Characteristics of Pediatric *vs* Adult Pheochromocytomas and Paragangliomas

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Context: Pheochromocytomas and paragangliomas (PPGLs) in children are often hereditary and may present with different characteristics compared with adults. Hereditary PPGLs can be separated into cluster 1 and cluster 2 tumors due to mutations impacting hypoxia and kinase receptor signaling pathways, respectively.

Objective: To identify differences in presentation of PPGLs between children and adults.

Design: A retrospective cross-sectional clinical study.

Setting: Seven tertiary medical centers.

Patients: The study included 748 patients with PPGLs, including 95 with a first presentation during childhood. Genetic testing was available in 611 patients. Other data included locations of primary tumors, presence of recurrent or metastatic disease, and plasma concentrations of metanephrines and 3-methoxytyramine.

Results: Children showed higher ($P < 0.0001$) prevalence than adults of hereditary (80.4% *vs* 52.6%), extra-adrenal (66.3% *vs* 35.1%), multifocal (32.6% *vs* 13.5%), metastatic (49.5% *vs* 29.1%), and recurrent (29.5% *vs* 14.2%) PPGLs. Tumors due to cluster 1 mutations were more prevalent among children than adults (76.1% *vs* 39.3%; $P < 0.0001$), and this paralleled a higher prevalence of noradrenergic tumors, characterized by relative lack of increased plasma metanephrine, in children than in adults (93.2% *vs* 57.3%; $P < 0.0001$).

Conclusions: The higher prevalence of hereditary, extra-adrenal, multifocal, and metastatic PPGLs in children than adults represents interrelated features that, in part, reflect the lower age of disease

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 30 November 2016. Accepted 26 January 2017.
First Published Online 31 January 2017

Abbreviations: HIF2α, hypoxia-inducible factor 2 alpha; HRAS, Harvey rat sarcoma viral oncogene homolog; MAX, MYC-associated factor X; NF1, neurofibromatosis type 1; PPGL, paraganglioma; RET, rearranged during transfection; TMEM127, transmembrane protein 127; VHL, von Hippel-Lindau.

presentation of noradrenergic cluster 1 than adrenergic cluster 2 tumors. The differences in disease presentation are important to consider in children at risk for PPGLs due to a known mutation or previous history of tumor. (*J Clin Endocrinol Metab* 102: 1122–1132, 2017)

Pheochromocytomas and paragangliomas (PPGLs) are neuroendocrine tumors derived from chromaffin cells of the adrenal medulla or associated with paravertebral autonomic ganglia. The tumors account for up to 0.6% of cases of adult hypertension and 1% of pediatric hypertension (1). Although rare, with a reported annual incidence of two to five cases per million, of which only 10% occur in children (2–4), PPGLs are potentially lethal.

At least 30% of PPGLs have a hereditary background, reflecting mutations in at least 14 tumor susceptibility genes (5, 6). These susceptibility genes can be divided into two cluster groups based on transcriptomic profiles revealed by gene expression microarray analyses (7–9). Cluster 1 tumors include those due to mutations of genes encoding the von Hippel-Lindau (VHL) suppressor, the four subunits of the succinate dehydrogenase complex (SDHA, SDHB, SDHC, and SDHD), and less commonly, the enzyme responsible for flavination of the SDHA subunit (SDHAF2), fumarate hydratase, malate dehydrogenase 2, and prolyl hydroxylases 1 and 2. Additional activating mutations of hypoxia-inducible factor 2 alpha (HIF2α) have also been identified, but these are mainly somatic in nature (10). All cluster 1 mutations result in stabilization of hypoxia-inducible factors and activation of the hypoxia signaling pathways (11).

The second cluster group includes tumors due to mutations of the neurofibromatosis type 1 (NF1) tumor suppressor gene, the rearranged during transfection (RET) proto-oncogene, genes encoding transmembrane protein 127 (TMEM127), and MYC-associated factor X (MAX). Mutations of the Harvey rat sarcoma viral oncogene homolog (HRAS) also belong to this cluster 2 group, but similar to HIF2α, appear to be somatic in nature (12). Mutations of cluster group 2 genes result in activation of kinase receptor signaling pathways, translation initiation, protein synthesis, and pathways involved in maintenance of neural/neuroendocrine identity (13).

As shown in several publications and most recently by Qin *et al.* (14), cluster 1 PPGLs are characterized by absence of epinephrine production (noradrenergic phenotype), whereas cluster 2 tumors produce epinephrine (adrenergic phenotype). These differences reflect absence *vs* presence of the enzyme phenylethanolamine *N*-methyltransferase, responsible for conversion of norepinephrine to epinephrine.

Existing data suggest a higher prevalence of hereditary disease in children that in adults (1, 5, 15) and phenotypic presentations of childhood PPGLs characterized by bilateral, multiple, and extra-adrenal tumors (16–19). However, the reported prevalence of hereditary disease in the aforementioned pediatric series varied considerably from 22% to 70%. The most recent published study from Bausch *et al.* (20) reported an even higher 80% frequency of germline mutations among pediatric cases. Despite the large pediatric cohort in that series, there was no direct comparison with an adult population.

