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Journal of Clinical Nephrology and Research

Review Article

Pheochromocytoma: A Single-Center Retrospective Review

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Submitted: 18 February, 2021

Accepted: 22 February, 2021

Published: 24 February, 2021

ISSN: 2379-0652

Keywords

- Pheochromocytoma
- Adrenal Gland Neoplasms
- Incidental Findings
- Adrenal medulla
- Adrenalectomy

Abstract

Background: The presentation of modern pheochromocytoma is changing alongside advances in medical practice. This retrospective review depicts the clinical presentation and biochemical properties of pheochromocytomas as a function of size and cause for workup.

Materials and Methods: Single-center retrospective chart review of imaging studies, biochemical testing results, and provider documentation written prior to surgical resections performed for pheochromocytoma between 1998 and 2018.

Results: Forty-four patients were found to have 49 pheochromocytomas on pathology. The most common presentation was through incidental imaging findings of an adrenal mass (38.6%), followed by symptoms (34.1%), and then screening for known genetic risk (27.3%). Median unenhanced CT attenuation was 36 HU (range 17-85). Median pheochromocytoma size on imaging was 3.4 cm (range 1.0-12.2 cm). Median mass size in symptoms, incidental mass, and genetic risk groups were 4.1 cm, 3.4 cm, and 2.3 cm respectively ($p = 0.090$). Bilateral disease was more common in patients with known genetic mutations (41.7%, $p = 0.040$). Patients with tumors > 4 cm had higher total metanephrines in urine ($p = 0.006$) and more symptoms on average than those with tumors ≤ 4 cm (3.1 vs. 1.7 respectively, $p = 0.017$).

Conclusion: In our single-center series, incidental adrenal masses and genetic testing were an increasingly common presentation leading to pheochromocytoma diagnosis on surgical pathology. Patients with known genetic syndromes more often had complex disease. Large tumors (>4cm) were associated with higher measurements of urine metanephrines and burdened patients with a greater number of symptoms.

ABBREVIATIONS AND SYMBOLS

PHEO: pheochromocytoma, **PGL**: paraganglioma, **HU**: Houndsfield Units, **CT**: computed tomography, **VHL**: von Hippel-Lindau, **NF1**: Neurofibromatosis Type 1, **MEN2**: Multiple Endocrine Neoplasia 2, **SDH B**: Succinate Dehydrogenase Complex B.

INTRODUCTION

Pheochromocytomas (PHEOs) are rare neuroendocrine tumors arising from chromaffin cells of the adrenal medulla (1). Extra-adrenal neuroendocrine tumors derived from sympathetic paraganglia are known as paraganglioma (PGL) and occur less frequently (2). PHEOs are generally well-vascularized and hypersecrete catecholamines which may cause symptoms such as headaches, excessive sweating, tachycardia, palpitations, and sometimes weight loss (3). As these symptoms are rather non-specific, and as some PHEOs are asymptomatic, there can be a delay in diagnosis leading to high cardiovascular morbidity and mortality (4, 5). PHEOs are increasingly discovered incidentally, composing nearly 5% of adrenal incidentalomas found on cross-sectional imaging (6, 7). These tumors appear as contrast-enhancing, heterogenous masses on CT, often with cystic or necrotic areas (8).

Pheochromocytoma is a rare cause of hypertension; its prevalence is estimated between 0.01% to 0.2% in the hypertensive population, however, the prevalence approaches 4% in populations with resistant hypertension (defined as elevated blood pressure despite use of three antihypertensive drug classes) (9). The clinical pattern of hypertension is variable amongst PHEO patients; approximately half develop sustained hypertension, another 45% experience paroxysmal hypertension, and the remaining 5-15% remain normotensive (10). Despite its rarity, PHEO is important to suspect and diagnose in a timely fashion not only because PHEOs harbor some malignant potential but also because catecholamine secretion may be associated with significant cardiovascular morbidity and mortality (11). When PHEO is suspected, clinical guidelines recommend measurement of urinary fractionated metanephrines or plasma free metanephrines as the initial test to establish evidence of PHEO prior to imaging (12).

