A Current Review of the Etiology, Diagnosis, and Treatment of Pediatric Pheochromocytoma and Paraganglioma

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Context: Pheochromocytomas and paragangliomas (PHEO/PGL) are neuroendocrine tumors that arise from sympathetic and parasympathetic paraganglia. Diagnosed rarely during childhood, PHEO/PGL are nonetheless important clinical entities, particularly given our evolving understanding of their pathophysiology.

Evidence Acquisition: We identified articles through the U.S. National Library of Medicine by using the search terms pheochromocytoma and paraganglioma. Results were narrowed to manuscripts that included children and studies related to the genetics of PHEO/PGL. Web-based resources for genetic disorders were also used. For all articles, we performed subsequent reference searches and verification of source data.

Evidence Synthesis: Up to 20% of PHEO/PGL are diagnosed in children. Most are functional tumors, and clinical presentation includes symptoms related to catecholamine hypersecretion and/or tumor mass effect. Increasingly, PHEO/PGL are identified during presymptomatic screening in children with genetic syndromes associated with PHEO/PGL (multiple endocrine neoplasia type 2, von Hippel-Lindau disease, and the paraganglioma syndromes). Plasma and/or urine metanephrines are the best diagnostic test for a functional tumor, and the management of pediatric patients is similar to adults. Genetic counseling should be undertaken in all cases. Although most pediatric PHEO/PGL are benign, these tumors can occasionally metastasize, a condition for which no curative treatment exists.

Conclusions: Although PHEO/PGL are rarely diagnosed during childhood, the pediatric provider should be able to recognize and screen for such tumors, particularly in the context of a known genetic predisposition. Optimal care of these children includes a multidisciplinary team approach at centers experienced in the evaluation and treatment of these uncommon yet fascinating endocrine neoplasms. **(*J Clin Endocrinol Metab* 95: 2023–2037, 2010)**

Pheochromocytomas (PHEO) and paragangliomas (PGL) are rare neuroendocrine tumors that arise from neural crest-derived cells or organs, known as paraganglia, and can occur in all locations where paraganglia are found. The neuroendocrine origin of these neoplasms is underscored by extensive positive immunostaining for chromogranin A (1). Functional tumors produce catecholamines and are also known as chromaffin tumors. (Chromaffin refers to the brown-black color resulting from the oxidation of catecholamines after staining with chromium salts.) PHEO (Fig. 1) is the term used for a catecholamine-secreting tumor that occurs in the adrenal

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2009-2830 Received December 31, 2009. Accepted February 17, 2010.
First Published Online March 9, 2010

Abbreviations: CT, Computed tomography; DOPA, fluorodihydroxyphenylalanine; FDA, fluorodopamine; FDG, fluorodeoxyglucose; GIST, gastrointestinal stromal tumor; MEN, multiple endocrine neoplasia; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; NF, neurofibromatosis; PET, positron emission tomography; PGL, paraganglioma; PHEO, pheochromocytoma; SDH, succinate dehydrogenase; VHL, von Hippel-Lindau.

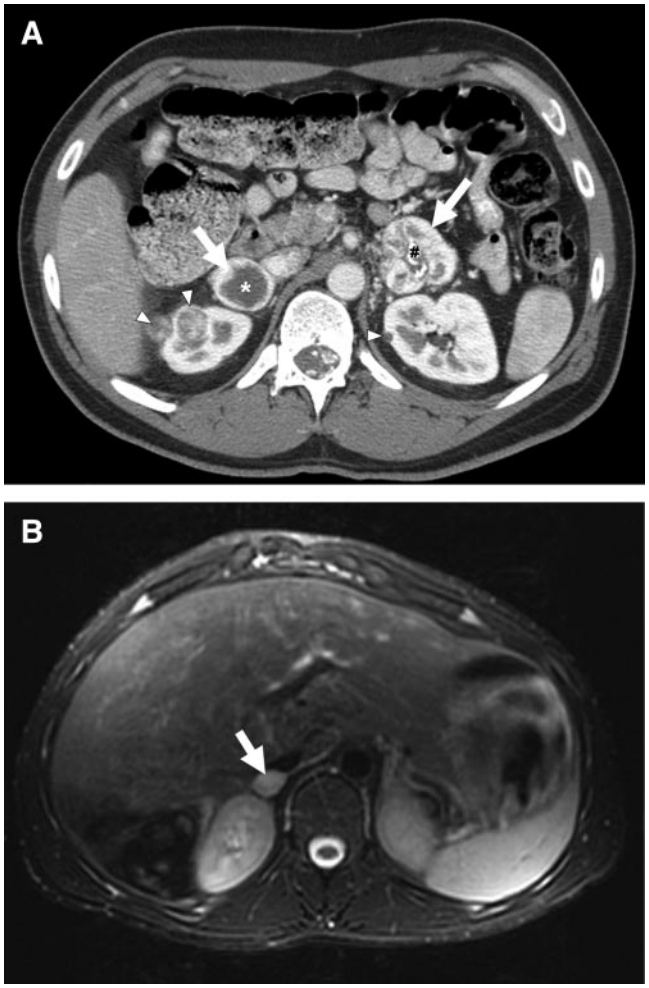

FIG. 1. PHEO. A, Bilateral PHEO (*white arrows*) in a patient with VHL disease. PHEO are vascular tumors with areas of central necrosis (*) and calcification (#). Note also the solid and cystic renal masses (*arrowheads*) bilaterally, consistent with renal cell carcinoma and benign renal cysts, respectively. B, T2-weighted axial MRI in a patient with an adrenergic right PHEO (*arrow*) in the context of MEN2b. Note the classic T2 hyperintensity.

medulla, the most common location, whereas PGL (Fig. 2) are extraadrenal tumors that arise from both sympathetic and parasympathetic paraganglia (2, 3). PGL are located anywhere from the base of the skull to the pelvis, but most commonly arise in the head and neck or in the abdomen near the renal vessels or the organ of Zuckerkandl, which is localized around the origin of the inferior mesenteric artery and is the largest extraadrenal collection of chromaffin tissue. The term PHEO is often used interchangeably with PGL, but it is best to maintain the distinction between these two tumor types due to underlying differences in genetics, clinical presentation, and malignant potential (Table 1).

