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Current Strategies for Managing Pheochromocytoma and Paraganglioma in Children and Adolescents

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Pheochromocytomas and paragangliomas are rare neuroendocrine tumors that are an important cause of secondary hypertension. The most frequently reported symptom is persistent hypertension, exceeding paroxysmal hypertension. In children with elevated blood pressure, secondary hypertension should always be considered and investigated. These tumors exhibit a wide variety of clinical presentations, including syndromic presentations and life-threatening hypertensive crises. Recent advancements in genetic analysis have identified a growing number of pathogenic mutations. In the pediatric population, 70-80% of tumors exhibit germline mutations in known genes, predisposing children to metastatic and multifocal disease. The diagnosis and treatment remain challenging and often require a multidisciplinary approach at a highly specialized center. Plasma-free metanephrines measurement is considered the criterion standard for diagnosis due to its high sensitivity and reliable pediatric reference values. Functional imaging is helpful for pheochromocytoma and paraganglioma due to its high sensitivity and specificity, and it plays a crucial role in assessing regional extension, multifocality, and the presence of metastases, which are more frequently reported in children. Following definitive diagnosis and appropriate perioperative management, surgery remains the primary treatment. Genetic testing and counseling should be considered in all pediatric patients with confirmed pheochromocytoma and paraganglioma. Evidence and clinical trials in children are limited; therefore, the present report aims to review the presentation, associations, diagnosis, and management of pheochromocytoma and paraganglioma in children and adolescents.

Keywords: Pheochromocytoma • Paraganglioma • Catecholamines • Hypertension • Review

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Introduction

A pheochromocytoma (PCC) is a tumor originating from adrenomedullary chromaffin cells that commonly produce 1 or more catecholamines, including epinephrine, norepinephrine, and dopamine. A paraganglioma (PGL) is also a catecholamine-secreting tumor but arises from extra-adrenal chromaffin cells located within the sympathetic paravertebral ganglia of the thorax, abdomen, and pelvis. However, some paragangliomas originate from parasympathetic ganglia situated along the glossopharyngeal and vagal nerves in the neck and at the base of the skull. These parasympathetic paragangliomas do not produce catecholamines. Pheochromocytomas (PCCs) and paragangliomas (PGLs) are collectively referred to as pheochromocytomas and paragangliomas (PPGLs) following current Endocrine Society guidelines [1]. This term will be used throughout this article for consistency.

PPGL are among the secondary causes of arterial hypertension in children, which constitutes a substantial and escalating global health challenge [2]. Although primary hypertension, often associated with the obesity epidemic, is experiencing a surge, careful consideration must be given to these and other secondary causes of arterial hypertension in the pediatric population [3,4]. Existing data suggest a higher prevalence of hereditary PPGL in children compared to adults, often manifesting as phenotypic presentations characterized by bilateral, multiple, and extra-adrenal tumors [5]. Data for the pediatric population are still limited. Due to the limited evidence base and clinical trials in children, some guidelines are still adapted from adult practices [6]. This article aims to review the presentation, associations, diagnosis, and management of PPGL in children, with a particular focus on recent advancements, including the International Consensus Statement by Casey et al [6]. Early detection and a better understanding of the disease among clinicians can lead to faster treatment and help prevent life-threatening hypertensive crises.

Incidence and Prevalence

PPGL are rare tumors. Their incidence is estimated between 0.4-9.5 cases per million people yearly in adults [7], and 1-2 cases per million per year in the pediatric population [8], representing only 20% of the overall population incidence [9-11]. The prevalence of PPGL ranges from 0.2% to 0.6% among hypertensive patients [12], and around 0.5-1.7% of pediatric arterial hypertension [9,13]. Pheochromocytomas are more common (80-85%) than paragangliomas (15-20%) [14]. The prevalence of undiagnosed PPGL tumors in autopsy studies is estimated at 0.05-0.1% [15].