Based on findings of a younger age of disease presentation in patients with noradrenergic than adrenergic PPGLs (21), we hypothesized that the higher prevalence of hereditary, metastatic, and extra-adrenal PPGLs in children than adults might reflect a predisposition of children to cluster 1 noradrenergic tumors. The present retrospective study, the first, to our knowledge, to explore differences in disease presentation in a large series of both children and adults, was undertaken to examine that hypothesis.

Materials and Methods

Subjects

This study involved retrospective analysis of data from 748 patients with PPGLs enrolled into clinical protocols at seven tertiary clinical care centers: (1) National Institutes of Health, Bethesda, Maryland; (2) University Hospital Carl Gustav Carus, Dresden, Germany; (3) Institute of Cardiology, Warsaw, Poland; (4) University Hospital of Munich, Munich, Germany; (5) Radboud University Medical Centre, Nijmegen, The Netherlands; (6) University Hospital of Wuerzburg, Wuerzburg, Germany; and (7) University Medical Center Schleswig-Holstein, Luebeck, Germany. Patients were investigated under an intramural review board or ethics committee–approved protocols at each center, with European centers covered under a single multicenter protocol (https://pmt-study.pressor.org/) distinct from that at the National Institutes of Health. Informed consent was provided by all patients, including written parental consent for those enrolled as children.

Recruitment into clinical protocols over 20 years up until 2016 was based on clinical suspicion or increased risk of PPGLs according to four main criteria: (1) presence of signs and symptoms (45.2% of patients); (2) incidental finding of an adrenal or abdominal mass during imaging studies for an unrelated condition (15.8% of patients); (3) previous history of PPGLs (22.1% of patients); or (4) presence of a hereditary syndrome or mutation of a tumor susceptibility gene (18.4% of patients).

Patients with PPGLs were divided into pediatric and adult groups based on an age of $\leq$18 years or $>$18 years at first diagnosis of tumors. Based on observations that biochemically positive PPGLs are often present 12 years or more before they are diagnosed (22), it can be expected that many PPGLs in

younger adults develop in childhood. Thus, in an additional analysis, adult patients were divided into two subgroups based on age of less than or more than 35 years at first diagnosis of tumors. Confirmation of PPGLs required histopathological examination of surgically resected or biopsied tumor tissue or a diagnosis of inoperable malignant disease based on functional imaging evidence of metastatic lesions. Locations of tumors were determined based on results of imaging studies and surgical and pathological records. Retrieved data included assessment of the history or presence of multifocal and recurrent disease. Malignancy was defined by the presence of metastases at sites distant from the primary tumor where chromaffin tissue is normally absent, including lungs, bones, liver, and lymph nodes, with diagnosis at the latter sites dependent on histopathology.

Genetic testing

Mutation testing, using leukocyte DNA, was carried out in 611 patients. Testing for germline mutations of *VHL*, *RET*, *SDHB*, *SDHD*, *SDHC*, *MAX*, and *TMEM127* genes was mainly by bidirectional Sanger sequencing and multiplex ligation probe amplification, the latter to test for deletions of selected genes (*e.g., VHL* and *SDHx*). For *NF1*, the diagnosis was based mainly on clinical manifestations according to established criteria (23). After 2014, testing included next-generation sequencing, which was directed primarily to testing of tumor tissue (n = 257) for somatic mutations of *RET*, *VHL*, *SDHB*, *SDHD*, *SDHC*, *SDHA*, *MAX*, *TMEM127*, *NF1*, *HRAS*, and *HIF2α* genes, with germline testing subsequently restricted to positive cases to establish the origin of the mutation.

Blood sample collections and laboratory analysis

Measurements of plasma-free normetanephrine, metanephrine, and 3-methoxytyramine concentrations, available from 661 patients at time of PPGL diagnosis, were performed using liquid chromatography with electrochemical detection (24) or by liquid chromatography with tandem mass spectrometry (25). For these measurements, heparinized blood was collected with instructions that patients should have fasted overnight and rested supine for at least 20 minutes before samples were drawn. Blood samples were kept on ice until plasma was separated and stored frozen at –80°C before analyses.

Catecholamine biochemical phenotypes

Designation of catecholamine biochemical phenotypes was based on relative tumor-derived increases in plasma concentrations of normetanephrine, metanephrine, and 3-methoxytyramine according to established methods (Supplemental Methods). Briefly, tumor-derived increments were calculated by subtracting the concentration of each metabolite in each patient with a PPGL from mean concentrations of normetanephrine (52 pg/mL), metanephrine (26 pg/mL), and 3-methoxytyramine (5 pg/mL) in a previously described reference group (25, 26). Epinephrine-producing adrenergic tumors were defined as those in patients who showed both an increase in plasma metanephrine above the upper cutoff of reference intervals (62 pg/mL) and a tumor-derived increment of metanephrine larger than 5% of combined increments of all *O*-methylated metabolites. All other tumors were defined as nonadrenergic, including both noradrenergic and the less common dopaminergic tumors.

Statistical analysis

Statistical analyses used the JMP statistics software package (SAS Institute, Cary, NC). Overall differences in continuous parameters between groups were assessed using the Kruskal-Wallis test. χ^2 and Fisher's exact tests were used to compare frequencies of adrenergic, hereditary, malignant, multifocal, recurrent, and extra-adrenal presentation among different groups.