PHEO/PGL comprise less than 7% of tumors arising from the sympathetic nervous system, and incidence rates are estimated at 0.3 cases per million per year or less (4, 5). Approximately 10–20% of cases are diagnosed during childhood at an average age of 11 yr, with a slight predominance in boys, particularly under the age of 10 (5–11). In children diagnosed with hypertension, it has been estimated that up to 1.7% have a catecholamine-secreting neoplasm (12). The vast majority of these tumors in childhood are PHEO, and they synthesize and secrete catecholamines (dopamine, norepinephrine, and epinephrine) and their metabolites (homovanillic acid, normetanephrine, and metanephrine, respectively) (1, 13, 14). PGL can be either functional (sympathetic) or nonfunctional (parasympathetic), depending on the site of origin and underlying mutational events (Table 1) (13, 15, 16). The vast majority of PGL arising in the head and neck are nonfunctional, whereas most intraabdominal PGL are secretory chromaffin tumors. Areas of ganglioneuroblastoma, ganglioneuroma, or neuroendocrine carcinoma are sometimes admixed with PHEO or PGL, in which case the term composite PHEO or PGL is used (1, 17, 18).

The purpose of the current manuscript is to present a contemporary review and approach to the pediatric patient with a suspected PHEO/PGL or who, due to having inherited a predisposing gene mutation, is at risk for the development of such a neoplasm.

Genetic Issues (Table 1)

PHEO/PGL often occur as sporadic tumors, but they also develop as part of hereditary tumor syndromes, chiefly von Hippel-Lindau (VHL) disease and multiple endocrine neoplasia (MEN) 2A and 2B, the familial PGL syndromes and, more rarely, neurofibromatosis (NF) type 1, MEN1, and the tuberous sclerosis complex (Table 1) (2, 5–7, 15, 19–30). Recently, a patient with erythrocytosis and recurring, sympathetic PGL was found to have a novel germline mutation identified in the prolyl hydroxylase domain 2 gene (*PHD2*) (31). Finally, the association of nonfamilial PGL, gastrointestinal stromal tumor (GIST), and pulmonary chondroma (Carney triad) has been described in rare patients, but a genetic etiology has yet to be identified (32, 33).

Approximately 56% of apparently sporadic PHEO that present in patients 18 yr of age or younger are due to an identifiable mutation in germline DNA, and the percentage with hereditary disease is as high as 70% in children less than age 10 (7). Hereditary PHEO/PGL are often multifocal and, in the case of PHEO, frequently bilateral. In general, a finding of multicentric tumors is highly suggestive of familial disease and is more common in childhood presentations of PHEO/PGL (6, 8, 34).

VHL disease is a major cause of chromaffin tumors diagnosed in childhood (6, 7, 15). PHEO/PGL occur in 10–20% of patients with VHL, particularly in those individuals with VHL2 and missense mutations of the *VHL*

