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*	Pheochromocytoma and paraganglioma syndrome	PPGL, GIST, papillary thyroid cancer, clear cell renal cell carcinoma
(gene unknown)	Carney triad	paragangliomas, GIST, pulmonary chondromas
FH	Hereditary leiomyomas and renal cell carcinoma	Pheochromocytoma (rare), uterine fibroids, clear cell renal cell carcinoma
EPAS1	Multiple paragangliomas with concomitant polycythemia	PPGL, polycythaemia, vascular malformations, somatostatinoma, ocular manifestations
TMEM127		PPGL, clear cell renal cell carcinoma
MAX		PPGL, pituitary neuroendocrine tumour
H3F3A		PPGL, giant cell tumour of bone (GCTB)
EGLN2		PPGL, polycythaemia, normal or mildly elevated erythropoietin (EPO)
DLST		PPGL, pituitary adenoma, endometrial cancer
PPGL – pheochromocytoma and paraganglioma; MEN – multiple endocrine neoplasia; GIST – gastrointestinal stromal tumour		

tations, excessive sweating, and headaches (54%) [6, 14]. Abdominal pain, nausea, vomiting, polyuria, and polydipsia are also relatively common symptoms [15]. Other characteristic features include pallor, muscle tremor, anxiety and panic attacks, as well as orthostatic hypotension [15]. Although diabetes and prediabetes may occur as metabolic consequences of a hyperadrenergic state, they are rare in the paediatric population [6, 12].

The unique clinical presentation of PPGL in children is likely related to the fact that these tumours are predominantly extra-adrenal and frequently multifocal, metastatic, and recurrent. As already noted, this pattern reflects their strong association with hereditary syndromes in the paediatric population.

Differences in clinical presentation may also result from the secreted catecholamines. Patients with norepinephrine-secreting PPGLs are at higher risk of HT due to its strong affinity for α_1-adrenergic receptors. In contrast, patients with epinephrine-secreting tumours are more prone to tachycardia and arrhythmias, reflecting the affinity of epinephrine for β_1-adrenergic receptors. Patients with dopamine-secreting tumours may present with normal blood pressure [6, 14]. The release of additional substances by the tumour, such as neuropeptide Y, parathyroid hormone, endothelin, vasoactive intestinal peptide (VIP), chromogranin A, adrenocorticotropic hormone (ACTH), atrial natriuretic peptide (ANP), somatostatin, erythropoietin, and interleukin-6, also contributes to the heterogeneous clinical presentation [15]. Notably, no

Table 2. Manifestations of pheochromocytomas and paragangliomas and their rates in children [13]

Manifestations	Rates (%)
Persistent HT	93
Paroxysmal HT	7
Headache	95
Excessive sweating	90
Resting tachycardia, palpitations	35
Visual disturbances	80
Neurological symptoms	65
Weight loss	15
Orthostatic hypotonia	10

direct correlation has been observed between catecholamine levels and blood pressure values [2].

Head and neck paragangliomas are rare in children and do not secrete catecholamines. Their symptoms may result from compression or invasion of adjacent structures, leading to tinnitus, hearing loss, dysphagia, hoarseness, cough, or cranial nerve palsy [12, 14]. Approximately 25% of PPGL cases may not produce excess catecholamines, and therefore be asymptomatic (so-called biochemically silent tumours). It is assumed that the absence of clinical symptoms is due to, among other factors, small tumour size and minimal catecholamine secretion, as well as the type and pattern of secretion, desensitization of adrenergic receptors, and other compensatory mechanisms of the body [16]. In the paediatric population, where hereditary PPGLs predominate and are often multifocal, metastatic, and more aggressive, the vast majority of patients (90%) present with symptoms of the disease [2].

Physical examination is usually unremarkable; however, abnormalities may include pale, clammy skin, dilated pupils, resting tachycardia, or features characteristic of specific genetic syndromes, as outlined in Table 1.

