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Abstract Fourteen children (10 boys and 4 girls, aged 8 to 17 years) had 20 pheochromocytomas treated over a 36-year period from 1959 to 1995 inclusive. Nine patients had 11 tumors before 1980; 5 children had 9 tumors up to 1987. There were no new children with pheochromocytomas at our hospital from 1988 to 1995. Hypertension, sweating, headache, and visual blurring were the most common symptoms and signs (average 5 months). The most reliable biochemical investigations were the urinary catecholamines and norepinephrine. Before 1980, intravenous pyelography and angiography were most successful in localizing the tumor, but since then ultrasonography and computerized tomography have been the radiological investigations of choice. Early involvement of the anesthesiologist in the preoperative control of the hypertension is essential; blood pressure (BP) control was achieved with phenoxybenzamine. The main anesthetic drugs used were: sodium thiopental, fentanyl, methoxyflurane, isoflurane, nitrous oxide, and metocurine. Sixteen tumors were adrenal and 4 were extra-adrenal (1 intrathoracic and 1 extradural). All except 2 tumors were completely resected; they ranged in size from 1.3 to 14 cm. Ligation of the tumor's venous drainage was usually associated with a sudden, temporary fall in systemic BP. There were 2 children with malignant tumors. Four patients had five recurrences (second pheochromocytoma) within 6 years, and all were heralded by a return of their original symptoms and signs. One girl was left with no adrenal tissue. The only complication was in a boy with a large, partly-resected malignant right adrenal tumor who had a subphrenic abscess drained and was left with a temporary bile fistula, cirrhosis, and chronic pain. All children were normotensive when discharged from hospital and remain alive and well with a follow-up of 7 to 36 years. There were no deaths. Long-term follow-up is essential.

Key word Pheochromocytoma

Introduction

The diagnosis and treatment of pheochromocytoma (pheo) in children has changed over the last 4 decades. To assess this in our hospital, we reviewed our 36-year experience with this tumor through 1995.

Materials and methods

From 1959 to 1995 inclusive, 14 children with 20 pheos were diagnosed and treated at the Hospital for Sick Children (HSC), Toronto. There were 10 boys and 4 girls from 8 to 17 years of age. Nine patients had 11 tumors before 1980 [35]; 5 others had 9 tumors from 1980 to 1987, but there were no new patients from 1988 to 1995. Four of the 14 children had 10 of the 20 pheos: 1 boy had 4 tumors; 2 girls and 1 boy 2 each; and 10 children had only 1. There was a family history of either pheo, von Hippel-Lindau disease, thyroid carcinoma, or renal stones in 4 patients, but no multiple endocrine adenomatosis (MEA) syndrome was found. Hypertension, sweating, headache, and visual blurring were the most common symptoms and signs; 1 girl presented with congestive heart failure and 1 boy with increasing paraplegia from an extradural cord metastasis (Table 1). Hypertension was defined as a systolic measurement of more than 120 mmHg. The range in our 14 patients was 100 to 260 mmHg (mean 160 mmHg). Three children had an initial blood pressure (BP) of more than 180 mmHg (190–260 mmHg). These symptoms and signs were present for 1 to 24 months and averaged 5 months.

Before the 1980s, urinary vanillylmandelic acid, catecholamines, metanephrine, and occasionally plasma renin activity and homovanillic acid were all used to measure the breakdown
products from the pheo, with the best results (100%) obtained from the catecholamines (Table 2). In the 1980s, urinary measurement of dopamine, norepinephrine, and epinephrine were used more often than the above tests with 100% positive results for norepinephrine. It was not necessary to use stimulation tests in this series. The seven phenotamine (Regitine) suppression tests were all positive; six were done before 1980.

Prior to 1980, intravenous pyelography (IVP) and angiography were the most commonly used diagnostic imaging modalities in localizing the tumor, but since then ultrasonography (US) and computerized tomography (CT) have been the radiologic investigations of choice (Table 3). The success rate was poorest with IVP (77%) and best with angiography (100%), although CT is now the commonest diagnostic test, with an accuracy of more than 90%.