Genetic Basis

PPGLs have a marked hereditary predisposition and one of the highest heritability rates observed for human tumors [16]. Approximately 40% of PPGL cases arise from germline mutations in susceptibility genes. In the pediatric population, a significantly higher proportion – 70% to 80% – of tumors exhibit germline mutations in known genes, predisposing patients to metastatic and multifocal disease [5,11]. Eight genes are responsible for most common hereditary PPGL syndromes (*RET, VHL, NF1, SDHA, SDHAF2, SDHB, SDHC, SDHD),* and over 20 genes have been implicated in PPGL susceptibility (*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*, and others) [16-19]. Further investigations are ongoing to identify additional causative genes.

SDH genes (*SDHA*, *SDHB*, *SDHC*, *SDHD*, and *SDHAF2*) are the most frequently reported genes involved in inherited PPGL predisposition [17]. Germline mutations within these genes account for approximately 20% of cases and can be associated with developing other *SDH*-related tumors [20]. Mutations in these genes contribute to multifocal and synchronous presentation, with parasympathetic paragangliomas arising in the head and neck or mediastinum, and sympathetic paragangliomas developing in the abdomen and pelvis.

PPGL demonstrate a well-documented association with several syndromic presentations: multiple endocrine neoplasia (MEN2A or MEN2B), von Hippel-Lindau (VHL) syndrome, and neurofibromatosis (NF), and a lesser extent, Carney triad and Carney-Stratakis syndrome. Hereditary PPGL is characterized by early tumor development, bilateral involvement in paired organs, multifocal tumor origin, and a heightened risk for tumor recurrence. Clinical manifestations related to mutations in the PPGL genes are presented in **Table 1** [16]. Intrafamilial phenotypic heterogeneity exists, with variable clinical presentations observed even within families harboring the same mutation.

While most tumors are benign, some hereditary PPGLs can become cancerous, especially with mutations in the *SDHB* gene [17,21]. Two rarer predisposition genes linked to malignant PPGL are *FH* and *SLC25A11* [22,23]. Due to the high incidence of mutations in the pediatric PPGL population, the tumors tend to be more aggressive and metastatic than in adults [24]. Up to 85.7% of PPGLs in children are metastatic, but the underlying mechanisms facilitating this process remain unknown [25,26].

Large-scale studies established the molecular classification of PPGLs in 3 genomic clusters: a pseudohypoxic cluster (cluster 1: mutations in *VHL*, *SDHx*, *HIF2A*, *PHD1*/*PHD2*, *FH*, and *MDH2*), a cluster of kinase receptor signaling and protein translation

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Table 1. Clinical findings associated with syndromic PPGL [14-17,21,23,47-50].

Syndrome	Mutation	Clinical manifestation
Multiple endocrine neoplasia type 2	*RET*	MEN2A: pheochromocytoma, medullary thyroid carcinoma, hyperparathyroidism, cutaneous lichen amyloidosis MEN2B: pheochromocytoma, medullary thyroid carcinoma, multiple mucocutaneous neuromas, marfanoid habitus, intestinal ganglioneuromas
von Hippel-Lindau disease	*VHL*	Central nervous system/retinal hemangioblastoma, renal cell carcinoma, pheochromocytoma, pancreatic neuroendocrine tumor, endolymphatic sac tumors, renal and pancreatic cysts
Neurofibromatosis type 1	*NF1*	PPGL, pigmentary lesions (café-au-lait macules, skinfold freckling and Lisch nodules), dermal neurofibromas, skeletal abnormalities, brain tumors (optic pathway gliomas and glioblastoma), peripheral nerve tumors (spinal neurofibromas, plexiform neurofibromas and malignant peripheral nerve sheath tumors), learning disabilities, attention deficits, and social and behavioral problems
SDHx-associated hereditary paraganglioma-pheochromocytoma syndromes	*SDHx* genes	PPGL, renal cell carcinoma, gastrointestinal stromal tumors, pituitary adenomas *SDHD*: head/neck paraganglioma Carney-Stratakis syndrome – the dyad of paragangliomas and gastric stromal sarcomas, which is caused by germline mutations in SDHD, SDHC and SDHB
Carney triad	Unexplained genetics, recurrent chromosome losses possibly leading to impaired *SDH* function	The triad of paragangliomas, gastric stromal tumors and pulmonary chondromas
Hereditary leiomyomatosis and renal cell carcinoma syndrome	*FH*	Hereditary leiomyomatosis, renal cell carcinoma and rarely phaeochromocytoma
Polycythemia and paraganglioma syndrome	*EPAS1*	PPGL, polycythemia, somatostatinoma, vascular malformations, ocular abnormalities
	TMEM127	PPGL, renal cell carcinoma
	MAX	PPGL, pituitary neuroendocrine tumors
	H3F3A	Giant cell tumors of the bones, pheochromocytoma, bladder and periaortic PPGL
	EGLN2	PPGL, polycythemia, normal or mild elevated erythropoietin (EPO)
	DLST	PPGL, pituitary adenoma, uterine carcinoma