Cardiovascular risk

Excessive catecholamine levels, which are typical of PPGL, represent a major risk factor for CV complications, including diverse forms of cardiomyopathy. Takotsubo cardiomyopathy, characterized by reversible left ventricular systolic dysfunction and often mimicking acute coronary syndrome, is the most frequently reported manifestation in the clinical literature.

Furthermore, hypertrophic cardiomyopathy may develop in cases of prolonged catecholamine- mediated HT.

Recent studies conducted in a large cohort of PPGL patients have provided new insights into the effects of chronic catecholamine exposure on the myocardium. Pre- and postoperative analyses of left ventricular morphology as well as systolic and diastolic function demonstrated that catecholamine excess can lead not only to left ventricular hypertrophy but also to impaired systolic function and subclinical diastolic dysfunction. Importantly, changes in cardiac structure and function were observed independently of blood pressure (both office measurements and ambulatory monitoring) as well as other traditional CV risk factors. This indicates that catecholamines exert a direct toxic effect on the myocardium, extending beyond their pressor activity. The potential reversibility of these cardiomyopathic changes following effective treatment, most commonly surgical removal of the catecholamine-secreting tumour, is a key finding of this research. This underscores the importance of early diagnosis and timely therapeutic intervention in PPGL patients to prevent cardiac complications and promote their reversal [17].

Health and life threats

PPGLs represent a significant risk factor for complications and can pose a threat to patients' lives. Acute clinical deterioration may occur as a result of tumour necrosis, which leads to a massive release of catecholamines into the bloodstream. This can manifest as hypertension or hypotension, hyperthermia, encephalopathy, and multi-organ failure. Additionally, patients with PPGL are at risk of experiencing sudden and difficult-to-control increases in blood pressure during general anaesthesia or surgical procedures [2].

Laboratory diagnosis

Assessment of plasma metanephrine (metanephrine, normetanephrine, and 3-methoxytyramine) is the recommended diagnostic screening method for PPGL [9]. Many studies have demonstrated that free plasma metanephrines (MNs) provide superior diagnostic accuracy, with sensitivity and specificity ranging from 97% to 100%, compared with plasma or urine catecholamines or their metabolites (such as homovanillic or vanillylmandelic acid) [6]. There are no reliable reference ranges for urinary metanephrine excretion available in children, and the use of adult norms may result in false-positive findings. For this reason, plasma testing is necessary. To obtain optimal results, it is recommended that the patient fast and remain in a supine position for at least 30 minutes before blood collection. However, it should be noted that this may be challenging in the youngest patients [18]. Furthermore, correct interpretation of the obtained results requires the use of age-specific reference ranges [19]. Clonidine suppression and glucagon stimulation tests are rarely used in adults due to their suboptimal sensitivity, and they are neither validated nor routinely performed in the paediatric population [6]. It is also worth emphasizing that other markers, such as chromogranin A or neuron-specific enolase, are not currently recommended.

In some patients, laboratory workup may reveal signs of hyperfiltration (decreased creatinine and increased glomerular filtration rate) arising from catecholamine excess, as well as activation of the renin–angiotensin–aldosterone system (RAAS) due to catecholamine-mediated renal vasoconstriction, which manifests as elevated renin (or increased plasma renin activity) and increased aldosterone concentrations.

Diagnostic imaging

Imaging plays a key role in the diagnosis of PPGL (Tab. 3). It enables confirmation of positive or borderline biochemical results, precise localization of the tumour, and assessment of its extent. Imaging is also essential for planning the optimal surgical approach, particularly in cases of multifocal or metastatic disease, as well as for monitoring therapeutic efficacy [20].

Ultrasonography (US) is considered a useful tool in the diagnosis of PPGL. Due to its wide availability and low cost, it can aid tumour detection [15]. However, it is important to note that a negative US result does not exclude PPGL.