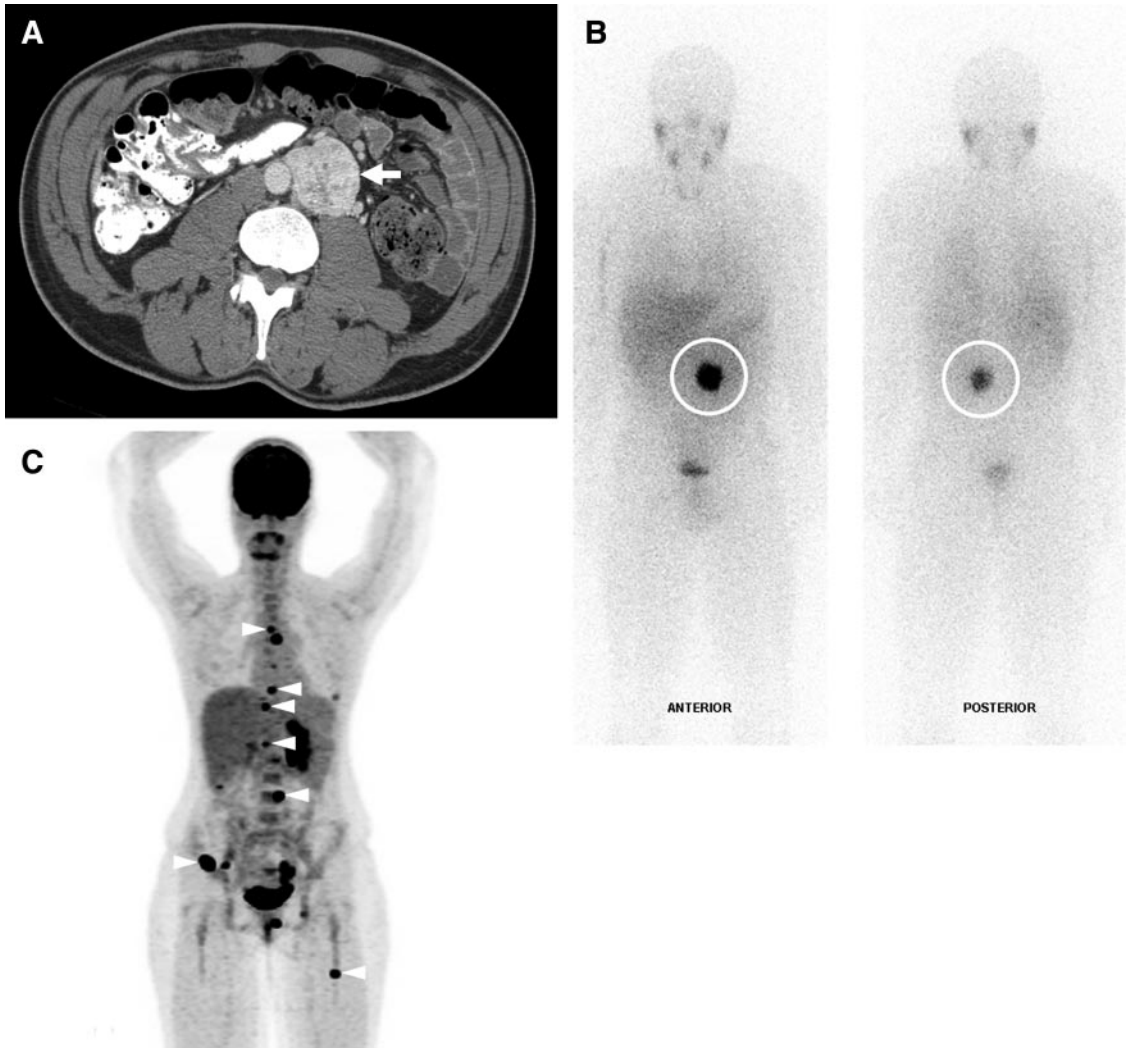

FIG. 2. PGL. A, Axial CT after contrast in a patient with symptoms of catecholamine excess and a noradrenergic biochemical profile. A PGL (*arrow*) is identified in a paraaortic location between the left renal artery and the origin of the inferior mesenteric artery in the region of the organ of Zuckerkandl. B, MIBG scan in the same patient, 24 h after the administration of [^{123}I]MIBG, demonstrating intense uptake in the tumor. C, [^{18}F]FDG PET scan in a patient with metastatic PGL and an *SDHB* mutation. Bony metastatic disease (*arrowheads*) predominates.

tumor suppressor gene (24, 35, 36). Almost all VHL-related PHEO/PGL are functional, but nonfunctional parasympathetic PGL occurring in the context of VHL have recently been described (37, 38). There is a codon-specific risk for the development of PHEO in MEN2, and activating mutations in exons 8, 10, 11, 13, and 14 (MEN2A) and exons 14–16 (MEN2B) of the *RET* protooncogene may cause PHEO in up to 50% of affected subjects (22, 23, 39, 40). Furthermore, somatic *RET* mutations can be detected in up to 20% of sporadic PHEO (41, 42). MEN2 has also very rarely been associated with parasympathetic PGL (37). There are pathological differences between tumors that arise as part of VHL disease compared with MEN2 syndrome. A background of adrenal medullary hyperplasia is associated with MEN2, and VHL-associated tumors have a distinct histological phenotype that can distinguish such tumors from those arising in the setting of MEN2 (1, 43, 44). PHEO occurs in fewer than 5% of patients with NF1 and usually only in adults with hypertension (24, 45, 46). PGL (and more rarely PHEO) occur as part of the familial PGL syndromes (PGL1-4). PGL1, PGL3, and PGL4 result from germline mutations in genes encoding one of the subunits of the mitochondrial complex II succinate dehydrogenase (*SDH*) enzyme gene, a component of the tricarboxylic acid cycle (30, 47–50). PGL1 (*SDHD* gene mutations) is associated primarily with parasympathetic head and neck PGL (also known as glomus tumor or chemodectoma), with a 68% penetrance of this phenotype by age 40 (29, 47); PGL3 (*SDHC* gene mutations) is rare and almost exclusively associated with parasympathetic head and neck PGL (47, 51). PGL4 (*SDHB* gene mutations) typically but not uniformly causes sympathetic PGL arising within the abdomen, pelvis, or thorax and tumors that carry a high malignant potential. Abdominal and/or thoracic PGL will manifest in 69% of affected subjects by age 60 (29, 47). *SDHx*-related tumors can also be asso-