MEN – multiple endocrine neoplasia; PPGL – pheochromocytoma and paraganglioma; EPO – erythropoietin.

pathways (cluster 2: mutations in *RET*, *NF1*, *TMEM127*, *KIF1B*, and *MAX*), and cluster 3 related to a Wnt signaling includes genes like *WNT4*, *DVL3*, *MAML3,* and *CHGA* [19,25,27].

The current diagnostic approach for PPGL no longer incorporates the previously employed "10% rule" (positive family history, risk for malignancy, bilateral disease, or extra-adrenal origin is each estimated at 10% of the diagnosed tumors) [15]. Advancements in our understanding of genetic determinism in PPGL have necessitated this shift. Current research emphasizes the increased importance of genetic predisposition in the development of PPGLs (up to 80% in children). It is also noted that bilateral adrenal involvement occurs in 20-40% of cases, and PPGLs occur simultaneously at multiple locations in 30-70% of cases [28].

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Table 2. Medications that can cause hypertensive crisis in patients with PPGL [1,12].

Drug class	Examples of drugs
Corticosteroids	Prednisone, dexamethasone, hydrocortisone, betamethasone
Dopamine-2 antagonists	Metoclopramide, sulpiride, amisulpride, tiapride, chlorpromazine, prochlorperazine, droperidol
Norepinephrine reuptake inhibitors (including tricyclic antidepressants)	Imipramine, clomipramine, amitriptyline
Monoamine oxidase inhibitors	Tranylcypromine, moclobemide, phenelzine
Sympathomimetics	Ephedrine, amphetamine, pseudoephedrine, fenfluramine, methylphenidate, phentermine, dexamfetamine
Peptide hormones	ACTH, glucagon
Anesthetics	Succinylcholine, tubocurarine, atracurium
β-adrenoreceptor blockers	Propranolol, sotalol, timolol, nadolol, labetalol
Opioid analgesics	Morphine, pethidine, tramadol

PPGL – pheochromocytoma and paraganglioma; ACTH – adrenocorticotropic hormone.

Table 3. Frequency of symptoms of pheochromocytoma and paraganglioma. Adapted from Barontini et al (2006) [33].

Symptom	Frequency of reporting in patients <20 years old (%)	Frequency of reporting in patients >20 years old (%)
Persistent arterial hypertension, often fluctuating	93	68
Paroxysmal arterial hypertension	7	26
Headache	95	90
Excessive sweating	90	92
Palpitations	35	72
Weight loss	15	72

Clinical Presentation

Elevated catecholamine release from the tumor causes a broad spectrum of clinical symptoms with a characteristic paroxysmal presentation due to episodic secretory activity. These symptoms vary significantly in severity and frequency, occurring either spontaneously or being provoked by precipitating factors such as physical exertion, abdominal straining, large meals, alcohol, stressful situations, and administration of certain medications (**Table 2**) [12,21].

Table 3 summarizes the frequency of clinical presentations, with persistent hypertension being the most prevalent symptom, exceeding paroxysmal hypertension. This trend holds true for children as well, where persistent hypertension affects 93% of cases, with an average age at diagnosis of 11-13 years old [15]. The triad of symptoms typical for the pediatric population includes palpitations, excessive sweating, and headaches [15,29]. Gastrointestinal symptoms, including abdominal pain, nausea, vomiting, polyuria, and increased thirst, are also relatively common [21]. The unique presentation is likely due to the fact that these tumors are predominantly located extra-adrenally, and often present as multifocal, metastatic, and recurrent, which is associated with the increased association with hereditary syndromes in the pediatric population. Other characteristic features include pallor, muscle tremor, anxiety, orthostatic hypotension, and symptoms associated with syndromic presentation [21]. Diabetes and prediabetes are potential metabolic consequences of a hyperadrenergic state, but they are less frequently reported in children [12,15].