Magnetic resonance imaging (MRI) is the imaging modality of choice in paediatric patients with suspected PPGL. It is preferred for screening because, unlike other techniques, it does not involve exposure to ionizing radiation [8, 20]. MRI allows for precise detection and assessment of metastatic PPGLs and tumours located

Table 3. Sensitivity, specificity, and limitations across different imaging modalities for pheochromocytomas and paragangliomas [2, 6, 8, 15, 21, 23, 25, 26]

Imaging modalities	Sensitivity	Specificity	Limitations
Ultrasonography (US)	76% *(Reisch et al. 2006)* [25]		
Computed Tomography (CT)	Small tumours: 90–92% Large tumours: 100% *(Reisch et al. 2006)* [25] 90% *(Lumachi et al. 2006)* [26] 88–100% *(Lenders et al. 2014)* [1]	93% *(Lumachi et al. 2006)* [26]	Detects tumours ≥5 mm.
Magnetic resonance imaging (MRI)	93.3% *(Lumachi et al. 2006)* [26] Paragangliomas of the head and neck: 90–95% *(Lenders et al. 2014)* [1]	93% *(Lumachi et al. 2006)* [26]	Sedation may be needed in paediatric patients to maintain immobility (longer duration of the exam) CT is the preferred imaging modality for lung metastases.
I-123 MIBG scintigraphy	75–90% *(Reisch et al. 2006)* [25] 90.6% *(Lumachi et al. 2006)* [26] Pheochromocytomas: 85–88% Paragangliomas: 56–75% *(Lenders et al. 2014)* [1]	100% *(Reisch et al. 2006)* [25] 100% *(Lumachi et al. 2006)* [26] Pheochromocytomas: 70–100%. Paragangliomas: 84–100% *(Lenders et al. 2014)* [1]	Thyroid blockade is needed to prevent unwanted tracer accumulation. Discontinuation of certain groups of medications is required, including vasoconstrictors, calcium channel blockers, and labetalol, due to their potential impact on the test results or interactions with the substances used. Extended: 18 to 24 hrs.
Positron emission tomography (PET), using 18 F-fluorodeoxyglucose (18 FDG)	74–100% *(Lenders et al. 2014)* [1] 66–78% *(Krokhmal et al. 2022)* [23]		Difficult detection of lesions < 3 to 5 mm. A positive test is not specific for PPGL, as the imaging reflects glucose uptake and metabolism by cells, including other tumour cells with high glucose demand.
68Ga-DOTATATE PET	72–100% *(Krokhmal et al. 2022)* [23]		Risk of false negative results in the absence of somatostatin receptors.

in the head and neck region. It is also recommended for patients with contraindications to other imaging modalities.

Computed tomography (CT) is recommended as a second-line imaging modality in the diagnosis of PPGL, primarily due to the associated exposure to ionizing radiation. Nonetheless, it offers excellent spatial resolution in the chest, abdomen, and pelvis and enables the detection of tumours ≥ 5 mm. The appearance of a PPGL on a CT scan is variable; tumours may be homogeneous or heterogeneous, may exhibit necrosis with calcifications, and may present as solid or cystic lesions [1]. A characteristic feature of PPGL is a density typically ≥10 Hounsfield units [2].

Nuclear medicine techniques are employed in cases of strong clinical suspicion of PPGL, in which the lesion cannot be localized using first-line imaging, as well as in situations suggesting multifocal or metastatic disease. These include [^{123}I]-metaiodobenzylguanidine (MIBG) scintigraphy, somatostatin receptor scintigraphy using [^{99m}Tc]-octreotide (a somatostatin analogue), and positron emission tomography (PET-CT) with radiotracers such as [^{18}F]-fluorodeoxyglucose (FDG), [^{18}F]-fluorodihydroxyphenylalanine (FDOPA), and the somatostatin analogue [^{68}Ga]-DOTATATE [6]. The decision to use these modalities in paediatric patients requires individualized assessment and must be carefully weighed against the potential risks and anticipated diagnostic benefits [18].

[^{123}I]-MIBG scintigraphy is particularly valuable for evaluating sporadic pheochromocytomas and metastatic disease, especially when treatment with [^{131}I]-MIBG is being considered. It is also recommended in situations with an increased risk of metastasis or recurrence, such as large primary or extra-adrenal tumours [2]. An additional advantage of [^{123}I]-MIBG scintigraphy is its ability to detect lesions that may not be visible on CT or MRI. However, it should be noted that not all PPGLs demonstrate sufficient uptake of this radiotracer, which may limit the sensitivity of the method.