TABLE 1. Major syndromes associated with PHEO and PGL

	Gene (chromosome)	% *de novo*[a]	Type of tumor	Clinical phenotype[b]	Earliest age of DX[c] (yr)	Age to begin screening[d]	Other clinical manifestations
MEN2A	*RET* (10q11.2)	5	PHEO (up to 50%) Very rare PGL	Sympathetic Adrenergic Malignancy rare Background of adrenal medullary hyperplasia	5–8[e] (22, 23) 12[f] (133, 134)	5–10 yr, particularly in high-risk mutations (codons 630, 634)	Codon-specific risk of MTC (~100%) Parathyroid adenoma/hyperplasia (30%) Variants with cutaneous lichen amyloidosis and Hirschsprung's disease Adrenal ganglioneuroma identified in rare cases
MEN2B	*RET* (10q11.2)	50	PHEO (50%)	Sympathetic Adrenergic Malignancy rare Background of adrenal medullary hyperplasia	12 (135)	5–10 yr	Very high risk for early-onset and metastatic MTC (100%) Mucosal neuromas of the lips, tongue, and eyelids Medullated corneal nerve fibers Distinctive facies with enlarged lips Megacolon/ganglioneuromatosis of the GI tract Marfanoid body habitus Absent tears in infancy Feeding problems and constipation in infancy Adrenal ganglioneuroma identified in rare cases
Carney triad	UNK	UNK	PGL (47%)[g] PHEO (16%)	Sympathetic and parasympathetic Located equally in head and neck, thorax, and abdomen Malignancy in 10%	12 (136)	NA	GIST Pulmonary chondroma Adrenocortical tumor Esophageal leiomyoma Primarily identified in young women

(*Continued*)

TABLE 1. Continued

	Gene (chromosome)	% *de novo*[a]	Type of tumor	Clinical phenotype[b]	Earliest age of DX[c] (yr)	Age to begin screening[d]	Other clinical manifestations
NF1	*NF1* (17q11.2)	50	PHEO (<5%) Very rare PGL	Sympathetic Adrenergic Malignancy rare PHEO usually in adults (mean age 42 yr)	7 (137)	If clinical NF1 and HTN	Café-au-lait macules with smooth borders Axillary and inguinal freckling Dermal and plexiform neurofibromas Lisch nodules of the iris Learning disabilities Scoliosis, vertebral dysplasia, pseudarthrosis, and bony overgrowth Optic and other CNS gliomas Malignant peripheral nerve sheath tumors Vasculopathy and HTN caused by renal artery stenosis NETs: insulinoma (rare) carcinoid (1%) (positive for somatostatin)
PGL1	*SDHD* (11q23)	UNK[h]	PGL (primarily head and neck) PHEO	Parasympathetic Occasionally sympathetic/ noradrenergic Malignancy rare	5 (7)	10 yr	86% penetrance by age 50 yr Parent of origin effects, with disease caused when inherited from the father Can be associated with GIST (Carney-Stratakis dyad)
PGL2	*SDH5*, aka *SDHAF2* (11q13.1)	UNK[h]	PGL (head and neck)	Parasympathetic	15–25 (53)	10 yr	Parent of origin effects, with disease caused when inherited from the father ~100% penetrance by age 50 yr
PGL3	*SDHC* (1q21)	UNK[h]	PGL (head and neck)	Parasympathetic Malignancy rare Rare cases of sympathetic PGL/PHEO	13 (138)	10 yr	Can be associated with GIST (Carney-Stratakis dyad)
PGL4	*SDHB*(1p36.1-p35)	UNK[h]	PGL (primarily abdominal) PHEO	Sympathetic Noradrenergic Malignancy very common (50%)	6 (47)	5 yr	77% penetrance by age 50 Can be associated with GIST (Carney-Stratakis dyad) Can be associated with RCC in adults

(*Continued*)

TABLE 1. Continued

	Gene (chromosome)	% *de novo*[a]	Type of tumor	Clinical phenotype[b]	Earliest age of DX[c] (yr)	Age to begin screening[d]	Other clinical manifestations
VHL	*VHL* (3p26-p25)	20	PHEO (20%) PGL (5%)	Sympathetic (rarely parasympathetic) Noradrenergic Malignancy rare (5%) and more likely with PGL	5 (7, 139)	5 yr	Hemangioblastomas of the CNS and retina Renal cysts and clear-cell RCC Pancreatic cysts and cystadenomas Endolymphatic sac tumors Papillary cystadenomas of the epididymis (males) and round ligament (females) Nonfunctioning pancreatic endocrine tumors (5–10%)

CNS, Central nervous system; DX, Diagnosis; GI, gastrointestinal; HTN, hypertension; MTC, medullary thyroid carcinoma; NA, not applicable; NET, neuroendocrine tumor; PGL, familial PGL syndrome or PGL; RCC, renal cell carcinoma; UNK, unknown.

[a] Percentage of subjects presenting with a negative family history and a *de novo* gene mutation; [b] Sympathetic tumors are functional and secrete catecholamines; parasympathetic tumors are nonfunctional. In general, head and neck PGL are parasympathetic, whereas PHEO and abdominal PGL are sympathetic. Noradrenergic tumors almost exclusively secrete norepinephrine and normetanephrine, whereas adrenergic tumors secrete epinephrine and metanephrine in addition to norepinephrine and normetanephrine; [c] Earliest age of diagnosis of PHEO/PGL based upon review of the literature and references; [d] In the opinion of the authors and based upon review of the literature, age at which annual screening for PHEO/PGL should be initiated for patients with a known gene mutation; [e] Ages of earliest PHEO onset reported in consensus guidelines via personal communication; [f] Age of earliest PHEO onset published in the medical literature; [g] Due to incomplete expression of the phenotype, PGL is not present in all patients suspected to have Carney triad (33); [h] Unknown, given variable expression of the phenotype in affected relatives.

ciated with GIST, which is also referred to as the Carney-Stratakis dyad (52). PGL2 has not been well characterized with only isolated pedigrees published in the literature (53–55). Recently, this syndrome has been identified to be secondary to heterozygous loss-of-function mutations in *SDH5*, a gene whose product is responsible for SDH-dependent respiration and for flavination of SDHA (56).

