Original Article

A retrospective study of surgically excised phaeochromocytomas in Newfoundland, Canada

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ABSTRACT

Objective: A retrospective study detailing the circumstances surrounding diagnosis and treatment of pheochromocytomas with the associated genetic disorders. **Materials and Methods:** All patients with surgically excised pheochromocytomas in the Health Sciences Center, St. John's, Newfoundland, Canada between January 2001 and December 2010 were retrospectively analyzed to determine associated familial syndromes, age, tumor size, symptomatology, and percentage of paragangliomas and bilateral pheochromocytomas. Pathology specimen reports, adrenalectomy lists and Meditech (electronic medical record) diagnostic codes provided a comprehensive database for this study. **Results:** Twenty-four patients were studied; familial disorder patients comprised 42% (10/24). Average age at diagnosis was 57 among the sporadic and 34 in familial disorder groups ($P = 0.006$). Average tumor size was 4.5 cm in the sporadic group and 3 cm in the familial disorder group ($P = 0.19$). All atypical cases including bilateral or extra-adrenal tumors and malignancy occurred in familial disorder patients. **Conclusions:** The proportion of familial disorder patients (42%) was higher in this study than would be expected, likely a result of the relatively high incidence of hereditary autosomal dominant disorders within Newfoundland. Among familial disorder patients, the average younger age at diagnosis and the smaller tumor size suggest syndromic pheochromocytomas may develop earlier, however they are more likely to be diagnosed sooner due to biochemical surveillance testing in known genetic disorder patients. We also demonstrate a relatively high incidence of surgically resected pheochromocytomas of 4.679/million/year in Newfoundland.

Key words: Familial, Newfoundland, phaeochromocytoma, von hippel lindau

Introduction

Pheochromocytomas are rare catecholamine-secreting tumors arising from chromaffin cells.[1] The diagnosis is usually suggested by history in a symptomatic patient, the classic triad consisting of episodic headache, sweating, and tachycardia.[2] However, most patients do not have this triad of symptoms. Sustained or paroxysmal hypertension is the most common sign of a pheochromocytoma, but approximately 5-15% of patients are normotensive.[1]

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Measurements of urinary and plasma fractionated metanephrines and catecholamines confirm the diagnosis,[3] and surgical excision is the treatment of choice.[4] In 90% of cases, these tumors are found in the adrenal medulla, while the remaining cases originate in chromaffin cells of the sympathetic ganglia located throughout the body.[4] In approximately 20-30% of cases, a pheochromocytoma may arise as part of an autosomal dominant genetic disorder, including multiple endocrine neoplasia type 2 (MEN2), neurofibromatosis type 1 (NF1), and von Hippel-Lindau disease (VHL).[5]

Newfoundland is a province that has proven useful for the study of genetic diseases, due to its geography and socioeconomic development.[6] Large families, founder effects and close family ties have led to the documentation of extensive pedigrees of autosomal dominant diseases.[6] For instance, in a study conducted in 1982-1986, VHL

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disease was investigated in a large family that originated in Newfoundland, documenting the number of affected members and the extent of their diseases.[7] All diagnosed pheochromocytomas in the province are referred to the tertiary referral center in St. John's for surgery as the combination of surgeons with expertise in adrenal surgery, endocrinologists and anesthesiologists experienced in the management of phaeochromocytoma is only available at the Health Sciences Center in St. John's.

In a review of the literature, no studies were discovered that detailed the incidence and mode of presentation of pheochromocytomas in Newfoundland. A retrospective study detailing the circumstances surrounding the diagnosis and treatment of pheochromocytomas was conducted to offer new insights into the mode of presentation of these tumors - especially the differences between the sporadic and familial groups.

Materials and Methods

We have retrospectively analyzed all patients with pheochromocytomas that were surgically excised in the Health Sciences Center, St. John's, Newfoundland, Canada between January 2001 and December 2010. Surgical pathology specimen lists, adrenalectomy surgical lists and Meditech diagnostic codes were used to compile the list of patients, and the study was approved by the Health Research Ethics Authority Board.