The increasing affordability and accessibility of genetic testing combined with improved understanding of associated genetic mutations has expanded screening for PHEOs and familial PHEO syndromes which has led to earlier detection in some populations (7). About 40% of PHEOs have been associated with germline mutations such as Succinate Dehydrogenase (SDH) complex mutations or as a part of other syndromes like Von Hippel-Lindau disease (VHL), Neurofibromatosis Type 1 (NF1), and Multiple Endocrine Neoplasia Type 2 (MEN2) (13). Screening for tumors in patients with known genetic mutations results in earlier detection and clinical manifestations which differ from those patients worked up due to symptoms (6,7).

The primary objective of our single-institutional study is to investigate differences in the clinical presentation, biochemical activity, and imaging findings of PHEOs based upon three categories of patient presentations leading to discovery: symptoms, incidental imaging finding, or screening for known familial syndromes.

METHODS

We conducted a single-center retrospective study of all patients who underwent adrenalectomy for removal of PHEO between January 1998 through December 2018 at Oregon Health & Science University in Portland, Oregon. The patient database was generated through a query for PHEO diagnosis codes. Patients were included in the study if an adrenalectomy was performed and a diagnosis of PHEO was confirmed in the pathology report. Patients who received imaging or laboratory testing for pheochromocytoma without surgical intervention were excluded as well as patients under the age of 18 on the date of surgery. This study was conducted with institutional review board (IRB) approval; approved consent from individual subjects was not indicated by the IRB for this retrospective study.

Patients with synchronous bilateral pheochromocytoma were analyzed as a single event and a sum of longest mass diameters was used in correlations of size to biochemical activity or symptoms. When redundant biochemical tests were documented for a patient, only the data from the latest pre-surgical test was included to be consistent for comparison across patients. Biochemically functional tumors were defined as either plasma metanephrines or urine fractionated or total metanephrines exceeding their respective reference ranges.

All data analysis was performed using SPSS statistical software. Non-parametric variables were described by median (IQR), with two-group comparisons made by Independent-Samples Mann-Whitney U Test and three-group comparisons made by Independent-Samples Kruskal-Wallis ANOVA. A standard one-way ANOVA was used to analyze parametric continuous variables described by means across the three groups. Categorical outcomes were analyzed by chi-square tests. Independent t-tests were used to compare parametric continuous variables between two groups.

RESULTS

A total of 44 patients (median age 51, 68% women) with a total of 49 PHEOs were included in our study. Isolated PHEO was the most common presentation (33 patients, 75%). The remaining 11 patients had more complex presentations as demonstrated in (**Table 1)**. There were 26 right-sided PHEOs and 23 left-sided PHEOs.

Thirty-four patients (77.3%) reported at least one symptom, including patients whose initial workup was due to incidental findings or genetic risk. The most commonly reported signs and symptoms were refractory or paroxysmal hypertension (n= 24, 54.5%), palpitations (n=20, 45.5%) and headache (n=15, 34.1%). Frequencies of reported symptoms are presented in **(Figure 1)**.

The median PHEO size on cross-sectional imaging was 3.4 cm (range 1.0 cm to 12.2 cm). Unenhanced CT attenuation values were available for 20 PHEOs with a median value of 36 Hounsfield Units (HU) (range 17 to 85 HU). Complete imaging reports were available for 19 patients; the three most common descriptors used were contrast-enhancing (63%), cystic (26%), and hyper vascular (23%).

Thirty-nine patients (88.6%) with PHEO had biochemistry data available (24-h urine labs in n=24 [55%]; plasma labs in n=32 [73%]). Thirty-eight (97.4%) of these patients were found to have biochemically functional tumors by urine or plasma sampling. A weak positive linear association between the total urine metanephrines and the size of pheochromocytomas is illustrated in (**Figure 2).**

In addition to the 12 patients with known genetic mutations, genetic testing was performed on 9 additional patients postoperatively. Of these, 5 patients were diagnosed with a new genetic syndrome. The genetic syndromes and their frequencies in our study population are shown in (**Table 2)**.