Advances in medicine have illuminated the genetic defects responsible for most of these familial syndromes (Table 1). As a result, genetic testing under the guidance of a qualified genetic counselor is imperative for all children who present with a PHEO/PGL, regardless of the family history (5, 15, 19, 20, 28) (Fig. 3). Recommendations have been made to help the clinician prioritize the order of genetic testing, with *VHL* being the major gene of interest in children with PHEO and *SDHB* being the suspected gene in patients with PGL and/or malignant disease (Fig. 3). Evaluation for *RET* protooncogene germline mutations is recommended only in the rare case of a child with an apparently sporadic PHEO who exhibits an adrenergic biochemical phenotype, because medullary thyroid carcinoma usually presents before PHEO in most individuals with MEN2 and due to the rarity of MEN2-related PHEO in childhood. NF1 is usually clinically diagnosed, and therefore, testing for mutations in the *NF1* gene in the context of an apparently sporadic tumor will be of very low yield and therefore is not recommended. Resources for genetic testing include the Online Mendelian Inheritance in Man (OMIM; http://www.ncbi.nlm.nih.gov/entrez?db=omim) and the internet site GeneTests (http://www.genetests.org), a publicly funded project that provides current and authoritative information on genetic testing and its use in the diagnosis, management, and genetic counseling of individuals with a genetic disorder or suspected genetic disorder.

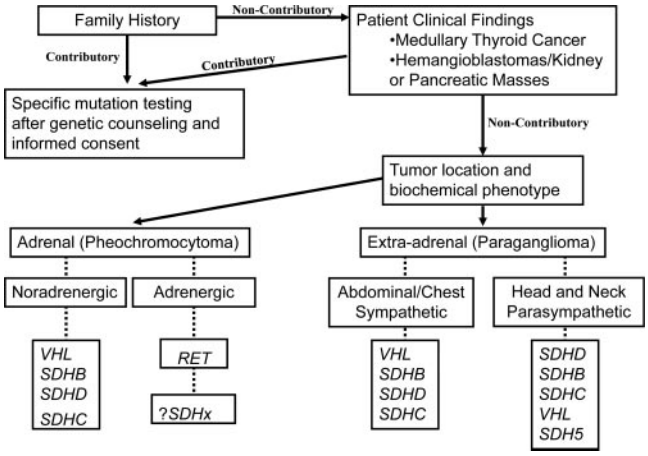

FIG. 3. Genetic testing in pediatric PHEO/PGL.

Malignant PHEO/PGL

The majority of PHEO/PGL are benign tumors, but approximately 12% of these neoplasms are malignant in the pediatric population (6). Based upon data from a British tumor registry, the incidence of malignant PHEO in children is estimated to be 0.02 per million per year (5). Some centers report a malignancy rate during childhood as high as 46% (57), although these data may reflect a referral bias. No single histological feature or immunohistochemical profile is independently able to predict metastatic potential, including extreme cytological atypia, capsular or vascular invasion, or areas resembling pediatric neuroblastoma (1). Features noted more frequently in malignant tumors include extraadrenal location, confluent tumor necrosis, absence of hyaline globules, coarse nodularity of the primary tumor, high proliferative index, and size greater than 5 cm, among others (17, 58). Scoring systems to predict malignant behavior have been proposed, including the 2002 PASS system (PHEO of Adrenal Scaled Score) and a subsequent scoring system in 2005 that also incorporated the biochemical characteristics of the tumor (59, 60).

Malignancy is therefore established only by the presence of distant metastases in a site where paraganglia are not normally located (*e.g.* lymph nodes, liver, lungs, and/or bone) (1, 17) (Fig. 2). The risk of malignant transformation is greater for extraadrenal sympathetic PGL than for PHEO or nonsecretory head and neck PGL. The highest risk for malignancy and death is in SDHB-related sympathetic PGL, which represents 50% or more of malignant tumors (47, 61–65). Although generally not malignant, head and neck PGL can result in significant morbidity from local growth and impingement of normal structures by the tumor mass.

Clinical Presentation

The clinical presentation of a sympathetic or functional PHEO/PGL in childhood depends on differences in catecholamine secretion and release as well as individual patient sensitivities to catecholamines (25). Children usually present because of symptomatic catecholamine hypersecretion or, less often, due to tumor mass effects (*e.g.* pain), as an incidental radiographic finding, or because of family screening for one of the hereditary syndromes discussed above (5, 57). Signs and symptoms of a sympathetic chromaffin tumor include hypertension, typically sustained in the majority of pediatric cases; paroxysmal episodes (*e.g.* the classic triad of headaches, palpitations, and diaphoresis); pallor; orthostatic hypotension and syncope; tremor; and anxiety (3, 6, 13, 15, 57, 66). Symptoms can also be nonspecific and include blurred vision; abdominal pain, diarrhea, and other gastrointestinal symptoms; weight loss; hyperglycemia; polyuria and poly-