Pediatric PPGLs exhibit a lower prevalence compared to adults. Still, they should always be considered as one of the potential causes of secondary hypertension in children. Diagnosis of arterial hypertension in children is based on different guidelines than in adults. Children are considered to have arterial

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hypertension when their systolic and/or diastolic blood pressure consistently exceeds the 95th percentile for their age, sex, and height on at least 3 separate occasions. For teenagers aged 16 and older, the diagnostic criteria align with adult standards, requiring a systolic blood pressure of 140 mmHg or higher and/or a diastolic blood pressure of 90 mmHg or higher [3]. Moreover, 24-hour ambulatory blood pressure monitoring can help detect masked hypertension or a non-dipping pattern [15]. Abnormal circadian blood pressure patterns may result from the high circulating levels of catecholamines.

The difference in clinical symptoms may be related to tumor secretion. Tumors that secrete norepinephrine have a higher risk of hypertension due to their stronger affinity for α_1-adrenergic receptors, epinephrine-secreting tumors have an increased risk of tachycardia and arrhythmias due to their affinity for β_1-adrenergic receptors, and dopamine-secreting pheochromocytomas may present with normal blood pressures [15,29]. Co-secretion of other substances 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 contribute to the heterogeneity of clinical presentation [21]. There is no direct correlation between the catecholamine level and the severity of hypertension [6,30].

Physical examination is typically unremarkable. Findings may include pale, moist skin, mydriasis, and syndromic features as detailed in **Table 1**.

PPGL represents a significant risk factor for patient morbidity and mortality. Acute clinical manifestations can be triggered by tumor necrosis, resulting in a massive catecholamine release into the systemic circulation. Symptoms may include hypertension or hypotension, hyperthermia, encephalopathy, and multiorgan failure. Additionally, patients with PPGL may experience a sudden, difficult-to-control increase in blood pressure during general anesthesia or surgery.

Approximately 25% of PPGL cases in the general population may be asymptomatic ("silent PPGL"). Several factors are postulated to contribute to this lack of clinical presentation, including small tumor size and minimal catecholamine secretion, as well as the type and pattern of catecholamine secretion, adrenoceptor desensitization, and other compensatory responses to the disease [31]. In the pediatric population, PPGL tumors are highly related to germline mutations, leading to metastatic, multifocal, and aggressive disease, and as a consequence, a significant majority (90%) of pediatric patients exhibit symptoms of the illness [32].

Head and neck paragangliomas are rare in children and typically do not produce catecholamines. Symptoms may result from the compression or infiltration of adjacent structures, leading to hearing loss, pulsatile tinnitus, dysphagia, hoarseness, cough, and cranial nerve palsies [12,29].

Biochemical Testing

Numerous studies have demonstrated the superior diagnostic performance of metanephrines (metanephrine, normetanephrine, 3-metoxythromine) measurements compared to serum and urine catecholamines or urinary vanillylmandelic acid and homovanillic acid [15]. Plasma-free metanephrines offer higher sensitivity and specificity than urinary metanephrines and are recommended for diagnostic evaluation in children [21]. Liquid chromatography with electrochemical detection or tandem mass spectrometry are suggested methods to achieve analytical accuracy [12]. For optimal plasma metanephrine assessment, patients should maintain a supine position for at least 30 minutes before blood sampling, but achieving this in younger patients can be challenging [26]. Age-specific pediatric reference intervals for plasma-free normetanephrine, metanephrine, and 3-methoxytyramine play a key role in interpretation of results, particularly in early infancy [33-35].

Twenty-four-hour urinary metanephrine excretion has high sensitivity (up to 97%) and specificity (up to 91%) and is considered an alternative to plasma testing, which, when performed correctly, demonstrates sensitivity ranging from 97% to 100%. To ensure accurate quantification of fractionated urinary metanephrines, concurrent urinary creatinine measurement is essential to verify complete urine collection [1]. The obtained results can be influenced by dietary factors, medications, and the episodic nature of catecholamine secretion [21].

