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# Pheochromocytoma and paraganglioma at a children's hospital in Argentina. A case series

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## ABSTRACT

Pheochromocytomas and paragangliomas are neuroendocrine tumors producing catecholamines. Pheochromocytomas occur in the adrenal medulla, while paragangliomas are those that occur outside the adrenal gland. Here we describe a case series of children with a pathological diagnosis of pheochromocytoma or paraganglioma who consulted at a tertiary care children's hospital in Argentina. A total of 21 patients (14 males) were included; their median age was 11.4 years; 8 children had pheochromocytoma and 13, paraganglioma. Arterial hypertension was observed in 14/21. Most paragangliomas were para-aortic (9/13). Since they are a potentially curable cause of hypertension, clinical suspicion is very important. An early diagnosis and the initiation of an adequate antihypertensive treatment, which allows the patient to undergo surgery with normal blood pressure, ensure a cure in most cases if tumor resection is complete.


***Keywords:*** *hypertension; pediatrics; pheochromocytoma; paraganglioma; catecholamines.*

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## INTRODUCTION

The overall prevalence of hypertension (HTN) in pediatrics is increasing.[1,2] The secondary causes of HTN are more common among young children.[3] For example, 6% are endocrine causes,[2] which include pheochromocytoma (PCC) and paraganglioma (PGL).[3] Both are tumors producing catecholamines released from chromaffin cells in the neural crest. PCCs occur in the adrenal medulla, while PGLs occur outside the adrenal gland, originating in the paravertebral lymph nodes of the chest, abdomen, and pelvis sympathetic nervous system and the parasympathetic lymph nodes of the head and neck. These tumors are rare, with an annual incidence of 1 in 300 000.[4] Children and adolescents account for 20% of cases. PCCs and PGLs may be responsible for 0.5–2% of HTN cases.[5–7] They are potentially curable, secondary causes of HTN.

Here we describe a case series based on data from a review of medical records of children younger than 16 years with a pathological diagnosis of PCC or PGL who consulted at a tertiary care hospital in Argentina between 7/1/1988 and 12/30/2021. Results were analyzed retrospectively. The objectives were to describe patients' age, tumor presentation and location, ancillary tests, treatment provided, and prognosis.

For diagnosis and treatment, the standards of care of our institution were followed. Access to the information was in accordance with all legal and ethical principles regarding research confidentiality (Law no. 25326 for the Protection of Personal Information). Data collected may not be used for purposes other than those for which they were obtained.

## RESULTS

A total of 21 patients were included (14 males), whose median age was 11.4 years. The pathology was consistent with PCC in 8 cases and with PGL in 13 (*Table 1*).

HTN was observed in 14 of the 21 children, corresponding to the 8 patients with PCC and 6 of the 13 with PGL. Half of the patients with PCC consulted due to HTN and the other half, due to symptoms compatible with excess catecholamines. Among children with PGL, the most common symptom was abdominal pain followed by HTN; 6 of the 8 children with PCC had weight loss, sweating, and palpitations, whereas these symptoms were observed in 4 of those the 13 patients with PGL (*Figures 1 and 2*); 5 of the 8 PCC cases were unilateral. Most PGLs were para-aortic (9/13). The more uncommon locations were the neck (2 cases), the larynx (1 case), and the bladder (1 case).

All patients with PCC had a vanillylmandelic acid (VMA) test, which was elevated in 5/8. Urinary catecholamines (UC) were tested in 7 patients; norepinephrine (NE) was high in all of them.

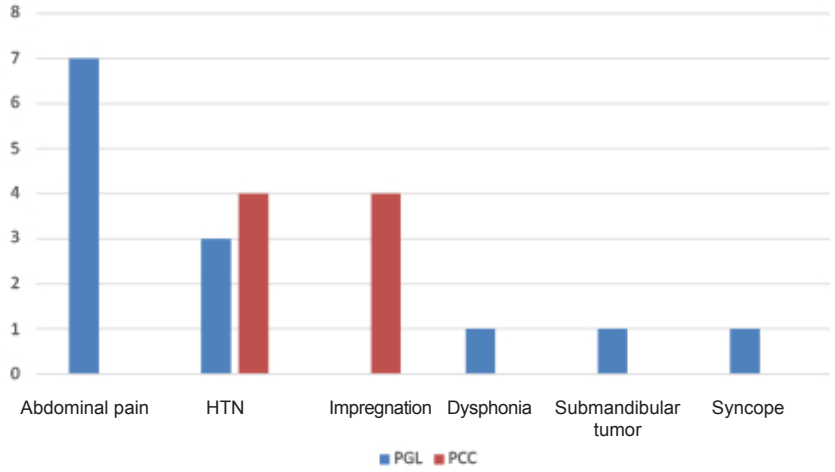
VMA was tested in 8/13 patients with PGL and was high in 5. The 3 children with a normal VMA test had para-aortic PGLs; 2 of them had asymptomatic tumors and had consulted due to nausea, vomiting, and abdominal pain, and