Comparing Pheochromocytoma Characteristics by Reason for Workup

Patients with PHEO were grouped and characterized by their

Table 1: Pheochromocytoma Mass Distribution.

PHEO Distribution	No. of Patients	No. of PHEOs
Isolated PHEO	33 (75%)	33 (67%)
Bilateral PHEOs	4 (9%)	8 (16%)
Second PHEO in asynchronous bilateral	3 (7%)	3 (6%)
PHEO with synchronous PGL	3 (7%)	3 (6%)
Synchronous bilateral PHEO and PGL	1 (2%)	2 (4%)
Total	**44**	**49**

Table 2: Genetic Syndromes Present in Study Population.

Syndrome or Mutation	No. of Patients (%)
Multiple Endocrine Neoplasia 2A	7 (33%)
Multiple Endocrine Neoplasia 1	1 (5%)
Neurofibromatosis 1	3 (14%)
Von Hippel Lindau	4 (19%)
SDHB Gene Mutation	2 (10%)
No mutation identified	4 (19%)
Total Mutations	**17 out of 21 tested**

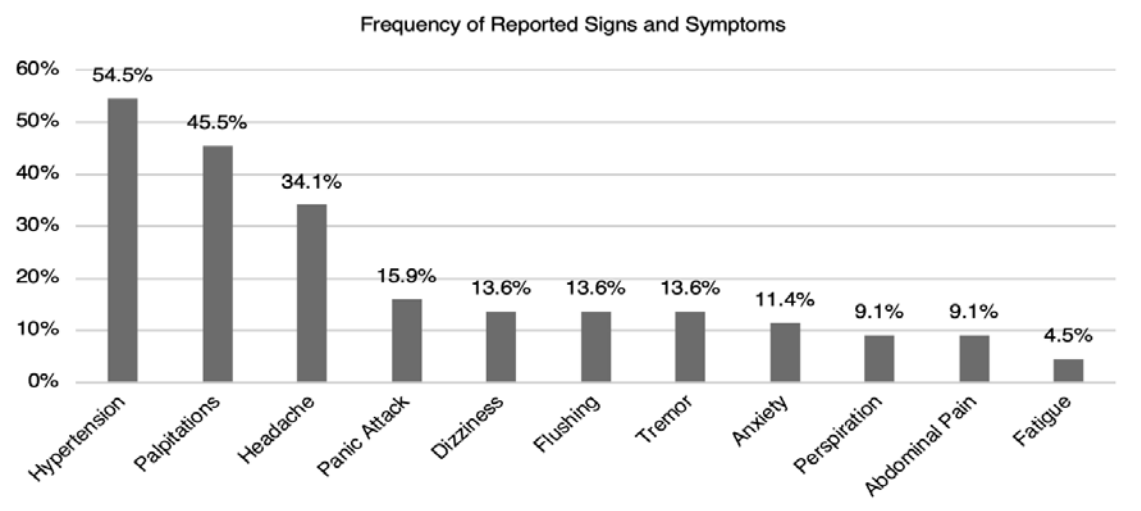

Figure 1 Frequency of Reported Signs and Symptoms in Pheochromocytoma (to be submitted separately as xls).