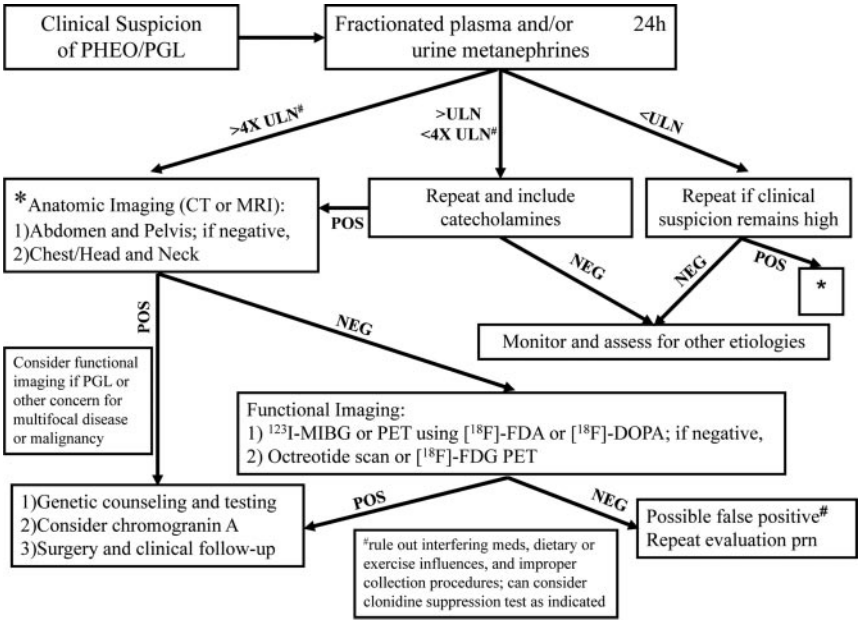

FIG. 4. Diagnosis of pediatric PHEO/PGL. NEG, Negative; POS, positive; ULN, upper limit of normal.

dipsia; low-grade fever; and behavioral problems/decline in school performance (13, 15, 66–68). Hematuria and paroxysmal symptoms during micturition can be the presenting features of a bladder PGL (13, 69). Complications of catecholamine excess can include hypertensive crisis, cardiomyopathy, pancreatitis, stroke, seizures, and even multiorgan failure and death (15, 66, 68).

Symptoms of parasympathetic, nonsecretory tumors include hearing loss, tinnitus, and other symptoms of mass effect such as voice hoarseness, pharyngeal fullness, dysphagia, cough, and pain. Given their neuroendocrine origin, PHEO/PGL can also rarely cosecrete other hormones, resulting in a clinical syndrome of ectopic hormone excess, such as gigantism (GHRH), Cushing syndrome (CRH or ACTH), hypercalcemia (PTHrP), the syndrome of inappropriate antidiuretic hormone secretion, and secretory diarrhea (vasoactive intestinal peptide) (13). PHEO/PGL identified during the course of prospective presymptomatic screening within the context of a familial disorder are often asymptomatic (70, 71). Although this clinical presentation is becoming more common, there is currently no consensus as to how to approach such patients with small asymptomatic tumors, particularly in those clinical settings with a low malignancy risk.

Diagnosis (Fig. 4)

Biochemical diagnosis

The diagnosis of PHEO/PGL has been simplified by advances in the assays used to detect and quantify levels of catecholamines and their metabolites in blood and urine. At present, the diagnostic test of choice is the measurement of fractionated plasma and/or urine metanephrines (metanephrines and normetanephrines), which are highly sensitive tests (approaching 100% sensitivity) for the diagnosis of a sympathetic chromaffin tumor (3, 13, 72–78). Methods using mass spectrometry to measure plasma free metanephrines appear to be superior (79, 80). The high sensitivity of metanephrine testing is based upon the fact that there is intratumor metabolism of catecholamines (*i.e.* norepinephrine to normetanephrine and epinephrine to metanephrine), a process that occurs independently of catecholamine release, which can occur intermittently or at low rates (76). An elevation of these analytes greater than 4-fold above the reference range is associated with almost 100% probability of the presence of a catecholamine-secreting tumor (81). Any drugs known to interfere with these assays (*e.g.* acetaminophen, tricyclic antidepressants, phenoxybenzamine, and decongestants, among others) (3) should be discontinued before testing. Moreover, to avoid a false-positive result from exercise and procedure-induced stress, plasma metanephrines are best measured in the supine position 30 min after an indwelling needle or catheter is inserted into the vein (3). Dietary restrictions are not routinely employed but should be considered if the assay used measures only deconjugated normetanephrines or if a dopamine-secreting tumor is suspected (82).

Functioning tumors can further be subclassified as being either noradrenergic or adrenergic based upon their pattern of catecholamine release (83, 84). Noradrenergic PHEO/PGL secrete norepinephrine and normetanephrine, as seen in VHL disease and in many tumors associated with the familial PGL syndromes. Adrenergic tumors secrete both epinephrine and norepinephrine and their metabolites, and these tumors are more commonly PHEO that arise sporadically or within the clinical context of MEN2 or NF1 (76, 83). One reason for this differential secretion of catecholamines is the decreased expression of phenylethanolamine *N*-methyltransferase (PNMT), the enzyme that converts norepinephrine to epinephrine, in VHL tumors as compared with those that arise as part of MEN2 (85).

Very rarely do tumors secrete dopamine preferentially. These tumors are usually extraadrenal *SDHx*-mediated paragangliomas (64, 86, 87), and there is no pathognomonic constellation of symptoms that will lead to this diagnosis. However, a dopamine-secreting tumor should be considered

in normotensive patients identified to have a mass that appears consistent with a PHEO/PGL, in which case dopamine and its metabolites, homovanillic acid and methoxytyramine, should also be measured (87–89).

Chromogranin A, a major secretory protein present in the soluble matrix of chromaffin granules, is a very effective tumor marker that may correlate with tumor size and malignant potential and improve the sensitivity of diagnostic testing and long-term follow-up (72, 90–92). Chromogranin A also appears to be a useful marker in the rare *SDHB*-related paraganglioma that is biochemically silent (16, 64).