**Table 1. Characteristics of the study population**

| Variable | Total (n = 21) | Pheochromocytoma (n = 8) | Paraganglioma (n = 13) |
|---|---|---|---|
| Age (years) Median (IQR) | 11.47 (9.39, 13.38) | 11.72 (10.10, 14.17) | 11.45 (8.85, 13.19) |
| Male sex | 14/21 | 6/8 | 8/13 |
| Weight (kg) Median (IQR) | 36 (28, 43) | 32 (26, 37) | 38 (30, 43) |
| Height (cm) Median (IQR) | 142 (131, 148) | 140 (136, 143) | 144 (131, 148) |
| SBP (mmHg) Median (IQR) | 145 (110, 170) | 165 (157, 171) | 114 (110, 140) |
| DBP (mmHg) Median (IQR) | 92 (70, 111) | 110 (110, 114) | 70 (64, 92) |

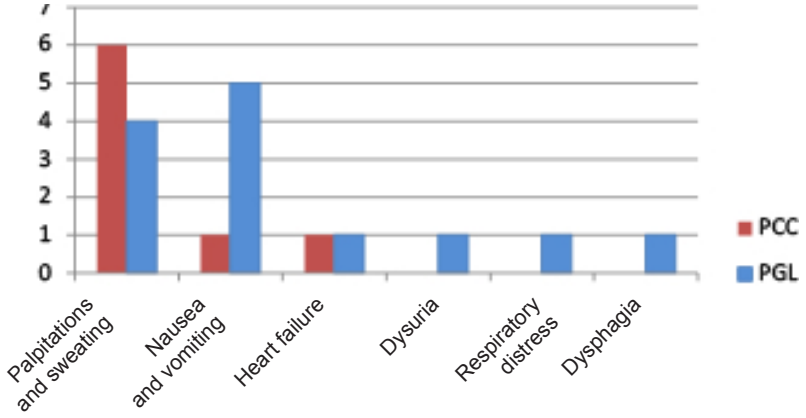
*IQR: interquartile range; SBP: systolic blood pressure; DBP: diastolic blood pressure.*

**Figure 1. Reason for consultation**




*HTN: hypertension; PGL: paraganglioma; PCC: pheochromocytoma.*

**Figure 2. Presenting symptoms**




*PCC: pheochromocytoma; PGL: paraganglioma.*

1 consulted due to HTN with heart failure. The tumor in these 3 children was observed with an abdominal ultrasound (*Table 2*).

In 3 children with PGL, no VMA or UC tests were done due to a low level of suspicion. One of them consulted due to abdominal pain and recurrent urinary tract infection and the tumor was found in the abdominal ultrasound. A girl consulted due to dysphonia and a neck tumor; the diagnosis was made by biopsy. And the third patient consulted due to HTN and reduced kidney size, suspected renovascular HTN and an intra-operative diagnosis of a para-aortic mass.

All PCC cases had a whole-body bone scan with $^{123}$I-MIBG (metaiodobenzylguanidine). The tumor was enhanced in 5/8. It was also done in 9 PGL patients and the tumor was observed in 6.

The tumor was noted by ultrasound in all PCC patients. Given the different sites where PGLs occurred, a computed tomography scan of the affected area was done in 12 children; the tumor had been previously observed by ultrasound in 9 of them.

Among children with normal blood pressure, 5 had abdominal pain; 1, dysphonia with respiratory distress; and 1, dysphagia and neck tumor. All 7 of them underwent imaging studies where the tumor was observed. Based on these data, a UC test was done in 5; 3 showed elevated epinephrine levels, which suggests that they may have had paroxysmal HTN that may have been diagnosed by ambulatory blood pressure

**Table 2. Ancillary tests and treatment**

| | Pheochromocytoma (n = 8) | Paraganglioma (n = 13) |
|---|---|---|
| **VMA** | | |
| Available | 8/8 | 8/13 |
| High | 5/8 | 5/8 |
| Normal | 3/8 | 3/8 |
| **Urinary catecholamines** | | |
| Available | 7/8 | 9/13 |
| Elevated NE | 7/7 | 5/9 |
| Normal NE | 0 | 4/9 |
| Elevated E | 5/7 | 5/9 |
| Normal E | 2/7 | 4/9 |
| Elevated NE and E | 5/7 | 4/9 |
| **Molecular test** | | |
| Available | 7/8 | 5/13 |
| No pathogenic variant detected or apparently sporadic | 2/7 | 3/5 |
| *VHL* | 3/7 | 0 |
| *NF-1* | 1/7 | 0 |
| *SDHA* | 1/7 | 0 |
| *SDHB* | 0 | 2/5 |
| **Surgical approach** | | |
| Conventional | 6/8 | 11/13 |
| Laparoscopic | 2/8 | 2/13 |
| **Pre-operative antihypertensive drugs** | 8/8 | 6/13 |
| Doxazosin/atenolol | 8/8 | 4/6 |
| Labetalol | 0 | 1/6 |
| Enalapril | 0 | 1/6 |