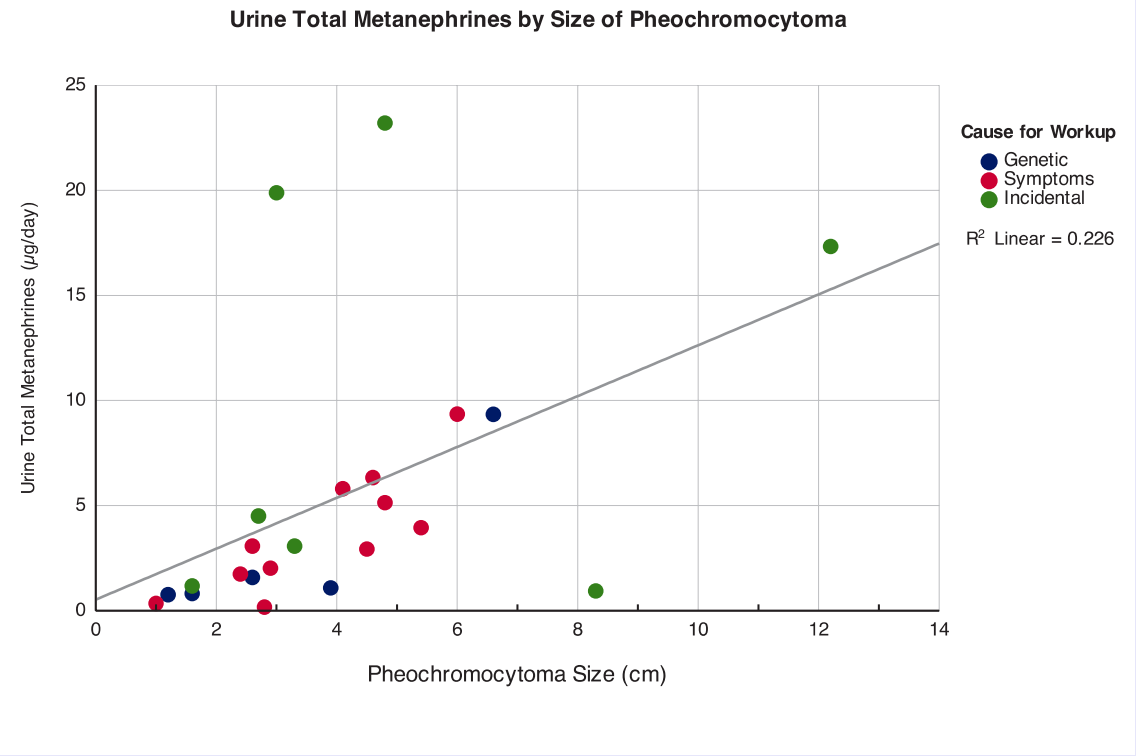

Figure 2 Urine Metanephrines by Size of Pheochromocytoma (to be submitted separately as EPS).

cause for evaluation: symptoms, incidental imaging findings, or an existing knowledge of personal or familial genetic risk (**Table 3**). PHEOs detected in patients screened for known genetic susceptibility trended towards a younger age at diagnosis with a median of 46 years vs. median ages of 53 and 62 in patients evaluated due to symptoms and incidental findings respectively, though these results failed to achieve significance (p = 0.095). The median mass sizes by group were 2.3 cm, 4.1 cm, and 3.4 cm in patients evaluated for genetic risk, symptoms, and incidental findings, respectively (p = 0.090). The reasons for imaging which resulted in incidental adrenal mass findings included back/flank/abdominal pain (n=5), routine cancer surveillance or surgical follow up (n=3), testicular/pelvic pain (n=3), appendicitis (n=1), CTA for suspected pulmonary embolus (n=1), hyperbilirubinemia (n=1), and unknown (n=1). Patients who were evaluated for symptoms of PHEO had a larger symptom burden on average compared to patients discovered incidentally or screened for known genetic susceptibility (3.5, 1.6, and 1.7 respectively, p =

Table 3: Characteristics of Pheochromocytoma by Reason for Workup.

	Symptomatic	Incidental	Genetic Risk	P Value
Number of Patients	15 (34.1%)	17 (38.6%)	12 (27.3%)	---
Number of Tumors	17	18	14	---
Median Age at Diagnosis, years (range)	53 (18-85)	62 (30-82)	46 (31-66)	0.095[a]
Women, n (%)	12 (80.0%)	11 (64.7%)	7 (58.3%)	0.469[b]
Median Tumor Size, cm (range)	4.1 (1.0-9.0)	3.4 (1.6-12.2)	2.3 (1.2-4.9)	0.090[a]
Mean Number of Symptoms	3.5	1.6	1.7	0.008[c]
Median Total Urine Metanephrines, µg/day (IQR)	3074 (1884-5470) n=11	3787 (1953-17967) n=8	1085 (818-1583) n=5	0.229[a]
Multiple of Upper Limit of Normal	3.1	3.8	1.1	---
Median Plasma Metanephrines (IQR), nmol/L	0.27 (0.18-1.68) n=11	1.52 (0.51-3.03) n=13	0.55 (0.19-0.81) n=8	0.188[a]
Median Plasma Normetanephrines (IQR), nmol/L	7.74 (1.64-15.32) n=11	5.76 (1.50-9.36) n=13	1.25 (1.06-2.57) n=8	0.236[a]
*Bilateral PHEO, n (%)	2 (13.3%)	1 (5.9%)	5 (41.7%)	0.040[b]
Concurrent PGL, n (%)	1 (6.7%)	1 (5.9%)	2 (16.7%)	0.562[b]