In patients with paroxysmal symptoms and normal metanephrine levels, confirmation of the diagnosis may be better achieved by biochemical screening of fractionated metanephrines and catecholamines during and just after a clinical event. Clonidine suppression and glucagon stimulation tests (93–95) have been studied in the diagnosis of catecholamine-secreting tumors but are rarely required and, in the case of the glucagon stimulation test, have been largely abandoned due to insufficient diagnostic sensitivity (96). Furthermore, these tests have not been validated in the diagnosis of childhood PHEO/PGL.

Radiographic studies

Once the biochemical diagnosis of catecholamine excess is established, radiographic studies should be undertaken to identify the location of the tumor(s) (15) (Fig. 4). The initial test of choice is cross-sectional imaging [either computed tomography (CT) or magnetic resonance imaging (MRI), which have similar diagnostic sensitivities] of the abdomen and pelvis, followed by imaging of the neck and chest if the initial studies are unrevealing (74, 76). Abdominal ultrasound may also be considered in children, if local expertise permits. PHEO/PGL are vascular tumors that commonly contain necrotic, cystic, and/or hemorrhagic areas (Figs. 1 and 2). On MRI, they may exhibit a classic hyperintense appearance on T2-weighted images (Fig. 1B). Functional testing using nuclear scintigraphy with ^{123}I-labeled metaiodobenzylguanidine (MIBG) (Fig. 2B) is a highly specific test that can confirm the catecholamine-secreting nature of a tumor, localize tumors not seen with cross-sectional imaging, and identify other sites of disease, although its use is more limited in malignant disease (76, 77, 97–99). Before MIBG scanning, care should be taken to ensure that the patient is not taking medications (for example over-the-counter decongestants, calcium channel blockers, or labetalol) that are known to decrease MIBG uptake (100). Because MIBG testing is not 100% sensitive, other nuclear imaging modalities can be considered: somatostatin receptor scintigraphy using ^{111}In-labeled Diethylenetriaminepentaacetic acid octreotide scan or ^{123}I-labeled Tyr3-Diethylenetriaminepentaacetic acid octreotide, [^{18}F]fluorodihydroxyphenylalanine (DOPA) positron emission tomography (PET), [^{18}F]fluorodopamine (FDA) PET, [^{18}F]fluorodeoxyglucose (FDG) PET, [^{11}C]epinephrine PET, or [^{11}C]hydroxyephedrine PET (76, 101, 102). Although some of these other functional studies, particularly [^{18}F]DOPA and [^{18}F]FDA PET, are likely to be superior to scanning with MIBG (103–105), not all centers have the capability of performing these studies. [^{18}F]FDG PET may be superior in the evaluation and work-up of malignant PHEO/PGL, particularly in *SDHB* mutation carriers (105–107).

Staging and Prognosis

There is currently no clinical staging system used for malignant PHEO/PGL. The prognosis for a completely resected tumor, particularly a PHEO, is excellent. Life expectancy for malignant disease is generally determined by the location of metastatic disease, with survival less than 5 yr in patients with liver and lung metastases and longer survival in those with primarily bony metastatic disease (76). Overall 5-yr survival rate varies between 34 and 60% (76), and survival can be quite prolonged, with almost a quarter of patients in some series living 15 yr or longer (108). In children with malignant tumors, the 5- and 10-yr disease-specific survival rates are estimated to be 78 and 31%, respectively, with a mean survival of 157 $\pm$ 32 months (57).

Treatment

Medical preparation for surgery

Once the diagnosis of a sympathetic PHEO/PGL has been confirmed biochemically, medical therapy should be initiated for 1–2 wk before surgery. This is done to minimize the complications that may arise from acute catecholamine surges during induction of anesthesia and manual manipulation of the tumor (9, 15, 109, 110). There is no universal algorithm that exists for the medical management of a catecholamine-secreting tumor, much less one diagnosed in a child. Nevertheless, α_1-adrenergic blockade is usually the therapy of choice, and the primary agent used in children is the noncompetitive α-blocker phenoxybenzamine (Dibenzyline; starting 0.2–1 mg/kg $\cdot$ d in divided doses) (5, 15, 74, 109). Side effects of phenoxybenzamine can include tachycardia, nasal congestion, and symptomatic orthostasis. Selective α-blockers such as prazosin (Minipress) and doxazosin (Cardura) and calcium channel blockers such as nifedipine (Procardia) and nicardipine (Cardene) can also be used (9, 95, 111, 112). Treatment with α-blockade improves symptoms, lowers blood pressure, and expands the vascular bed and blood volume. Because phenoxybenzamine is a long-

acting medication, it may increase the risk of postoperative hypotension (3, 9, 77, 95). Metyrosine (Demser, starting dose 125–250 mg once or twice daily) is a competitive inhibitor of tyrosine hydroxylase, the rate-limiting step of catecholamine biosynthesis, and it can also be used as part of the preoperative preparative regimen (113). However, due to its potential significant side effects (particularly sedation, diarrhea, and extrapyramidal manifestations) and unclear utility, particularly in pediatric patients, its use is not routinely recommended by the authors. Symptomatic postural hypotension may be seen at the beginning of therapy with these agents, so it is imperative to start at low doses and titrate upward until the blood pressure is normal for age and height (http://www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm), and the patient is minimally orthostatic. Once α-blockade has been established, a β-blocking agent (*e.g.* propranolol, atenolol, or metoprolol) can be added to control reflex tachycardia (114). A β-blocker should never be used as a single agent because of the possibility of worsening symptoms and hypertension due to unopposed catecholamine effects at α-adrenergic receptors (3). A few days before surgical intervention, oral salt loading (either via increased dietary intake or with sodium chloride tablets) is recommended to expand the blood volume to prevent severe postoperative hypotension. Some centers also routinely admit patients for iv fluids before PHEO/PGL resection (114).