Associated familial syndromes, age, gender, tumor size and sites, symptomatology at diagnosis, diagnostic measures, imaging, metaiodobenzylguanidine (MIBG) scintigraphy results and pathological findings were recorded.

An unpaired *t*-test was used to compare familial and sporadic groups on parameters of age and size of the tumor. In addition, positive and false negative MIBG groups were compared for statistical difference in tumor size. A logistic regression analysis was performed, to check for predictive value of tumor size on MIBG positivity. All statistical analyses were completed with SPSS software, SPSS Inc., Chicago, IL, USA.

Results

The study group included a total of 24 patients, 11 (46%) of which were female.

Ten of the 24 patients (42%) had 1 of 3 familial disorders. Table 1 outlines percentages of sporadic and familial cases, with average tumor size and the average age at diagnosis for each group. The mean age of the familial group was significantly lower than that of the sporadic group ($P = 0.006$).

There was no statistically significant difference in tumor size between sporadic and familial groups ($P = 0.19$).

Table 2 outlines the way in which each case was diagnosed. Of the 24 patients, 18 were diagnosed by 24 h urine metanephrines. In the remaining 6 cases, 4 tested negative and 2 were not tested for urine metanephrines. These patients were diagnosed by imaging or alternative forms of metanephrine testing as outlined in the table.

Table 3 outlines the clinical symptoms and signs experienced by each patient prior to diagnosis. Of the 6 patients who were asymptomatic, 5 had a familial disorder.

There were a total of 14 pre-operative MIBG scintigraphy scans on 13 patients. One patient with 2

Table 1: Comparison of sporadic and familial cases regarding the percentage of patients, tumor size, and age at first diagnosis

Groups	Percentage	Mean±SD (range)	
		Tumor size (cm)	Age
Sporadic	54 (13/24)	4.5±1.6 (2.9-9.0)	55.6±15.8 (18-76)
Familial	42 (10/24)	3.2±3.0 (1.0-10.5)	33.6±18.4 (13-66)
VHL	29 (7/24)		
NF1	8 (2/24)		
MEN2	4 (1/24)		

SD: Standard deviation, VHL: Von hippel-lindau, MEN2: Multiple endocrine neoplasia type 2, NF1: Neurofi bromatosis type 1

Table 2: Methods of diagnosis for 24 patients with pheochromocytoma

Method of diagnosis	Percentage
24 h urine metanephrines	75 (18/24)
Random urine metanephrine/creatinine ratio	4 (1/24)
Plasma metanephrines	4 (1/24)
Incidental finding on CT	8 (2/24)
MRI screening in known genetic disorder patient	8 (2/24)

CT: Computed tomography, MRI: Magnetic resonance imaging

Table 3: Clinical features at presentation of 24 patients with pheochromocytoma

Signs/symptoms	Patient percentage
Classic triad (headache+diaphoresis+tachycardia)	21 (5/24)
Hypertension	33 (8/24)
Labile blood pressure	4 (1/24)
Palpitations	8 (2/24)
Headache	8 (2/24)
Abdominal pain	4 (1/24)
Adrenal hemorrhage	4 (1/24)
Asymptomatic	25 (6/24)

pheochromocytomas, diagnosed 3 years apart, had an MIBG before each excision. Of the 14 MIBG scans performed, 7 had false negative results. There was no significant difference in tumor size between positive and false negative MIBG groups ($P = 0.15$) and tumor size did not predict MIBG positivity ($P = 0.19$).

Table 4 outlines the atypical cases amongst the 24 patients, including tumor recurrence, multiple tumors, malignancy, and extra-adrenal site. All atypical cases occurred in patients with familial disorders. The extra-adrenal paraganglioma case was a VHL patient who previously had bilateral adrenalectomies for adrenal pheochromocytomas.

Table 5 outlines the specific alpha and beta blockers used pre-operatively. Because urine metanephrines were negative, pheochromocytoma was not suspected in one case. This patient received no pre-operative alpha or beta blockade and was admitted to intensive care unit post-operatively for management of severe hypertension.