0.008). Total urine metanephrines, plasma metanephrine, and plasma normetanephrine concentration did not significantly differ across workup groups. Bilateral disease was present in a significantly higher proportion of patients with known genetic susceptibility 41.7% compared to 13.3% and 5.9% in patients evaluated due to symptoms and incidental findings, respectively (p = 0.040).

Characteristics by Size

Patients with pheochromocytoma were grouped by PHEO mass diameter ≤ 4 cm and > 4 cm, with bilateral PHEOs being included as a sum of their mass diameters (**Table 4**). Two patients could not be included in this analysis; one did not have imaging studies available and the other had only a renal mass described on imaging with PHEO diagnosed following nephrectomy and bilateral adrenalectomy in the setting of known VHL. Patients with PHEO > 4 cm demonstrated higher median urine total metanephrines than those with PHEO ≤ 4 cm (p = 0.006). The larger mass group also reported a greater average number of symptoms (p = 0.017).

DISCUSSION

In our study, PHEO was discovered as an incidental adrenal mass one-third of the time, a finding consistent with several recent studies (4, 7), but also contrasting to other studies with observed rates as high as 61% (6). While over one-third of PHEOs were incidentally discovered, over 75% of all patients had reported at least one related symptom at discovery. The most commonly reported signs and symptoms were hypertension, palpitations, and headaches. Very few study patients (less than 5%) presented with the complete classic triad of palpitations, headache, and perspiration – a finding which challenges conventional teaching alongside several other recent studies (7, 14). Perhaps unsurprisingly, patients who began diagnostic workup for PHEO symptoms also reported the greatest number of symptoms compared to those with incidentalomas or genetic predisposition.

Another increasingly common presentation for PHEO is screening in the setting of known genetic risk for familial syndromes such as NF1, VHL, and MEN2 (13). In our study, more than a quarter of patients fell within this category. In these patients, we observed trends towards a younger age at diagnosis and smaller tumors on imaging. This genetically susceptible group also had a higher incidence of bilateral disease and reported fewer symptoms at the time of diagnosis. Interestingly, in our study, we observed one patient with known MEN1 syndrome who developed PHEO during routine surveillance after removal of a pancreatic neuroendocrine tumor. While adrenal lesions occur in 20-55% of MEN1 cases, they are typically adrenocortical adenomas or hyperplasia (15, 16). The occurrence of PHEO in MEN1 is exceedingly rare compared to MEN2 syndromes (with an estimated penetrance <1%, compared to ~50% penetrance in MEN2 syndromes) (17).

Follow-up genetic testing in patients newly diagnosed with PHEO is critical, as studies have associated up to 40% of all PHEOs with known genetic mutations (18). Although current guidelines emphasize engaging all PHEO patients in shared decision making regarding genetic testing, in our series only 21 patients (47.7%) underwent such testing (12, 19). This low rate of testing is likely multifactorial including changes to guidelines over the 20-year period of this retrospective study (12), loss of patients to follow-up, or patients declining genetic testing after counseling. Bilateral PHEO or concurrent PGL was discovered in roughly one fourth of patients from symptoms and incidentaloma groups, and all but one of these patients were subsequently discovered to harbor mutation (5). The occurrence of complex disease is more often associated with genetic mutations than isolated masses, though all patients should receive recommendations for genetic evaluation following a diagnosis of PHEO.