[^{18}F]-FDG PET is also used in the diagnosis of PPGL, providing high sensitivity in detecting small or highly metabolic lesions [21]. Although its overall detection rate

is comparable to that of other nuclear medicine techniques, [^{68}Ga]-DOTATATE PET offers higher specificity and superior contrast between pathological lesions and surrounding tissues, making it particularly valuable in identifying multifocal or metastatic disease [21]. Recent scientific studies confirm the superiority of [^{68}Ga]-DOTATATE PET over [^{18}F]-FDG PET in detecting metastatic PPGL associated with *SDHB* gene mutations [8]. The [^{68}Ga]-DOTATATE PET modality has also been approved for use in paediatric patients by the U.S. Food and Drug Administration (FDA) [21].

Pharmacotherapy

PPGL patients are put on pharmacological treatment to control symptoms, particularly in the immediate preoperative period (Tab. 4).

Perioperative management

Surgical removal of PPGL is associated with a substantial risk of intraoperative haemodynamic instability and cardiovascular complications. To mitigate this risk, current guidelines recommend systemic administration of preoperative α-blockers for all patients, including those who are normotensive or have biochemically silent tumours [22]. Beta-blockers may be introduced only after adequate alpha blockade has been achieved, in order to prevent reflex tachycardia and catecholamine-induced tachyarrhythmias [6]. Preoperative management should be initiated at least 7–14 days before the planned surgical intervention. The primary goal is to achieve adequate normalization of blood pressure (BP) and heart rate. BP levels should be reduced to <130/80 mmHg in adolescents aged ≥16 years and to less than the 95th percentile for age, sex, and height (optimally toward the 50th percentile shortly before surgery) in younger children. Current guidelines emphasize that achieving the desired haemodynamic targets may take more than a few weeks in some paediatric patients [1]. The prolonged preparatory phase is likely related to the substantial catecholamine burden, as large or multiple tumours result in chronically elevated catecholamine levels, as well as the need for careful titration of medications and the generally higher sympathetic nervous system activity observed in children [6]. Adequate preoperative fluid intake and a high-sodium diet are essential in PPGL patients to prevent severe hypotension following tumour resection. Hyperfiltration, which is observed in many patients, contributes to sodium and water depletion. Sudden cessation of exposure to high catecholamine levels following tumour removal may lead to a marked drop in blood pressure. Preoperative fluid supplementation and a high-sodium diet aim to expand intravascular volume, thereby stabilizing BP levels and reducing the risk of postoperative hypotension [1]. Long-term, continuous monitoring is required after surgery.

Surgical treatment

Surgery remains the treatment of choice for PPGL, and operative management is planned individually for each patient, taking into account multiple clinical and anatomical factors. However, it is important to emphasize that even seemingly complete tumour resection does not eliminate the risk of residual disease or future recurrence [2].

The preferred surgical approach for small pheochromocytomas (up to 5–6 cm) is laparoscopic resection, whereas larger tumours (> 5–6 cm) and paragangliomas are typically managed with open laparotomy. This is due to their higher risk of malignancy and their frequent location in anatomically challenging regions [6, 18]. The choice of

Table 4. Preoperative treatments used for HT in children with pheochromocytomas and paragangliomas [2, 6]