Clonidine suppression or glucagon stimulation tests are occasionally employed in adults when metanephrine measurements yield equivocal results. However, these tests exhibit suboptimal sensitivity and are not validated or routinely used in pediatric populations [15].

Imaging Studies

Imaging plays a crucial role in the management of pheochromocytoma and paraganglioma (**Table 4**). Its applications include confirming biochemical findings when positive or borderline, defining tumor location, extent, and optimal surgical approach, including assessing for multifocal or metastatic disease, and monitoring treatment efficacy [36].

Ultrasound examination is considered helpful in diagnosis, but a negative result is not definitive. Due to its wide availability and low cost, it can help detect PPGL [21].

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Table 4. Sensitivity, specificity, and limitations of various methods of radiological imaging of PPGL [21,28,37,51].

	Sensitivity	Specificity	Limitations
Ultrasound	76% (*Januszewicz et al 2006*)		
Computed tomography (CT)	Small tumors: 90-92%. Big tumors: 100% (*Januszewicz et al 2006*) 90% (*Lumachi et al 2006*) 88-100% (*Lenders et al 2014*)	93% (*Lumachi et al 2006*)	– Tumors larger than or equal to 5 millimeters
Magnetic resonance imaging (MRI)	93.3% (*Lumachi et al 2006*) Head and neck paragangliomas: 90-95% (*Lenders et al 2014*)	93% (*Lumachi et al 2006*)	– A child might require sedation due to long examination time – For pulmonary metastates CT is preferred
[^{123}I]-MIBG	75-90% (*Januszewicz et al 2006*) 90.6% (*Lumachi et al 2006*) Pheochromocytomas: 85-88%. Paragangliomas: 56-75% (*Lenders et al 2014*)	100% (*Januszewicz et al 2006*) 100% (*Lumachi et al 2006*) Pheochromocytomas: 70-100%. Paragangliomas: 84-100% (*Lenders et al 2014*)	– Thyroid blockade – Discontinuation of certain medications such as decongestants, calcium channel blockers, and labetalol – Long exam time (18-24 hours)
[^{18}F]-FDG PET	74-100% (*Lenders et al 2014*) 66-78% (*Krokhmal et al 2022*)		– Lesions smaller than 3 to 5 mm are hard to detect – Not specific to PPGL since positive images reflect glucose uptake and its metabolism by cells, including any cancer cells that have a high demand for glucose
[^{68}Ga]-DODATATE PET	72-100% (*Krokhmal et al 2022*)		– A false negative rate due to lack of somatostatin receptors

CT – computed tomography; MRI – magnetic resonance imaging; PPGL – pheo-chromocytoma and paraganglioma; MIBG – metaiodobenzylguanidine; FDG – fluorodeoxyglucose; FDOPA – fluorodihydroxy phenylalanine; DOTATATE – DOTA-Tyr3-Octreotate; PET – positron emission tomography.

Magnetic resonance imaging (MRI) is the imaging of choice for pediatric patients, and is used for screening because it does not involve ionizing radiation [28,36]. It is especially preferred in patients with metastatic PPGLs and in diagnosis of tumors located in the head and neck, as well as in patients with contraindications to other imaging studies.

Computed tomography (CT) is recommended as the second-choice imaging due to the associated risks of ionizing irradiation. The advantage of this modality is its excellent spatial resolution for the thorax, abdomen, and pelvis. CT scans can detect tumors larger than or equal to 5 millimeters. The tumor may be homogeneous or heterogeneous, necrotic with some calcifications, solid, or cystic [1]. The density of the PPGL tumors is ≥10 Hounsfield units.

Functional imaging, including [^{123}I]-metaiodobenzylguanidine (MIBG) scintigraphy, [^{18}F]fluorodeoxyglucose (FDG) PET–CT, [^{18}F] fluorodihydroxyphenylalanine (FDOPA), and [^{68}Ga]-DOTATATE PET, are indicated when biochemical testing is inconclusive or to assess for regional extension, multifocality, or presence of metastases [15]. The decision to employ functional imaging in pediatric patients is complex and must be carefully weighed against potential risks [26]. Each examination is best suited for the evaluation of certain types of disease [37].