Results

Demographic and tumor characteristics

Of the 748 patients with PPGLs, 12.7% first occurred during childhood (Table 1). Compared with adults, children presented less frequently with adrenal tumors (36.8% *vs* 65.4%; $P < 0.0001$), but more frequently with extra-adrenal tumors (66.3% *vs* 35.1%; $P < 0.0001$). Although there was no difference in the presentation of bilateral adrenal tumors between adults and children, the prevalence of multifocal extra-adrenal tumors, including combined adrenal and extra-adrenal tumors, was 2.4-fold higher ($P < 0.0001$) in children than adults. In contrast, the presentation of solitary adrenal tumors was 2.4-fold higher in adults than in children ($P < 0.0001$).

Among the 611 patients who underwent genetic testing, 80.4% (74/92) of all children and 52.6% (273/519) of all adults were identified with germline mutations of tumor susceptibility genes, confirming a higher ($P < 0.0001$) prevalence of hereditary PPGLs in children than adults (Table 1). Among children, the prevalence of recurrent primary tumors, excluding metastases, at the sites of previously resected tumors or at new locations was 2.1-fold higher ($P < 0.0001$) than among adults. The prevalence of metastatic disease was also 1.7-fold higher ($P < 0.0001$) in children than in adults (Table 1).

Biochemical characteristics

Results for plasma concentrations of normetanephrine, metanephrine, and 3-methoxytyramine, available among the 661 patients at the time of tumor diagnosis, indicated lower ($P < 0.0001$) plasma concentrations of metanephrine in children than adults, with no differences for normetanephrine and methoxytyramine (Fig. 1).

Only 4 of 56 (7.1%) pediatric patients with hereditary pheochromocytoma, all diagnosed with cluster 2 mutations, presented with both elevated plasma concentrations of metanephrine and increases of metanephrine larger than 5% of the summed total increases of all three metabolites [Fig. 2(a)]. This contrasted with a 4.2-fold higher ($P = 0.0003$) proportion (67/226) of adult hereditary cases who presented with both elevated plasma concentrations of metanephrine and increases of metanephrine larger than 5% of the summed total increases of all three metabolites. By the criteria outlined in the

Table 1. Demographic and Tumor Characteristics of Pediatric and Adult Patients With PPGLs

Characteristics	Pediatric	Adult	*P* Value
N	95	653	
Age at initial diagnosis[a]	13.3 ± 3.5	44.7 ± 14.4	
Male	55.8% (53/95)	48.1% (314/653)	0.0980
Primary tumor locations			
Solitary adrenal	22.1% (21/95)	56.2% (367/653)	<0.0001
Solitary extra-adrenal	33.7% (32/95)	21.6% (141/653)	<0.0001
Bilateral adrenal	11.6% (11/95)	8.7% (57/653)	0.2020
Multifocal[b]	32.6% (31/95)	13.5% (88/653)	<0.0001
Hereditary cases[c]	80.4% (74/92)	52.6% (273/519)	<0.0001
Recurrent primary tumors[d]	29.5% (28/95)	14.2% (93/653)	<0.0001
Metastatic disease	49.5% (47/95)	29.1% (190/653)	<0.0001
No. N/D phenotype	93.2% (68/73)	57.3% (337/588)	<0.0001

Abbreviations: N/D, noradrenergic/dopaminergic.

[a]Age is shown as mean ± standard deviation.

[b]Multifocal locations indicate multiple extra-adrenal tumors or extra-adrenal and adrenal tumors but exclude bilateral adrenal tumors unless accompanied by one or more extra-adrenal tumors.

[c]Results were retrieved from 611 patients who underwent genetic testing.

[d]Recurrent primary tumors are defined as recurrences at an original site of tumor resection as well as new primary tumors at other locations a year or more after diagnosis of the first primary tumor.

Materials and Methods section, these patients were all designated with epinephrine-producing adrenergic tumors.

Among patients with sporadic PPGLs, only one child among 17 (5.9%) presented with an adrenergic tumor, a proportion much lower (P = 0.0002) than the 51.0% (185/363) of adult cases of sporadic PPGLs with adrenergic tumors [Fig. 2(b)].

All five children with adrenergic tumors, including the four with hereditary tumors [Fig. 2(a)] and the single case with sporadic disease [Fig. 2(b)], presented with adrenal pheochromocytomas [Fig. 1(c)]. Among patients with adrenal pheochromocytomas, the prevalence of tumors with a noradrenergic or dopaminergic phenotype was twofold higher ($P < 0.0001$) in children relative to adults (88.0% *vs* 44.4%). Among all 661 patients with PPGLs in whom measurements of metanephrines were available at the time of diagnosis, the prevalence of tumors with a noradrenergic or dopaminergic phenotype was 1.6-fold higher ($P < 0.0001$) among children compared with adults (Table 1).

