

Management of pediatric pheochromocytoma

A review of the literature

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Introduction

Pheochromocytoma is a tumor originated from the chromaffin tissue of the adrenal medulla or from extra-adrenal paraganglionic tissue.

Pheochromocytomas are extremely rare in the pediatric population, accounting for 1% of pediatric hypertension.

Material and Methods

The Authors conducted a systematic review of the pediatric PCC focusing on the indications and surgical technique.

Results

Surgery remains the mainstay of treatment of pheochromocytoma in children.

Prior to surgery all children must be prepared with alpha-blockade with adequate fluid and salt replacement in order to reduce surgical complications.

Discussion and Conclusions

Minimally invasive adrenalectomy is the gold standard for benign lesions of the adrenal gland. The lateral transperitoneal adrenalectomy is the standard approach. Laparoscopic bilateral partial adrenalectomies should be considered in children with bilateral PCC in order to avoid lifelong glucocorticoid and mineralocorticoid replacement.

1. INTRODUCTION

Pheochromocytoma (PCC) is a tumor originated from the chromaffin tissue of the adrenal medulla or from extra-adrenal paraganglionic tissue. 1

PCC is extremely rare in the pediatric population, accounting for 1% of pediatric hypertension.

2

20% of all PCCs are diagnosed in the pediatric population and in 40 % of cases are associated with genetic mutations. 3,4 Hereditary PCC can occur in multiple endocrine neoplasia type 2 (MEN2), von Hippel-Lindau syndrome (VHL), neurofibromatosis type 1 (NF1) and familial paraganglioma syndromes.

The clinical presentation of PCCs in childhood is extremely variable with sustained hypertension described as the most frequent symptom (60-90% of cases).5

The biochemical diagnosis represents the first step when PCC is suspected and consist of measurement of plasma free metanephrine or 24-h urinary fractionated metanephrines.6 The genetic testing should be performed for al pediatric PCCs.

As regards the tumor localization the magnetic resonance imaging (MRI) of the abdomen and pelvis has excellent sensitivity (90-100%) avoiding radiation exposure of children. 7

Surgery remains the mainstay of treatment of PCC in children.

Prior to surgery all children must be prepared with alpha-blockade with adequate fluid and salt replacement in order to reduce surgical complications. 8

Laparoscopic adrenalectomy when performed by an expertise surgeon is the preferred approach9.

For bilateral PCC, laparoscopic cortical-sparing adrenalectomies must be a choice when possible in order to avoid chronic glucocorticoid deficiency.10

Open approaches can be considered for large, locally advanced and metastatic neoplasms.

2. METHODS

The Authors conducted a systematic review of the pediatric PCC focusing on the indications and surgical technique. Trials and retrospective studies were identified by conducting a comprehensive search of Medline, Embase, Science Citation Index, Current Contents, and PubMed databases, using medical subject headings (MESH) 'pediatric pheochromocytoma', 'surgery', 'minimally invasive adrenalectomy' and 'surgical approaches'. A manual search of the bibliographies of relevant papers was also carried out to identify relevant studies for possible inclusion. Data extraction and critical appraisal were carried out by three authors independently (CM, CG, GC).

3. DISCUSSION

PCC arises from chromaffin cells of the adrenal medulla. The first case was described by Frankel in 1886.11

PCC is extremely rare in the pediatric population, accounting for 1% of pediatric hypertension.2

20% of all PCC are diagnosed in the pediatric population and in 40 % of cases are associated with genetic mutations.3,4 Hereditary PCC can occur in multiple endocrine neoplasia type 2 (MEN2), von Hippel-Lindau syndrome (VHL), neurofibromatosis type 1 (NF1) and familial paraganglioma syndromes.

If compared with adult, pediatric PCCs are more frequently extra-adrenal, bilateral and multifocal.12-15

The clinical presentation of PCC in childhood is extremely variable and frequently patients are asymptomatic. 16

Symptoms are related to the elevated levels of catecholamines and sustained hypertension is the symptom described more frequently (60-90% of all pediatric PCCs).