We hypothesized that the size of the tumor would positively correlate with the total measured urine metanephrines. Our decision to analyze characteristics based on the sum of bilateral PHEOs was made to provide consistency for comparison to prior studies that have employed these methods (6). Our study found

Table 4: Characteristics of Pheochromocytoma by Size on Imaging.

	Size on Imaging		
	≤ 4 cm	**> 4 cm**	**P Value**
Mean Symptoms Reported	1.7 n = 23	3.1 n = 19	0.017[a]
Median Total Urine Metanephrines, µg/day (range)	1583 (170-19,883) n = 13	5800 (939 – 23,200) n = 11	0.006[b]

evidence of a weak positive linear association between the two. Given that biochemical activity is understood to produce the characteristic symptoms of PHEO, this finding may explain why patients with PHEO ≥ 4 cm reported more symptoms on average than those with smaller masses. No statistical difference was observed in the distribution of total urine metanephrines between the three workup groups. However, appraisal of this comparison is limited by the reduced sample (24 patients) of study patients that had urine metanephrines available. The reason for this limited sample size stems in part from evolving preferences in biochemical testing modalities (plasma vs. 24-hour urine, catecholamines vs. metanephrines) over time, and from missing biochemistry data in the case of 5 study participants.

The observed median unenhanced attenuation value of 36 HU is consistent with larger studies such as those performed by Canu et al. (n= 375, 35 HU) and Gruber et. al (n=101, 35 HU) (6, 20). Notably, the minimum non-contrast attenuation value observed for PHEO in our study was 17 HU, a finding which is consistent with studies suggesting that a cutoff of ≤ 10 HU has a very high sensitivity (99.6%) for ruling out PHEO (21). In the workup of adrenal incidentalomas, measures of density and size can be used to differentiate adrenal cortical adenomas and hyperplasia from non-adenomas. As such, Hamrahian et al. noted a100% specificity for identifying benign adenomas in adrenal masses ≤ 4 cm with ≤ 20 HU on non-contrast CT (22). The low-density mass of 17 HU in our study might have been considered benign had the size (4.4 cm) not been taken into consideration.

Finally, only one patient was found to have a hormonally inactive PHEO. This patient was already known to have MEN2A syndrome and personal history of prior PHEO adrenalectomy before the study period. On follow up screening, a small 1.6 cm mass on the contralateral adrenal gland was suspicious for asynchronous bilateral disease. While the urine catecholamine and metanephrine results were negative, a metaiodobenzylguanidine scan showed increased uptake in the new adrenal mass which ultimately led to surgical removal and pathology-confirmed PHEO diagnosis. Although the presence of hormonally inactive PHEOs is well-known, there have been no studies documenting its incidence given the rarity with which it presents. A Korean study by Park et al. found 3 hormonally inactive PHEOs in a cohort of 49 (6.1%), which is higher than what we observed (2.1%) in our study (23).

CONCLUSION

Incidental adrenal mass finding and screening of patients with known genetic risks are an increasingly common mode of PHEO discovery. Patients with genetic risk more often had bilateral disease at presentation and reported fewer symptoms. Large tumors (>4 cm) were associated with higher total urine metanephrines and a greater number of reported symptoms. Complex disease presentations (bilateral PHEO or concurrent PGL) were commonly associated with previously-established or subsequently-discovered mutations in all but one case. However, all PHEO patients should undergo genetic evaluation to assess their individual risk regardless of disease presentation.