Genetics

Among the 611 patients who underwent genetic testing, both children and adults showed a higher prevalence of germline mutations of the cluster 1 than of the cluster 2 group of genes (Table 2). However, the prevalence of cluster 1 mutations involving *VHL* and *SDHx* genes was 1.9-fold higher ($P < 0.0001$) in children than in adults. In contrast, the prevalence of cluster 2 mutations involving *RET*, *NF1*, *TMEM127*, and *MAX* was threefold higher (P = 0.0008) in adults than children (13.3% *vs* 4.3%; $P < 0.0001$), clarifying that the overall higher prevalence of hereditary PPGLs in children than adults is restricted to PPGLs due to cluster 1 mutations.

Among our cohort, 19 patients were identified with somatic mutations. In particular, four children were identified with *HIF2α* mutations and two with *VHL* mutations in tumor tissue but not in the germline. Among adult patients, five were identified with *HIF2α* somatic mutations, two with *HRAS* mutations, three with *RET* mutations, and two with *VHL* somatic mutations. One additional adult patient, as described by us elsewhere (26), was found to have methylation of the *SDHC* promoter. These somatic mutations or epigenetic variants thus showed a similar pattern to findings with germline mutations with proportionally more cluster 1 mutations among the pediatric than the adult cohort and a reverse pattern for cluster 2 mutations. With additional inclusion of the aforementioned somatic mutations and epigenetic variants, 80.0% (76/95) of all pediatric patients had cluster 1 mutations compared with only 4.2% (4/95) with cluster 2 mutations, completely different ($P < 0.0001$) proportions from the 32.5% (212/653) and 11.3% (74/653) of adult patients with respective cluster 1 and 2 mutations.

Metastatic and recurrent disease

For both adults and children, metastatic disease was more prevalent ($P < 0.0001$) in patients with cluster 1 than cluster 2 mutations (52.9% and 40.7% *vs* 0% and 5.8%), largely reflecting the high rate of metastatic disease in patients with SDHB mutations (Table 2). Although the overall prevalence of metastatic disease was higher ($P < 0.0001$) in children than in adults (Table 1),

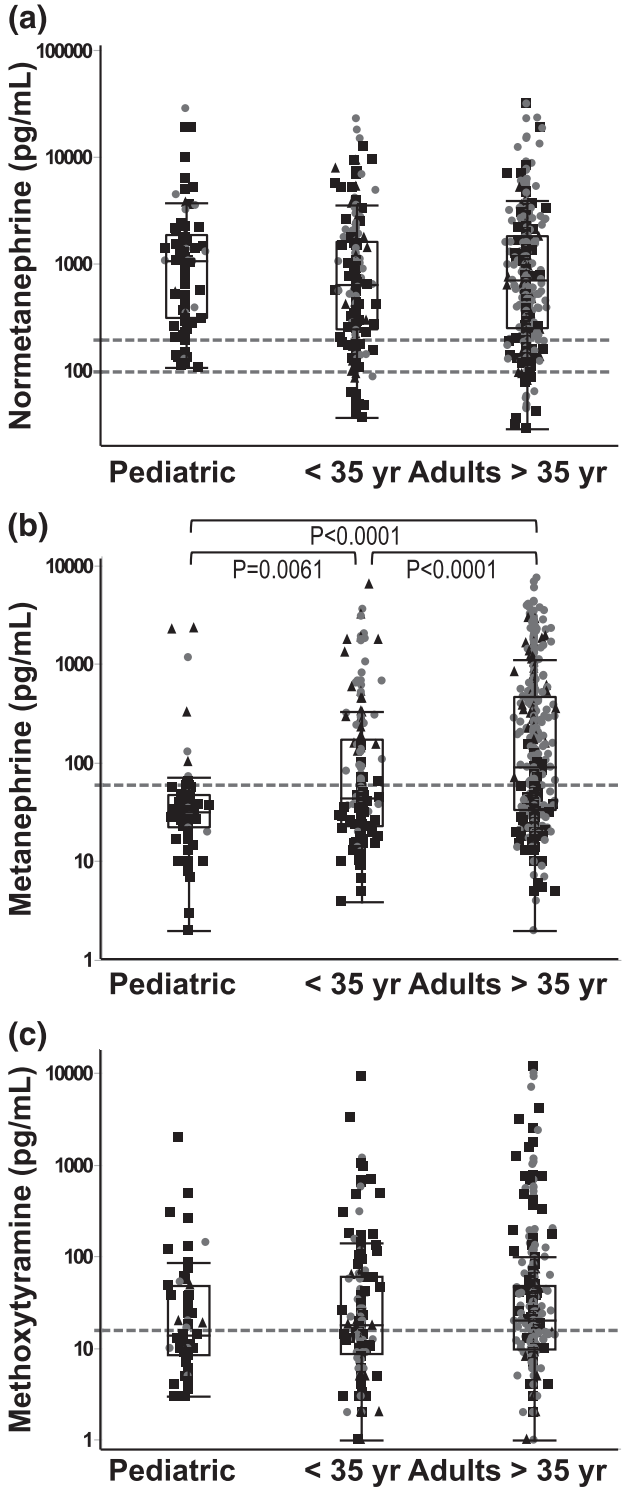

Figure 1. Plasma concentrations of (a) normetanephrine, (b) metanephrine, and (c) methoxytyramine in children and young (<35 years old) and old (>35 years old) adult patients.

there were no differences when examined separately for cluster 1 or cluster 2 mutations (Table 2). Nevertheless, the percentages of children with metastatic disease remained higher compared with adults for both hereditary (50.0% *vs* 31.8%; $P < 0.0001$) and sporadic groups (47.6% *vs* 27.2%; $P < 0.0001$).