Treatment	Dosage	Maximum recommended dose
Phenoxybenzamine	00.2 mg/kg/day (max 10 mg/dose) Increase the dose by 0.2 mg/kg/day every 4 days. Target dose: 0.4–1.2 mg/kg/day ÷ 6–8 hrs	2–4 mg/kg/day (60 mg/day)
Doxazosin	1–2 mg/day Increase the dose by 2–4 mg/day. Target dose: 2–4 mg/day ÷ 8–12 hours	4–16 mg/day
Prazosin	0.05–0.1 mg/kg/day ÷ 8 hours	0.5 mg/kg/ day (20 mg/ day)
Terazosin	1 mg/day Increase the dose to 1–4 mg/day	20 mg/ day
Propranolol*	1–2 mg/kg/day ÷ 6–12 hours. Increase the dose to 4 mg/kg/day ÷ 6–12 hours	640 mg/ day
Atenolol*	0.5–1 mg/kg/day ÷ 12–24 hours. Increase the dose to 2 mg/kg/day ÷ 12–24 hours	100 mg/ day
Metoprolol*	1–2 mg/kg/day ÷ 12–24 hours. Increase the dose to 2 mg/kg/day ÷ 12–24 hours	200 mg/ day
Labetalol*	1–3 mg/kg/day ÷ 8–12 hours. Increase the dose to 10–12 mg/kg/day ÷ 8–12 hours	1200 mg/ day
Bisoprolol*	Start with a dose of 1.25 mg to 5 mg/day	10 mg/ day
Amlodipine	0.06–0.1 mg/kg/day ÷ 12–24 hours. Increase the dose to 0.3 mg/kg/day ÷ 12–24 hours	0.6 mg/kg/day (10 mg/day)
Metyrosine	20 mg/kg/day ÷ 6 hours. Increase the dose to 60 mg/kg/day ÷ 6 hours	2500 mg/ day
* β-blockers can be used only after blocking α-receptors, beta-1 blockers are preferred		

surgical technique is additionally influenced by the results of genetic testing, the surgeon's experience, and the estimated probability of malignancy.

Metastases

There are no specific biochemical or histopathological PPGL markers reliably predicting malignant behaviour. According to the World Health Organization (WHO), PPGLs are classified as malignant only when they spread to sites where chromaffin tissue is not normally found, such as the bones, lymph nodes, lungs, or liver. In such cases, lesions identified in these locations cannot represent a primary tumour site [20]. Malignant transformation is relatively rare in pheochromocytomas (10–15%) but more common in paragangliomas (35–40%). As previously noted, malignant tumours are more common in children [23].

Molecularly targeted therapies are gaining importance in the management of metastatic PPGLs in adults; however, their use in in paediatric patients remains largely investigational and is currently limited to clinical trial settings [18, 22].

Surgical resection remains the preferred treatment approach. If complete tumour removal is not possible, debulking surgery or metastasectomy may be considered in children with metastatic PPGL to alleviate symptoms associated with catecholamine excess [18]. In selected patients with slow disease progression, low tumour burden, or oligometastatic involvement, active surveillance may also be an appropriate management strategy [18].

Radioisotope therapy may be used in patients with moderate or slow disease progression, moderate to high tumour burden, and positive [^{131}I]MIBG imaging or somatostatin receptor scintigraphy. It uses [^{131}I]MIBG or somatostatin analogues, respectively [22]. Notably, [^{131}I]MIBG therapy was approved by the FDA in 2018 for children with metastatic PPGL aged > 12 years of age [18].

Tyrosine kinase inhibitors or temozolomide may be considered as first-line treatment in adults with slowly or moderately progressive tumours not eligible for [^{131}I]MIBG therapy [22]. Although tyrosine kinase inhibitors are gaining popularity in the management of various paediatric malignancies, they have not yet been approved for use in children with metastatic PPGL [18].

In cases of rapidly progressing metastatic PPGL, combination chemotherapy with cyclophosphamide, vincristine, and dacarbazine (CVD regimen) may be the treatment of choice [22]. However, it should be noted that there are no prospective clinical trials confirming the efficacy of the CVD regimen in the paediatric population [18].

It is also important to note that most of the aforementioned therapies are palliative. Targeted gene therapy, tailored to the specific genetic architecture of PPGL, remains an area requiring further research [6].

Monitoring

Given that 70–80% of paediatric PPGL patients have a mutation, these patients require ongoing monitoring. Surveillance guidelines for individuals with a genetic predisposition or a history of PPGL vary depending on the specific mutation. Children and adolescents diagnosed with PPGL have an increased risk of recurrent, multifocal, and malignant disease requiring long-term follow-up [6].