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Table 5. Medications used for preoperative management of arterial hypertension in pediatric PPGL adapted from Jain et al (2020) [15].

Drug class	Dosage	Maximum recommended dose
α-adrenergic receptor blockers		
Phenoxybenzamine	0.2 mg/kg/day (max. 10 mg/dose) Increase the dose by 0.2 mg/kg/day every 4 days Goal: 0.4-1.2 mg/kg/day ÷ 6-8 h	2-4 mg/kg/day (60 mg/day)
Doxazosin	1-2 mg/day Increase the dose by 2-4 mg/day Goal: 2-4 mg/day ÷ 8-12 h	4-16 mg/day
Prazosin	0.05-0.1 mg/kg/day ÷ 8 h	0.5 mg/kg/day (20 mg/day)
Terazosin	1 mg/day Increase the dose to 1-4 mg/day	20 mg/day
β-adrenergic receptor blockers		
Propranolol	1-2 mg/kg/day ÷ 6-12 h Increase the dose to 4 mg/kg/day ÷ 6-12 h	640 mg/day
Atenolol	0.5-1 mg/kg/day ÷ 12-24 h Increase the dose to 2 mg/kg/day ÷ 12-24 h	100 mg/day
Metoprolol	1-2 mg/kg/day ÷ 12-24 h Increase the dose to 2 mg/kg/day ÷ 12-24 h	200 mg/day
α- and β-adrenergic receptor blocker		
Labetalol	1-3 mg/kg/day ÷ 8-12 h Increase the dose to 10-12 mg/kg/day ÷ 8-12 h	1200 mg/day
Calcium channel blocker		
Amlodipine	0.05-0.1 mg/kg/day ÷ 12-24 h Increase the dose to 0.3 mg/kg/day ÷ 12-24 h	10 mg/day
Tyrosine hydroxylase inhibitor		
Metyrosine	20 mg/kg/day ÷ 6 h Increase the dose to 60 mg/kg/day ÷ 6 h	2500 mg/day

[^{123}I]-MIBG is of great use in sporadic pheochromocytoma and metastatic disease when radiotherapy using [^{131}I]-MIBG is planned or when there is an increased risk of metastasis and recurrence due to a large primary or extra-adrenal tumor [38]. [^{123}I]-MIBG scintigraphy can detect tumors not seen on CT or MR imaging. [^{18}F]-FDG PET is well suited to detect small and hypermetabolic lesions [37]. Although [^{18}F]-FDG PET has similar rates of detection, [^{68}Ga]-DOTATATE has greater specificity and comparatively better contrast between lesions and background tissues [37]. Recent studies have shown the superiority of [68Ga]-DOTATATE PET over [18F]-FDG PET in detecting *SDHB*-related metastatic PPGLs [28]. With the recent US Food and Drug Administration approval of the safety profile of [^{68}Ga]-DOTATATE PET, it can also be used in pediatric patients [37].

Screening in Families

Genetic testing is essential for 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 and for second-degree relatives in *SDHD*- and *SDHAF2*-related cases. Carrier testing can be considered for second-degree relatives of individuals with *SDHB*, *SDHA*, *SDHC*, *TMEM127*, *MAX*, or other PPGL-associated gene mutations, especially in cases of metastatic disease. While first-degree relatives typically warrant ongoing surveillance, second-degree relatives or those with genes associated with low penetrance may only require a single screening evaluation [39].

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The optimal age for initiating genetic testing varies based on the specific gene mutation and the nature of surveillance required for mutation carriers. While well-established at 5 years for VHL syndrome, the optimal age for other hereditary PPGL syndromes remains uncertain. Proposed minimum ages include 5 years for *SDHB*-related PPGL and 10 years for *SDHA*-, *SDHC*-, and *SDHD*-related PPGL [12].

While conventional Sanger sequencing remains valuable for certain cases, especially in patients with syndromic presentations, and might be the only option available in some centers, next-generation sequencing (NGS) using targeted gene panels has become the preferred method due to the high degree of heterogeneity in clinical presentation of PPGL [26].