Other signs and symptoms of catecholamine excess are palpitation, nausea, vomiting, weight loss, polyuria, headache, sweating, pallor and visual disturbances and should address the suspicion of PCC.17

The median age of presentation of pediatric PCC is 11 years and the male to female ratio is 2:1. 18,19

Genetic testing should be done for all pediatric PCC. Mutations of the gene encoding subunits D and/or B of the succinate dehydrogenase (SDH) are related with familiar paragangliomas with a higher risk of malignancy. 20

The activating mutations of the proto-oncogene rearranged during transfection (RET) result in the tumor syndrome MEN2. This syndrome is autosomal dominant. PCCs associated with this syndrome can be bilateral in 50-80% of cases but are rarely malignant.

In VHL disease is autosomal dominant and rarely determine pediatric PCC. However PCCs related to VHL are often bilateral.21

PCCs determined by NF1 gene mutations are extremely rare (<5%) and genetic testing for these mutations should not be routinely performed.

The biochemical diagnosis represents the first step when PCC is suspected and consist of measurement of plasma free metanephrine or 24-h urinary fractionated metanephrines.6

Only after a conclusive biochemical diagnosis is possible to start with tumor localization studies. The MRI of abdomen and pelvis has excellent sensitivity (90-100%)and avoid radiation exposure of children.7

In addition should be perform a 123metaiodobenzylguanidine (MIBG) scintigraphy in order to specify a PCC from other abdominal lesions, to detect paragangliomas in multiple location and signs of a malignant PCC.

Prior to surgery all children must be prepared with alpha-blockade (prazosin/ phenoxybenzamine) with adequate fluid and salt replacement in order to reduce surgical complications.8

Beta-blockade should be administrated only in cases of residual tachycardia or arrhythmias after adequate therapy with alpha-blockade.22

Surgery remains the mainstay for treatment of PCC in children. Minimally invasive adrenalectomy (MIA) is the gold standard for benign lesions of the adrenal gland. There are three MIA approaches: lateral transperitoneal adrenalectomy (LTA), prone retroperitoneal adrenalectomy (PRA), and lateral retroperitoneal adrenalectomy (LRA).

The LTA is the standard approach. It is the preferred technique for large malignant lesions because it makes possible a good exposure of the adrenal gland and of the surrounding structures. Moreover, it allows good lymph node dissection along the inferior vena cava or the aorta.

The PRA has some advantages: direct access to the gland, bilateral adrenalectomy possible without changing position of the patient, easier identification of the vein, low risk of injury of peritoneal organs. The main limitation is the limited working space. Some authors prefer this approach for lesion of less than 5 cm.23

The LRA approach has the same advantages of the PRA, but the access to the gland is less easy and bilateral adrenalectomy is not possible without changing patient position.

MIA is the technique of choice for pediatric PCC. The choice of the preferred approach (transperitoneal or retroperitoneal) depends on the size of the lesion and of the preference/experience of the surgeon.

The children with SDH mutations have a higher risk of malignancy, so a total adrenalectomy should be preferred. In VHL and MEN2 the risk of malignancy is low, but the risk of metachronous lesions is higher. Laparoscopic bilateral partial adrenalectomy should be considered in children with bilateral PCC in order to avoid lifelong glucocorticoid and mineralocorticoid replacement. 24-30

4. CONCLUSION

The biochemical diagnosis represents the first step when PCC is suspected and consists of measurement of plasma free metanephrine or 24-h urinary fractionated metanephrines. Only after a conclusive biochemical diagnosis is possible to start with tumor localization studies. The genetic testing should be performed for all pediatric PCCs. MIA is the gold standard for benign lesions of the adrenal gland. The LTA is the standard approach. The choice of the transperitoneal or retroperitoneal approach depends on the size of the lesion and of the preference of the surgeon. In order to avoid lifelong glucocorticoid and mineralocorticoid replacement, laparoscopic bilateral partial adrenalectomy should always be considered in children with bilateral PCC.

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