Compared with adults, children showed a higher ($P = 0.0019$) prevalence of nonsynchronous metastatic disease (*i.e.*, metastases diagnosed a year or more after initial diagnosis of a primary tumor) than metastatic disease diagnosed synchronously at first diagnosis of PPGLs (Table 3). Locations of metastases overall did not differ except for those of the liver, which showed a higher ($P = 0.0230$) prevalence in adults than children (Table 3).

There were no significant differences in rates of recurrent disease between patients with cluster 1 and cluster 2 mutations (Table 2). Although the rate of recurrent disease did not differ among hereditary pediatric and adult cases, children with sporadic PPGLs presented more often with recurrent disease (38% *vs* 7%; $P < 0.0001$) compared with adults.

Younger vs older adults

Age-related changes in disease presentation

Differences in presentation of disease in children compared with adults for some manifestations also extended into adulthood as reflected by changes in age-related cumulative frequencies of hereditary disease, different tumoral biochemical phenotypes, locations of primary tumors, and development of recurrent or metastatic disease (Fig. 3). Consequently, compared with older adults, younger adults showed many but not all of the same differences in disease presentation observed between children and adults (Supplemental Table 1). In particular, higher prevalence of hereditary disease and noradrenergic, multifocal tumors in children compared with adults and lower prevalence of adrenergic and adrenal tumors in adults compared with children were repeated in younger adults compared with older adults. Age-related differences in cumulative frequencies of adrenergic tumors were also reflected in higher ($P < 0.0001$) plasma concentrations of plasma metanephrine in older adults than both younger adults and children and higher ($P < 0.0061$) concentrations of metanephrine in younger adults than children (Fig. 1). In contrast, the higher prevalence of metastatic disease, particularly nonsynchronous metastatic disease, was confined to children. Also, although the prevalence of bilateral tumors showed no overall difference between adults and children, this presentation peaked in young adults, who showed a higher prevalence of bilateral tumors than older adults.

Discussion

This study involving a large cohort of pediatric and adult patients with PPGLs outlines a higher prevalence of noradrenergic PPGLs in children than in adults. Furthermore, we establish that the childhood predominance

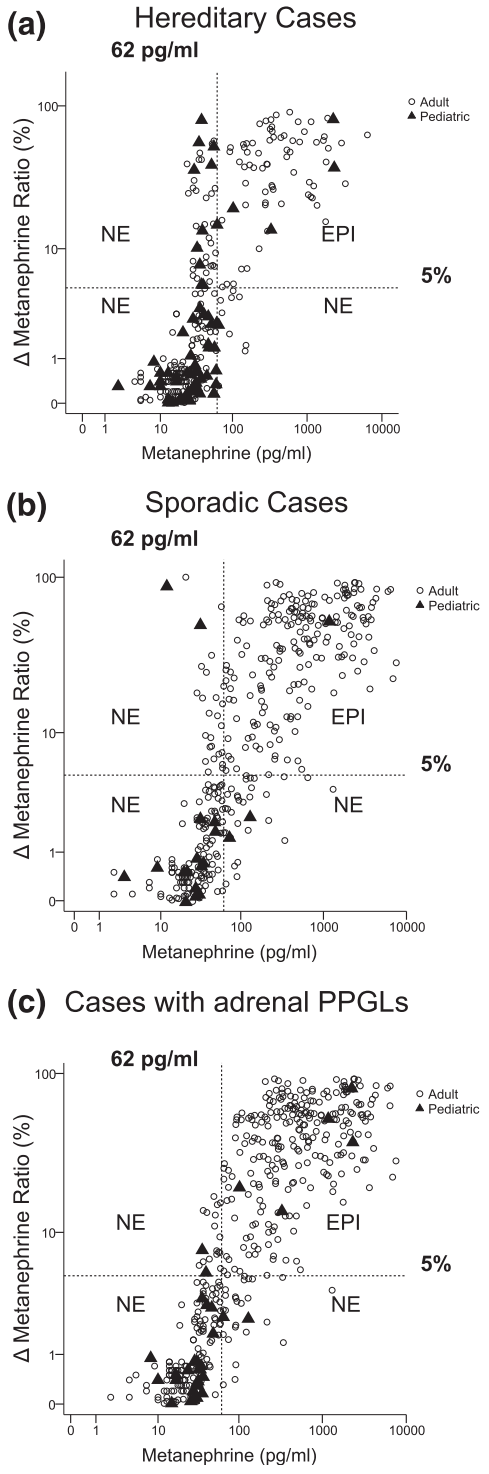

Figure 2. Biochemical phenotypes of (a) pediatric and adult sporadic, (b) hereditary, and (c) adrenal-located PPGLs. Characterization of PPGLs with and without appreciable epinephrine (EPI) production [adrenergic (EPI) vs noradrenergic (NE) phenotypes] was established according to the scatterplot relationship of plasma concentrations of metanephrine *vs* increases of plasma metanephrine as a percentage of increases of the summed total of all *O*-methylated metabolites above reference (Δ metanephrine ratio). The dashed vertical line depicts the upper reference limit (62 mg/mL) used to establish increased *vs* normal plasma concentrations of metanephrine. The dashed horizontal line depicts the cutoff at 5% used to establish appreciable metanephrine (epinephrine) production according to total production of all *O*-methylated metabolites.

of noradrenergic PPGLs reflects in part the higher prevalence of tumors due to cluster 1 mutations among pediatric compared with adult cases. These observations may reflect different developmental origins of cluster 1 and 2 tumors and are of relevance for personalized management and surveillance programs for both genetically at-risk children and those requiring long-term follow-up after development of PPGLs during childhood.