Before 1980 [32] Innovar (droperidol/fentanyl), succinylcholine chloride, pancuronium, methoxyflurane, sodium thiopental, and phenotamine were all used during anesthesia [1]. Current anesthetic management at our institution consists of the following: preoperative phenoxybenzamine (1–2 mg/kg p.o. g.i.d.) for at least 4 days before operation, increased until there is an orthostatic drop in BP and a 5% drop in the hematocrit; preoperative sedation with pentobarbital sodium (2 mg/kg per rectum) or diazepam (0.3 mg/kg p.o.); atropine is usually not given; further sedation with IV fentanyl; the general anesthetic is started with NaO/O2 and isoflurane with intermittent IV p.c./O2 and isoflurane with intermittent IV p.o.); atropine is usually not given; further sedation with IV fentanyl for the remainder of the procedure.

Results

Sixteen pheos were adrenal in origin (8 left, 8 right, 1 bilateral) and 4 were extra-adrenal (2 para-aortic, 1 thoracic, 1 extradural). Two were malignant [7]. All the tumors (except in the 2 boys with malignant pheos) were completely resected; they ranged in size from 1.3 to 14 cm. One tumor caused extrinsic narrowing of the right renal artery but was completely resected, preserving the right kidney and leaving no postoperative hypertension [1, 22]. Ten children had a sudden intraoperative elevation of systolic BP to more than 180 mmHg (range 180–240, mean 200) with induction of anesthesia and/or tumor manipulation; all but two resolved without pharmacologic intervention. The two exceptions required control with a 0.01% solution of sodium nitroprusside. Following excision of the pheo, the systolic blood pressure fell precipitously and required rapid administration of crystalloid and colloid to maintain normal BP. Four patients remained hypertensive in the operating room after venous ligation of the tumor due to a second benign pheo [2] and unresected and/or metastatic malignant pheo [2].

All children went home normotensive. Four patients had five recurrences (a second pheo) within 6 years of their first tumor; the recurrences were heralded by a return of the original symptoms and signs. Three of these recurrences were in the opposite adrenal. All were resected, but 1 girl was left with no adrenal tissue and is neurologically asymptomatic 11 years later. The second had a very large right adrenal tumor; after chemotherapy he remains asymptomatic 11 years later. The second had a very large right adrenal mass mostly excised, but was left with a temporary bile fistula, obstructive jaundice, cirrhosis, chronic pain, and failure to thrive. He remains on chemotherapy with symptomatic bone metastases 8 years later [7]. This was the only complication in the series; there were no deaths.
Discussion

Pheochromocytoma continues to be an exciting but rare pediatric tumor [8, 16], there has not been a child with a new pheo at this hospital from 1987 to 1995 inclusive. Twenty percent of all pheos are found in the pediatric population [29], and more than one-third of these children have multiple tumors [34]. The mode of inheritance is autosomal dominant with a high degree of penetrance [15, 37]. Pheos are associated with several syndromes [2, 26, 29] and classifications, [2, 3, 26, 29]: neuroectodermal, MEA, Sipple Syndrome [12, 32], and fluorogenic amine content, amine precursor uptake, and the presence of the amino acid decarboxylase (APUD) system [2, 9, 12, 20, 29, 32, 37, 38].

Making the diagnosis of a pheo in a child is not difficult if the common symptoms and signs, especially hypertension (episodic or sustained), are appreciated [8, 16]. The diagnosis should be established by measurements of plasma and/or urine catecholamines [21]; 24-h measurements of urinary dopamine, norepinephrine, or epinephrine have been the preferential tests of choice since the 1980s. Stimulation tests are too dangerous and are no longer done [21, 26, 29, 34, 37]; inhibition tests (e.g., phentolamine) can produce false-negative results. We have not performed a clonidine suppression test, which is used in the adult population since hypertension is prevalent.

Radiologic localization of the tumor is now minimally invasive, safe, and accurate; US and CT are the procedures of choice [12, 26, 29]. CT has a 96% accuracy [36] except for small midline tumors in the retrogastric and retropancreatic areas [30]. Other, newer methods such as magnetic resonance imaging and scintigraphy [18, 31, 33] can be useful for elusive tumors. Occasionally, angiography is essential in the preoperative evaluation [11] and for embolization [13].

In children, hypertension due to pheo tends to be more severe and sustained than it is in adults and leads to a contracted blood volume [2, 34]. Preparation of the patient for operation not only involves assessment and treatment of end-organ damage (e.g., catecholamine myocarditis with heart failure) [10], but also adequate alpha-adrenergic blockade, blood volume re-expansion, and the treatment of any arrhythmias. Involvement of the anesthesiologist in the preoperative control of the hypertension is essential. Regardless of how preoperative alpha-adrenergic blockade is achieved, the benefits are dramatic.