REFERENCES

1. Lloyd RV ed, Endocrine Pathology: Differential Diagnosis and Molecular Advances. Totowa,Humana Press. 2004; 227-243.
2. .Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. Lancet (London, England) 2005; 366: 665-675.
3. Cotesta D, Petramala L, Serra V, Pergolini M, Crescenzi E, et al. Clinical experience with pheochromocytoma in a single centre over 16 years. High Blood Pressure & Cardiovascular Prevention. 2009; 16: 183-193.
4. Amar L, Servais A, Gimenez-Roqueplo AP, Zinzindohoue F, Chatellier G, et al. Year of diagnosis, features at presentation, and risk of recurrence in patients with pheochromocytoma or secreting paraganglioma. J Clin Endocrinol Metab. 2005; 90: 2110-2116.
5. .Zelinka T, Petrak O, Turkova H, Holaj R, Strauch B, et al. High incidence of cardiovascular complications in pheochromocytoma. Horm Metab Res. 2012; 44: 379-384.
6. Gruber LM, Hartman RP, Thompson GB, McKenzie TJ, Lyden ML, et al. Pheochromocytoma Characteristics and Behavior Differ Depending on Method of Discovery. J Clin Endocrinol Metab. 2019; 104: 1386-1393.
7. Falhammar H, Kjellman M, Calissendorff J. Initial clinical presentation and spectrum of pheochromocytoma: a study of 94 cases from a single center. Endocrine connections. 2018; 7: 186-192.
8. Thompson GB, Young WF, Jr. Adrenal incidentaloma. Curr Opin Oncol. 2003; 15: 84-90.
9. Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, et al. Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association. Hypertension. 2018; 72: 153-190.
10. Zuber SM, Kantorovich V, Pacak K. Hypertension in pheochromocytoma: characteristics and treatment. Endocrinol Metab Clin North Am. 2011; 40: 295-311.
11. .Prejbisz A, Lenders JW, Eisenhofer G, Januszewicz. A Cardiovascular manifestations of phaeochromocytoma. J Hypertens. 2011; 29: 2049-2060.
12. .Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014; 99: 1915-1942.
13. .Amorim-Pires D, Peixoto J, Lima J. Hypoxia Pathway Mutations in Pheochromocytomas and Paragangliomas. Cytogenet Genome Res. 2016; 150: 227-241.
14. Cohen DL, Fraker D, Townsend RR. Lack of symptoms in patients with

histologic evidence of pheochromocytoma: a diagnostic challenge. Ann N Y Acad Sci. 2006; 1073: 47-51.

15. Wang W, Han R, Ye L, Xie J, Tao B, et al. Adrenocortical carcinoma in patients with MEN1: a kindred report and review of the literature. Endocr Connect. 2019; 8: 230-238.

16. .Okada R, Shimura T, Tsukida S, Ando J, Kofunato Y, et al. Concomitant existence of pheochromocytoma in a patient with multiple endocrine neoplasia type 1. Surg Case Rep. 2016; 2: 84.

17. .Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab. 2012; 97: 2990-3011.

18. .Sarkadi B, Patocs A Hereditary Diseases Predisposing to Pheochromocytoma (VHL, NF-1, Paraganglioma Syndromes, and Novel Genes). Exp Suppl. 2019; 111: 129-147.

19. Neumann HP, Pawlu C, Peczkowska M, Bausch B, McWhinney SR, et al. Distinct clinical features of paraganglioma syndromes associated with SDHB and SDHD gene mutations. Jama. 2004; 292: 943-951.

20. Canu L, Van Hemert JAW, Kerstens MN, Hartman RP, Khanna A, et al. CT Characteristics of Pheochromocytoma: Relevance for the Evaluation of Adrenal Incidentaloma. J Clin Endocrinol Metab. 2019; 104: 312-318.

21. Buitenwerf E, Korteweg T, Visser A, Haag C, Feelders RA, et al. Unenhanced CT imaging is highly sensitive to exclude pheochromocytoma: a multicenter study. Eur J Endocrinol. 2018; 178: 431-437.

22. Hamrahian AH, Ioachimescu AG, Remer EM, Motta-Ramirez G, Bogabathina H, et al. Clinical utility of noncontrast computed tomography attenuation value (hounsfield units) to differentiate adrenal adenomas/hyperplasias from nonadenomas: Cleveland Clinic experience. J Clin Endocrinol Metab. 2005; 90: 871-877.

23. Park Jh, Choi SY, Soh EY Asymptomatic pheochromocytoma. Korean J Clin Oncol.2010;6:84-89.

Cite this article

Elstrott BK, Khan L, Ribakare D, Alali A, Olyaei A, et al. (2021) Pheochromocytoma: A Single-Center Retrospective Review. J Clin Nephrol Res 7(1): 1101.