Regular monitoring of BP and plasma metanephrines is essential [12]. Intensified surveillance similar to that used in high-risk adult patients (those with tumours linked to a genetic predisposition, tumours >5 cm, or extra-adrenal locations) is recommended in children. It should be noted that paediatric patients with PPGL require follow-up extending into adulthood [24].

Although *SDHx* mutations are often associated with biochemically silent PPGL, thorough surveillance is strongly recommended. This includes annual clinical evaluations beginning at diagnosis, or from the age of 5 years in asymptomatic *SDHB* mutation carriers and from the age of 10 years in asymptomatic *SDHA/C/D* mutation carriers [18]. Since SDHB mutation carriers have a markedly increased risk of malignancy, they require particularly intensive monitoring, including regular abdominal MRI every 18 months and MRI of the neck, chest, and pelvis every 3 years. Although patients with *SDHB* mutations develop metastases as early as 5 years from diagnosis, studies have shown good 20-year prognosis and survival. Metastases in paediatric patients with *SDHB* mutations are most likely to appear first in the bones followed by lymph nodes, lungs, and liver. A tumour size ≥ 5 cm and multifocal or recurrent tumours warrant closer follow-up for earlier detection of metastases. In contrast, surveillance protocols for carriers of mutations in the other succinate dehydrogenase subunits remain less clearly defined [6]. Individuals with *RET* or *VHL* mutations require annual plasma or urinary metanephrine screening starting at 5 years of age, whereas patients with *NF1* should undergo screening every 3 years, starting between 10 and 14 years of age [18].

Genetic counselling

Genetic testing is essential for both patients diagnosed with PPGL and their asymptomatic family members who may carry the same genetic mutation. Surveillance strategies should be tailored based on the specific gene and the patient's relationship to the affected relative.

International guidelines recommend genetic testing for first-degree relatives in all hereditary PPGL syndromes, as well as for second-degree relatives in cases of *SDHD*- and *SDHAF2* mutations. Furthermore, genetic testing can be considered for second-degree relatives of individuals with *SDHB*, *SDHA*, *SDHC*, *TMEM127*, *MAX*, or other PPGL-linked gene mutations, especially in metastatic cases. While first-degree relatives typically require continuous surveillance, second-degree relatives or those with genes associated with low phenotypic penetrance may only require a single screening evaluation [12].

The optimal age for initiating genetic testing varies based on the specific gene mutation and the nature of required surveillance. For von Hippel–Lindau (VHL) syndrome, testing is recommended beginning at 5 years of age.

For other hereditary PPGL syndromes, the ideal starting age has not been clearly established. Current proposals suggest a minimum age of 5 years for *SDHB*-associated PPGL and 10 years for PPGL associated with *SDHA*, *SDHC*, and *SDHD* mutations [12]. Comprehensive genetic testing using next-generation sequencing (NGS) panels is recommended in children diagnosed with PPGL due to the heterogeneity of clinical presentation and the absence of a clear genotype–phenotype correlation. In contrast, family members of patients with a known mutation may undergo targeted testing using conventional Sanger sequencing [18].

Conclusions

Excess catecholamines in patients with PPGL give rise to a diverse clinical presentations, including life-threatening hypertensive crises, and significantly increased cardiovascular risk. Measurement of free plasma MNs is considered the gold diagnostic standard due to its high sensitivity and specificity, as well as the availability of reliable, age-adjusted reference intervals in the paediatric population. Nuclear medicine techniques allow visualization of lesions that may be undetectable with other imaging methods. Surgical resection, preceded by appropriate perioperative preparation, remains the primary treatment for PPGL. About 70–80% of paediatric patients with PPGL have a mutation. Genetic predisposition significantly increases the risk of recurrence, multifocal disease, and malignant transformation, underscoring the need for lifelong clinical surveillance. Consequently, genetic counselling and testing are recommended for all children and adolescents with PPGL, as well as their at-risk family members.

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