In 1951 the perioperative mortality of patients with pheo was 45%; this has dropped to less than 3% since the introduction of the alpha-adrenergic blocking drugs in 1967 [27]. Phenolbenzamine has been the mainstay of pharmacologic therapy in our institution [25], however, despite aggressive pharmacologic loading with phenolbenzamine, 10 of our 14 patients still developed some degree of hypertension (mean 200 mmHg) during induction of anesthesia and/or tumor manipulation.

Beta-adrenergic blockade is indicated only in those situations where significant cardiac arrhythmias and/or tachycardia are present; this is rarely necessary in the pediatric patient because these tumors tend to be noradrenergic-secreting [14]. Beta-adrenergic blockade should never be induced prior to using an alpha-adrenergic blocking agent. Ventricular extrasystoles usually are not a problem, and children tolerate tachycardia more readily than adults.

Although removal of the pheo is essential to its cure, the anesthetic is still the most difficult, taxing, and potentially dangerous aspect of the operating room process [4, 5, 23, 27]. The times of significant intraoperative danger to the patient are during anesthetic induction and intubation, tumor manipulation, and immediately following ligation of the tumor's venous drainage. Constant arterial and central venous pressure are critically important. Arterial pressure may occur during the case requiring immediate and aggressive treatment. The large volumes of crystalloid and/or colloid needed during ligation of the tumor's venous drainage make the use of a central venous pressure monitor mandatory. Marked swings in Halothane was not employed in our patients because it has the property of sensitizing the myocardium to the arrhythmic activity of catecholamines [2, 14, 29, 34, 37]. Many different techniques have been used successfully in the intraoperative management of pheo patients. Roizen et al. [27] determined that pheo patients can be managed successfully with regional anesthesia, isoflurane, enfurane, halothane, or N2O with opioids and that the choice of technique was not the crucial factor determining outcome after resection of the tumor.

General anesthesia for excision of a pheo may be divided into two stages: the first is characterized by efforts to keep the systemic BP controlled (down) while the tumor is isolated and its blood supply and drainage ligated. The second is characterized by efforts to prevent hypotension after the first stage has been completed. Since complete alpha-adrenergic blockade is not possible [28], acute increases in systemic BP may occur during manipulation of the tumor. Corrective therapy (phentolamine 1–5 mg i.v.) will not be necessary unless the systolic blood pressure remains elevated above 180 mmHg. Cardiac arrhythmias are rare, but can occur during tumor manipulation; lidocaine and propranolol should be used if they persist. Within seconds of ligation of the venous drainage of a pheo the high concentration of circulating norepinephrine falls; if volume replacement has been inadequate up to this point, the BP may fall. Colloid should be administered under pressure until the systemic BP ceases to fall and the central venous pressure is stabilized between 9 and 12 cm H2O.

In the past, we have taken the position that a fall in BP at the time of venous ligation of the tumor is proof that no other tumor is present, and we still believe this to be true. Although, aggressive volume replacement can cope with the dilating vascular tree at the time of venous ligation to the extent that minimal BP instability may be
observed. If a precipitous fall in systemic blood pressure does not occur, it is advisable to search for a second tumor. It has been our experience that ligation of venous drainage from the tumor is always associated with a precipitous fall in systemic blood pressure and when this did not occur a second tumor was searched for and found. Postoperative blood glucose levels should be monitored to detect hypoglycemia [20, 39].

In the literature, 70%–80% of childhood pheos arise in the adrenal medulla [8, 14, 26, 34, 37]; thoracic tumors are very rare [17, 19, 24]. The prognosis in children with successfully resected pheos will depend on the benign or malignant characteristics of the tumor, the presence of associated conditions, and recurrences [19]. There is great controversy in the histologic classification of pheos, and the most reliable criterion of malignancy is the finding of a large primary tumor with diffuse local infiltration and distant metastases [37]. Benign tumors may show local invasion with no distant dissemination.

Although all of our patients with recurrences (second pheos) presented with a return of their original symptoms and signs, we still recommend long-term follow-up, preferably for life [26, 29]. This should include annual measurements of BP, urinary metabolites, and continued vigilance for associated conditions. When there is familial occurrence all members of the family should be screened [1].

References