Pharmacological Treatment

Pharmacological treatment is given in patients with secreting PPGL to alleviate symptoms, particularly before planned surgery (**Table 5**).

Perioperative Management

Surgical resection of PPGLs carries a significant risk of intraoperative hemodynamic instability and cardiovascular complications. To mitigate this risk, relevant guidelines recommend routine preoperative administration of systemic alpha-blockers for all patients, even those with biochemically silent and normotensive presentations [40]. Beta-blockers are employed after alpha-blockade to counteract reflex tachycardia and catecholamine-induced tachyarrhythmias in PPGL patients [15]. According to the Endocrine Society guidelines, preoperative medical optimization for 7-14 days is recommended to achieve normalization of blood pressure and heart rate. Blood pressures are closely monitored in the preoperative period, with a target of less than 130/80 mmHg for teenagers over 16 years old and less than the 95th percentile for age, sex, and height for younger children, even leading up to surgery for those closer to the 50th percentile. The guidelines also acknowledge that some pediatric patients may require several weeks or longer to achieve target blood pressure and heart rate goals. This is likely due to the catecholamine burden from larger or multiple tumors, the need to titrate medications to limit adverse effects, and differences in sympathetic activity in children [41]. Treatment should also include a high-sodium diet and increased fluid intake to reverse catechol-amine-induced blood volume contraction preoperatively to prevent severe hypotension after tumor removal [1]. Postoperative patients require long-term, consistent surveillance.

Surgical Treatment

Surgical resection is the only curative treatment for PPGL. This method aims to eliminate the risks of hypersecretion and tumor growth. The choice of surgical approach is determined based on multiple factors, including germline genetic test results, the size of the tumor, body mass index, the surgeon's experience, and the likelihood of malignancy. After considering all these factors, the surgery is planned individually. Primary tumor resection does not eliminate the risk of tumor persistence and recurrence [42]. Laparoscopic removal is the preferred definitive treatment of pheochromocytomas up to 6 cm. Open laparotomy is reserved for patients with large pheochromocytomas (over 6 cm) and paragangliomas due to their higher risk of malignancy and tendency to localize in difficult anatomical regions [15,42]. Data presented in the International Consensus Statement on the diagnosis and management of pheochromocytoma and paraganglioma in children and adolescents from 2024 support laparoscopic surgery for tumors up to 5 cm and open surgery for tumors larger than 5 cm [26].

Treatment of Metastatic Tumors

Malignancy is relatively rare in pheochromocytomas (10-15%) but is quite common in paragangliomas (35-40%) [43]. Histopathology cannot reliably distinguish between metastatic and malignant paragangliomas. The World Health Organization uses the term metastatic to designate paragangliomas that have spread to sites (eg, lymph nodes or bones) where chromaffin cells or paraganglia are not normally present [36].

Surgery is the only curative therapy, and is indicated as the first-line therapy for locoregional disease or oligometastatic disease in selected patients. However, it can also be used to provide symptomatic relief or to reduce tumor mass effects for patients with widespread metastases [9].

Molecular targeted therapy is playing an increasingly important role in the treatment of metastatic pheochromocytomas and paragangliomas in adults. However, for children, this approach is still under investigation in clinical trials [26,40]. If complete tumor resection is not possible, debulking surgery or metastasectomy can be considered in children with metastatic PPGLs [26].

In patients with slow-to-moderate progression, moderate-to-high tumor burden, and positivity on [^{123}I]-MIBG imaging or somatostatin receptors scintigraphy, radionuclide therapy using somatostatin analogs or [^{131}I]-MIBG, respectively, may be applied [40]. [^{131}I]-MIBG treatment was approved in 2018 by the FDA for use in children with metastatic PPGL older than 12 years [26].

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For slowly to moderately progressing tumors that are not eligible for [^{131}I]-MIBG, tyrosine kinase inhibitors or temozolomide may be considered first-line therapies in adults [40]. Despite their increasing use in other pediatric cancers, tyrosine kinase inhibitors have not yet been approved for use in the treatment of pediatric patients with metastatic PPGL [26].