In a report from 1960, Hume (1) noted that most PPGLs in childhood seemed to secrete predominantly norepinephrine, an observation that until this study has not been confirmed by measurements of metanephrines to establish catecholamine phenotypic features more accurately. In that classic report of Hume (1), other findings of more often extra-adrenal and multifocal locations of PPGLs among pediatric than adult patients have been supported by other series, some of which additionally reported a high prevalence of hereditary and metastatic disease in pediatric patients (4, 15, 17, 20, 27, 28). However, only three of these studies involved comparisons with adult cohorts, and both involved limited patient numbers (4, 15, 17).

The present comparative study involving both adults and children not only confirms a higher prevalence of extra-adrenal, multifocal, metastatic, recurrent, and hereditary PPGLs in children than adults but establishes the link between these phenotypic features to a higher prevalence of noradrenergic and related cluster 1 hereditary tumors in pediatric than adult patients.

Earlier age of presentation of multifocal tumors among patients with cluster 1 gene mutations has been suggested previously to reflect second-hit mutations in embryogenesis before neural crest-derived cells migrate to their final locations (29). Support for the concept of embryological origins of some PPGLs has since been provided by findings of mosaicism involving activating *HIF2α* somatic mutations in patients with PPGLs and polycythemia (30, 31) as well as identical *HIF2α* mutations in different tumors from the same patient (32). Furthermore, mosaicism has been reported for *VHL* somatic mutations (33), again indicating that cluster 1–type mutations can occur early in embryonic development.

In line with the aforementioned concepts, other reports have highlighted the importance of *HIF2α* in neural crest development; cluster 1 gene mutations, which stabilize *HIF*s, have thereby been proposed to create an environment favoring survival of chromaffin progenitor cells that lack epinephrine production (8, 34, 35). This proposed developmental pathway for cluster 1 PPGLs thereby offers an explanation for the high prevalence of hereditary and largely noradrenergic cluster 1–type PPGLs in children compared with adults.

Table 2. Gene-Specific Characteristics of Pediatric and Adult Patients With PPGLs

	Pediatric	Adult	*P* Value
Cluster 1 mutations			
VHL	27.2% (25/92)	10.2% (53/519)	<0.0001
Metastatic	12.0% (3/25)	5.7% (3/53)	0.3070
Recurrent	18.5% (5/25)	5.7% (3/53)	0.0730
SDHB[a]	39.1% (36/92)	17.3% (90/519)	<0.0001
Metastatic	86% (31/36)	68.9% (62/90)	0.0350
Recurrent	19.4% (7/36)	20.0% (18/90)	0.5780
SDHD[a]	9.8% (9/92)	10.6% (55/519)	0.4660
Metastatic	33.3% (3/9)	30.9% (17/55)	0.5680
Recurrent	66.7% (6/9)	58.2% (32/55)	0.4380
SDHA/C[a]	0% (0/92)	1.2% (6/519)	—
Metastatic	—	16.7% (1/6)	—
Recurrent	—	0.0% (0/6)	—
Total for cluster 1	76.1% (70/92)	39.3% (204/519)	<0.0001
Metastatic	52.9% (37/70)	40.7% (83/204)	0.0820
Recurrent	25.7% (18/70)	26.0% (53/204)	0.4340
Cluster 2 mutations			
RET[a]	3.3% (3/92)	8.9% (46/519)	0.0270
Metastatic	0.0% (0/3)	4.4% (2/46)	—
Recurrent	66.7% (2/3)	17.4% (8/46)	0.0910
NF1	1.1% (1/92)	3.7% (19/519)	0.1750
Metastatic	0.0% (0/1)	5.2% (1/19)	—
Recurrent	0.0% (0/1)	10.5% (2/19)	—
MAX/TMEM127[a]	0% (0/92)	0.7% (4/519)	—
Metastatic	—	25.0% (1/4)	—
Recurrent	—	50.0% (2/4)	—
Total for cluster 2	4.3% (4/92)	13.3% (69/519)	0.0008
Metastatic	0% (0/4)	5.8% (4/69)	—
Recurrent	50.0% (2/4)	17.4% (12/69)	0.1420

[a]Percentage is shown according to the total number of patients tested for germline mutations. For *NF1*, diagnosis was based on clinical manifestations and, for *SDHA*, *TMEM127*, and *MAX*, was restricted to limited patient numbers as described in Materials and Methods. Percentages of metastatic and recurrent disease are shown according to the particular mutated gene.