Discussion

As Newfoundland is an island, we can assume that all pheochromocytomas diagnosed in the province come to our center. This enables us to calculate the approximate incidence of surgically resected pheochromocytomas. The 2001 population of the province was 512,930 persons[8] giving us incidence of surgically resected pheochromocytomas of 4.679/million/year in Newfoundland. This is higher than previously reported from European populations where rates of 2/million/year have been reported.[9-11] One study from Queensland, Australia calculated incidence of 1.55/million population per year.[12] The actual incidence of pheochromocytoma in Newfoundland is likely to be higher given that some patients are not diagnosed or unable to have surgery because of comorbidities. Some pheochromocytomas are diagnosed only at autopsy while others are subclinical and found incidentally on imaging.[12,13]

This study, in comparison with the published literature, has a higher percentage of familial disorders than would be expected. Three other retrospective studies on the analysis of pheochromocytoma patients cited 17-25% familial pheochromocytomas, compared to 42% in this study.[4,14,15] This finding is possibly secondary to Newfoundland's unique genetic pool from founder effects that lead to a larger proportion of familial disorders, including a large multigenerational kindred with VHL.[7]

The mean age of the familial group, with 7 of the 10 syndromic tumors diagnosed before the age of 30, was significantly younger than that of the sporadic group. This is consistent with the literature: for example, Neumann *et al.* found that younger age at presentation was significantly associated with germline mutations of MEN2 and VHL.[16] In addition, Walther *et al.* found that younger age was associated with the VHL missense mutation.[17] This suggests earlier development of pheochromocytomas in familial disorders. This has been elegantly described recently with data from the Freiburg International Paraganglioma Registry.[18] Syndromic pheochromocytomas, however, are also more likely to be diagnosed earlier in the course of the disease due to biochemical surveillance testing in known genetic disorder patients.

In the current study, 5 of the 6 patients who were asymptomatic at diagnosis had a familial disorder. In the study by Walther *et al.*, 35% of VHL patients with pheochromocytomas were asymptomatic and normotensive; in the study by Neumann *et al.*, 92% of pheochromocytoma patients with VHL or MEN2 germline mutations had no associated signs or symptoms at presentation. Such a high incidence of asymptomatic familial disorder patients has significant implications when considering stringent biosurveillance and screening of this population, as many of them will not have the classic signs or symptoms that would otherwise prompt such investigations.

There has been a documented association between germline mutations and atypical pheochromocytomas,[16,17] which is consistent with this study: All patients with bilateral, multifocal, malignant or extra-adrenal pheochromocytomas had a familial disorder.

Table 4: Atypical pheochromocytoma cases and associated familial disorders

Atypical case	Percentage	Familial disorder
Recurrent pheochromocytoma diagnosed in remaining adrenal gland	8 (2/24)	VHL and MEN-2
Two pheochromocytomas diagnosed in same adrenal gland	4 (1/24)	VHL
Malignant pheochromocytoma	4 (1/24)	MEN-2
Extra-adrenal paraganglioma	4 (1/24)	VHL

VHL: Von hippel-lindau, MEN2: Multiple endocrine neoplasia type 2

Table 5: Number of patients who preoperatively received alpha and beta blocking agents

Alpha blockade					Beta blockade	
PBM*	Prazosin	PBM+prazosin	Terazosin	Phentolamine	Labetolol	Propranolol
10	5	2	1	1	18	1

PBM*: Phenoxybenzamine

Conclusion

In summary, pheochromocytomas are rare catecholamine producing tumors that are most often sporadic. They can, however, be associated with a number of familial syndromes and this study revealed a higher proportion of familial cases than expected. When compared to the sporadic group, mean age in the familial group was significantly lower at diagnosis. This has been previously described in the literature.[19] All atypical cases and the majority of asymptomatic presentations occurred in familial cases. This study reiterates the importance of taking a detailed family history in all patients with pheochromocytoma. Specific targeted measures should be taken to detect manifestations of familial syndromes. Further testing to detect germline mutations should be considered in appropriate cases.

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