For metastatic PPGLs with rapid progression and a high visceral tumor burden, cyclophosphamide/vincristine/dacarbazine (CVD) chemotherapy may be the treatment of choice [40], but there are no prospective clinical trials to establish the effectiveness of CVD in children [26]. For patients with slow progression, low tumor burden, and oligometastatic disease, active surveillance may be considered [40]. It is important to acknowledge that most of these therapies are palliative, and targeted gene therapy depending on the tumor gene expression needs to be further explored [15].

Treatment of Recurrent Tumors

There is no compelling evidence to suggest that any therapeutic intervention, such as radiotherapy or systemic therapy, can substantially diminish the likelihood of tumor recurrence or metastasis following successful removal of a primary or recurrent tumor. Adjuvant radiotherapy may be contemplated in patients exhibiting repeated locoregional recurrences. Moreover, in patients with incomplete resection of a primary or recurrent tumor or metastatic lesions, supplementary local radiotherapy or targeted radionuclide therapy could be considered on an individual basis [44].

Surveillance

Surveillance guidelines for patients with genetic predispositions or a history of PPGL vary based on the specific gene mutation.

Given that 70-80% of pediatric patients had a germline mutation in a gene associated with PPGL, these patients require ongoing monitoring. Consequently, children and adolescents diagnosed with PPGL have an increased risk for recurrent, multifocal, and malignant disease requiring long-term follow-up [15]. Regular monitoring of blood pressure and plasma and urine metanephrine levels is essential [12]. The current protocols recommend surveillance through regular examinations for all pediatric patients with PPGL, as is done for high-risk adult patients (ie, patients with genetically determined disease, tumors larger than 50 mm, and extra-adrenal location) for whom life-time follow-up is indicated. Pediatric oncologists should be aware of the importance of extending the follow-up of children with PPGL into adulthood [45].

Individuals with RET (MEN2) or VHL mutations require annual biochemical screening with urinary or plasma metanephrines from age 5, while those with NF1 benefit from triennial screening starting at age 10-14. Children with a pathogenic or likely pathogenic mosaic variant in VHL should be offered life-long clinical surveillance [26]. While SDH mutations often present with biochemically silent PPGL, close screening is advised, with annual clinical symptoms review from the time of presentation or from age 5 years for asymptomatic *SDHB* carriers and age 10 for *SDHA/C/D* carriers [26]. *SDHB* mutation carriers, who are at increased risk of malignancy, necessitate intensive monitoring, including regular abdominal MRI every 18 months and MRI of the neck, thorax, and pelvis every 3 years. Although it is reported that patients with SDHB mutations develop metastases as early as 5 years from diagnosis, the data have shown that the 20-year prognosis and survival are good. Metastases in pediatric patients with *SDHB* mutation develop earliest in the bones, followed by lymph nodes, lungs, and liver. A tumor size ≥5 cm and multiple or recurrent tumors warrant closer follow-up for earlier detection of metastatic lesions [46]. Surveillance protocols for other *SDH* mutation carriers remain less defined [15].

Personalized Management

The optimal management of patients requires a multidisciplinary approach in highly specialized reference centers with extensive experience in management of pheochromocytoma and paraganglioma. Given the significant hereditary component of PPGL, genetic counseling, and testing are recommended for all patients with confirmed PPGL, those exhibiting syndromic features suggestive of hereditary syndromes, and individuals with a personal or family history of the disease. Next-generation sequencing (NGS) is recommended as the standard diagnostic tool [47].

Future Directions

Pediatric pheochromocytoma and paraganglioma remain significant clinical challenges, particularly regarding diagnosis and treatment. Advancing genetic analysis, incorporating children into data registries and clinical trials, and developing and disseminating internationally recognized guidelines specifically for this population are crucial for optimizing patient outcomes.

Conclusions

In children and adolescents with pheochromocytoma and paraganglioma, approximately 70-80% of cases are hereditary, conferring an increased risk of tumor recurrence, multifocality, and

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malignant transformation. This necessitates life-long surveillance. Genetic counseling and testing are essential for all pediatric patients, and genetic evaluation of family members is strongly recommended. Furthermore, dedicated research in pediatric PPGL management is crucial, given the unique clinical and genetic characteristics observed in this population.

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