Surgical therapy

Surgical resection is the mainstay in the treatment of PHEO/PGL, and the procedure of choice for most PHEO is laparoscopic adrenalectomy, either using transperitoneal or retroperitoneal approaches (115–119). Preoperative biopsy is not indicated and potentially dangerous (120). Laparotomy should be contemplated in patients with large PHEO and/or a concern for underlying malignancy based upon the clinical presentation or radiographic appearance of the tumor. If a bilateral procedure is planned, the posterior retroperitoneoscopic approach has the added benefit of not altering patient positioning during the operation, ultimately resulting in a shorter operating time. In the setting of bilateral PHEO, cortical-sparing procedures should be considered for the adrenal with the least tumor bulk (117, 121). The cortical-sparing approach is particularly attractive in young children and children at risk for noncompliance with the lifelong glucocorticoid and mineralocorticoid replacement required after bilateral adrenalectomy. A successful cortical-sparing procedure involves accurate preoperative imaging (such as CT with reconstructed views to assess the surrounding vasculature) to identify the portion of cortex most likely to be spared, adequate exposure of the adrenal gland in a bloodless field, and extreme care not to mobilize the portion of adrenal to be preserved. Because it is extremely difficult to preserve a vascularized portion of adrenal cortex sufficient to prevent corticosteroid dependence without also leaving some amount of adrenal medulla, there is a risk for recurrent PHEO in the remnant. Data on the frequency of recurrence in cortical-sparing adrenalectomies are currently limited, but studies have shown recurrence rates in this setting to be between 10 and 38% (8, 57, 121, 122). However, not all recurrences were necessarily in the same location as the previous operation. The surgical approach for removal of a PGL depends upon the location of the tumor but in selected cases can also be performed laparoscopically (15, 118).

It is important that the anesthesiologist be familiar with the intraoperative management of PHEO/PGL because blood pressures can vary widely and dysrhythmias can occur, particularly during induction of anesthesia and manipulation of the tumor (109). Postoperatively, the patient should be monitored closely for the two major complications of hypotension and hypoglycemia (3, 109). In patients who have had a cortical-sparing adrenalectomy in the context of bilateral PHEO resection, we typically perform a high-dose cosyntropin stimulation test before hospital discharge to determine the need for adrenal steroid replacement.

Treatment of malignant PHEO/PGL

Patients with unresectable malignant tumors or distant metastatic disease can usually be successfully palliated through the use of the medications discussed above. Radiation therapy or radiofrequency ablation can help with symptomatic metastatic disease, and iv bisphosphonates can be considered for symptomatic treatment of bony metastases, particularly in patients with bone pain or lesions that increase the risk of pathological fracture. Currently available systemic treatment modalities are only palliative in nature and include [^{131}I]MIBG, somatostatin analogs, and chemotherapy (58, 61, 123–128). The major chemotherapeutic regimen used in the treatment of malignant disease has historically been cyclophosphamide, vincristine, and dacarbazine (CVD), and this regimen can provide tumor regression and symptom relief in up to 50% of patients, but it does not prolong overall survival (76, 108, 129, 130). Recent reports of successful treatment using the oral tyrosine kinase inhibitor, sunitinib, suggest that the newer targeted therapies may hold promise for the treatment of this disease (131, 132).

Follow-Up

Because PHEO/PGL can have unpredictable behavior and metastasize late in the clinical course, and because children in particular are at risk for the development of metachronous tumors, long-term follow-up with biochemical

screening (*i.e.* plasma or urine metanephrines) and intermittent imaging studies are required (1, 3, 5, 15). Because recurrence rates are increased, diligent follow-up must particularly be undertaken in children who have had gland-sparing procedures for multicentric PHEO (8, 57, 121, 122). For children with an identified genetic mutation predisposing them to the development of a PHEO/PGL, annual screening is advised, with the age of initial screening determined by the specific gene mutation (Table 1). Chromogranin A may be a useful marker of recurrence, particularly in those patients with a baseline elevation at the time of their original diagnosis. Furthermore, cross-sectional imaging, usually MRI because of the lack of radiation exposure, is recommended periodically for follow-up of patients at high risk of recurrence or for developing a PHEO/PGL (such as seen with the *SDHx* gene mutations), because these tumors may not always be identified through routine biochemical screening (16).

Conclusion

Although PHEO/PGL are very rarely diagnosed during childhood, it is imperative for the pediatric clinician to be able to recognize and screen for such tumors, particularly in the context of known familial disease. Advances in medicine have expanded our knowledge regarding the etiology, diagnosis, treatment, and long-term follow-up of these tumors. Optimal care of these children includes a multidisciplinary approach by endocrinologists, surgeons, genetic counselors, and radiologists/nuclear medicine experts who are experienced in the evaluation and treatment of these uncommon yet fascinating endocrine neoplasms.

Acknowledgments

We thank Dr. Matthew Stephen for his review of this manuscript.

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Disclosure Summary: The authors have nothing to disclose.

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