Our findings of higher prevalence of metastatic PPGLs in children than adults can also be traced to the higher risk of metastatic disease associated with cluster 1 mutations, particularly *SDHB* mutations more prevalent in children than adults. Although high prevalence of metastatic disease and *SDHB* mutations in childhood PPGLs is in agreement with the study of King *et al.* (28), this finding is not consistent with other studies reporting rates of malignant PPGLs among children from 2.4% to 19% (16, 17, 36, 37). This discrepancy may in part reflect referral bias involving high numbers of patients with metastatic disease at the specialist centers participating in the current study. However, lower rates of childhood metastatic PPGLs reported in other studies may also be

Table 3. Metastatic Disease in Pediatric and Adult Patients With PPGLs

Characteristics	Pediatric	Adult	*P* Value
Metastatic disease[a]			
Synchronous[a]	25.5% (12/47)	43.2% (82/190)	0.0019
Nonsynchronous[a]	74.5% (35/47)	56.8% (108/190)	
Location of metastases			
Bones	73.9% (34/46)	69.9% (128/183)	0.3690
Lungs	39.1% (18/46)	25.7% (47/183)	0.0540
Liver	23.9% (11/46)	40.9% (75/183)	0.0230
Lymph nodes	50.0% (23/46)	45.6% (84/184)	0.3690

[a]Metastatic disease is defined as either synchronous or nonsynchronous depending on findings of metastases (lungs, liver, bones, lymph nodes, or other sites where chromaffin or autonomic progenitors are normally absent) at the time of first diagnosis of disease or at one or more years after first diagnosis, respectively.