*Available: it indicates the number of children in whom the indicated ancillary test was performed.*
*VMA: vanillylmandelic acid; NE: norepinephrine; E: epinephrine.*
VHL*: von Hippel-Lindau gene;* NF-1 *gene: neurofibromatosis 1 gene;* SDHA*: succinate dehydrogenase complex flavoprotein subunit A gene;* SDHB*: succinate dehydrogenase complex flavoprotein subunit B gene.*

monitoring (ABPM). Among the 7 patients without HTN, 4 had multicentric tumors.

The molecular biology test was done in 12 children at Hospital General de Niños Ricardo Gutiérrez (*Table 2*). Bilateral PCC was observed in 3 children, all carriers of sporadic variants of the *VHL* (Von Hippel-Lindau) gene.

All were managed surgically; a conventional surgical approach was the most frequent. Pre-operative antihypertensive treatment was started in the 14 patients who had HTN at consultation (*Table 2*).

Residual tumor was noted in 5 children. One of them had PCC and a pathogenic variant of the *VHL* gene with bilateral tumor. The other 4 had PGL; 3 corresponded to para-aortic tumors (2 had sporadic variants of the *SDHB* gene) and 1, to a neck tumor.

Multicentric tumors were observed in 6 children with PGL. Four patients died. They had liver, brain, and bone metastasis. The other 2 were referred to adult health care facilities for follow-up. Both had non-resectable metastasis and sporadic variants of the *SDHB* gene.

## DISCUSSION

Consistent with Bholah et al.,[3] our series included twice as many males, whose average age was between 11 and 13 years.[4] It is striking that most had PGLs. Such difference was also published by Pamporaki et al.,[8] who observed a higher frequency of extra-adrenal tumors (66.3% versus 35.1%) in children compared to the adult population. Tersant et al. found that the proportion of adrenal and extra-adrenal tumors was almost the same.[9]

Children usually have sustained HTN.[5,10] This was observed in all PCC cases and almost half of PGL cases in our series. Two children had severe HTN associated with heart failure. The typical triad

(hyperhidrosis, headache, and palpitations) is observed in 47% to 57% of patients.[3-5] According to our results, the prevalence was higher (77%). Consistent with Seamon et al., abdominal pain was the most common symptom among patients who did not have HTN.[11] All were diagnosed as incidentalomas by imaging studies. ABPM may be used in patients with normal blood pressure and in whom PGL is highly suspected to look for masked HTN or a lack of restful sleep.[4]

If suspected, plasma and/or urine metanephrine should be tested. Metanephrines are more sensitive and specific than the AVM and CU tests.[10,11] However, a 24-hour urine collection in children is not easy to perform and this test is not available in our hospital. Imaging studies were done in many patients due to clinical suspicion. Establishing the etiology of PGLs is complex. Symptoms depend on the type of hormone secreted, and PGLs may even be asymptomatic.[3] For this reason, differences were observed in ancillary tests performed. In our series, it was possible to see the tumor in patients with HTN using an imaging method.

Pamporaki et al.[8] found a higher prevalence of extra-adrenal, multifocal, metastatic, recurrent lesions and molecular alterations in pediatric patients, which reached up to 80%. According to our results, 58.3% of patients who had a molecular study performed had a genetic alteration. Molecular diagnosis allows the early detection of associated diseases and familial cases.[8,11] Although there is no isolated marker of malignancy, pathogenic variants in the *SDHB* gene are related to the development of malignancy.[8,12] Both patients with this alteration developed metastasis. A genetic study is recommended in all patients with PGL or PCC.[9,12]

The main treatment approach is surgical resection, which is curative in most cases.[3] Laparoscopic resection is preferable.[4,13] Our series included a large percentage of open surgeries because many tumors were removed when laparoscopic surgery was not available. Preoperative antihypertensive management is critical to prevent blood pressure fluctuations during anesthetic induction, the onset of a hypertensive crisis, and hypotension after withdrawal.[3,4,10] Tumor manipulation may cause a release of catecholamines resulting in a severe hypertensive crisis with arrhythmia, myocardial ischemia, pulmonary edema, or stroke. It is recommended to start treatment with alpha blockers 7 to 14 days before the surgery. A beta blocker should be added at 48 hours to reduce reflex tachycardia. It is very important that patients consume an adequate amount of fluids and sodium to prevent postural hypotension caused by volume contraction.[10]

This study was conducted entirely in children and variables were analyzed from a clinical perspective. At present, there are not many publications with such characteristics available in our country. It is important to continue investigating and developing new sources of information because the pediatric subgroup has been poorly studied and many recommendations have been extrapolated from adults. ■

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