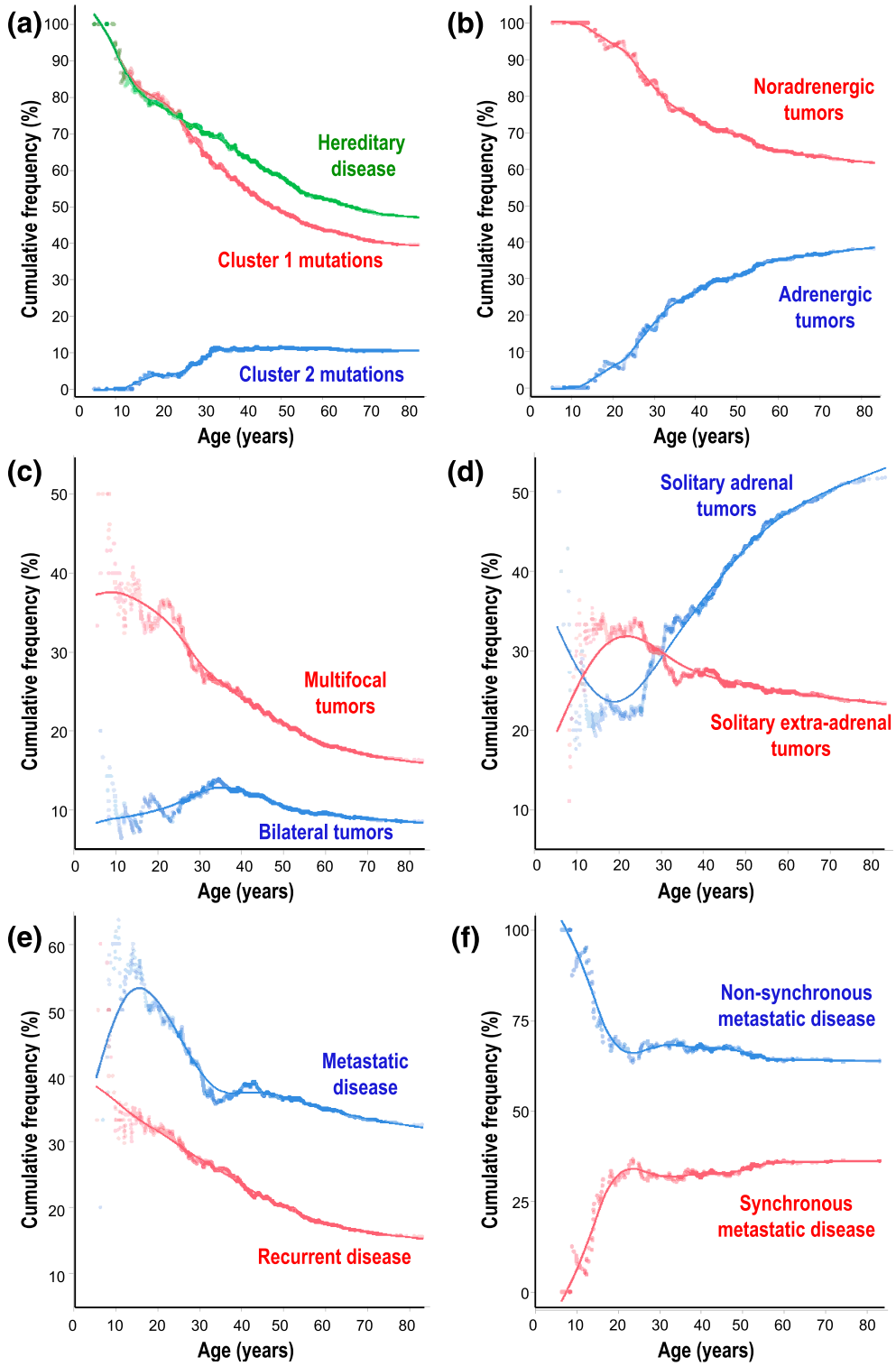

Figure 3. Cumulative frequencies as a function of age in hereditary disease, including (a) tumors due to cluster 1 *vs* cluster 2 mutations, (b) noradrenergic *vs* adrenergic tumors, (c) multifocal *vs* bilateral adrenal tumors, (d) solitary adrenal *vs* extra-adrenal tumors, (e) metastatic disease *vs* recurrent nonmetastatic disease, and (f) nonsynchronous *vs* synchronous metastatic disease.

partly explained by insufficient patient follow-up (38). As indicated by our series, and particularly important for pediatric cases of PPGLs, occurrence of metastatic disease was most often not synchronous with presentation of primary tumors. Most often, metastatic disease was diagnosed in adulthood after initial presentation of the primary tumor in childhood at outside centers, with usually little or no periodic follow-up to check for disease recurrence. Without such follow-up, recurrent or metastatic progression may be underestimated.

Based on findings of a 12-year lag in positive biochemical results indicative of PPGLs to actual diagnosis of the tumors (22), it seems likely that many cases of childhood PPGLs are not detected until adulthood. Our observations that young adults showed similar presentations of PPGLs as children further suggests that the 12.7% prevalence of childhood PPGLs in the current study likely underestimates the true prevalence. Thus, in addition to a need for improved follow-up of childhood PPGLs, there is also likely a need for improved recognition of the tumors by pediatricians.

Our study, like all previous studies on pediatric PPGLs, has limitations associated with potential for referral bias, retrospective nature, and incomplete follow-up and genetic testing. Referral bias might be expected to lead to higher proportions of hereditary, metastatic, and recurrent disease, but this should not compromise comparisons of adult and pediatric populations. In contrast, incomplete follow-up and genetic testing would be expected to result in lower proportions of hereditary, metastatic, and recurrent disease. Although fully prospective studies could minimize these limitations, such studies would require a long time frame (>10 years) and considerable flexibility in meeting demands of accelerating scientific advances (*e.g.*, new mutations and technologies).

Despite the aforementioned limitations, our study not only supports previous findings, but also builds on these to advance patient management. The higher prevalence of hereditary, malignant, and recurrent disease and the differences in the sites of primary tumors and metastases in children compared with adults, in particular, highlights the importance in pediatric medicine of following Endocrine Society clinical practice guidelines recommending that patients with PPGLs be managed by multidisciplinary teams at specialist centers with appropriate expertise (39). All children with PPGLs should undergo genetic testing with choice and interpretation of testing dictated by family history or presence of syndromic and clinical features. Such features include the biochemical phenotype of the tumor, which can also indicate adrenal *vs* extra-adrenal locations. Although computed tomography is recommended by Endocrine Society guidelines as the method of first choice for locating PPGLs (39), high–signal intensity T2-weighted magnetic resonance imaging is the more appropriate modality for the pediatric population with focus on the detection of extra-adrenal tumors, especially those in unusual locations.

For postoperative care, the high risk of recurrent or metastatic disease associated with childhood PPGLs mandates not only diligent follow-up, but also appropriate transition from pediatric into adult care. Periodic biochemical surveillance for PPGLs is recommended for all mutation carriers, regardless of disease history, but is particularly important starting at an early age (*i.e.*, five years) in those children harboring cluster 1 mutations. Surveillance programs for PPGLs should be tailored according to the mutation and, where indicated, should include screening for other tumors associated with mutations (*e.g.*, retinal hemiangioblastomas in *VHL* mutation carriers), again highlighting the importance of multidisciplinary team approaches. For children with mutations of *SDH*x genes, biochemical testing should include measurements of plasma methoxytyramine, also important as a biomarker for extra-adrenal and metastatic disease (39, 40); this is particularly important for children carrying *SDHB* gene mutations, who carry a high risk of malignancy. Because large tumor size is a risk factor for metastatic disease, earlier detection through regular surveillance programs may offer the best means to avoid subsequent development of metastatic disease.

Conclusion

The higher prevalence of hereditary, extra-adrenal, and metastatic PPGLs in children than adults represent interrelated features that in part reflect the lower age of disease presentation of noradrenergic cluster 1 PPGLs than adrenergic cluster 2 tumors. The differences in disease presentation are important to consider in both presurgical and postsurgical management of childhood PPGLs as well as during routine surveillance of at-risk children.

Acknowledgments

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This work was supported by the Deutsche Forschungsgemeinschaft (EI855/1/2; to C.P., M.P., and G.E), the European Union Seventh Framework Program (FP7/2007-2013) under Grant 259735 (ENSAT CANCER; to M.P., F.B., H.J.L.M.T., M.R., R.O.S., and G.E.), the Fondo de Investigaciones Sanitarias (PI14/00240; to M.R.), and the National Institutes of Health (to B.H., M.L., C.A.S., and K.P.).

Disclosure Summary: The authors have nothing to disclose.

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