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Rev Chil Pediatr. 2020;91(5):767-772
DOI: 10.32641/rchped.v91i5.1828

CLINICAL CASE

Adrenergic crisis as a debut form of a neuroblastoma

Crisis adrenérgica como forma de debut de un neuroblastoma

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Received: February 20, 2020; Approved: May 17, 2020

What do we know about the subject matter of this study?

Neuroblastoma is the most common extracranial solid tumor in pediatrics and can appear along the entire sympathetic nerve chain. Its most frequent clinical form of presentation is abdominal distension or pain.

What does this study contribute to what is already known?

We present an atypical form of debut in neuroblastoma with arterial hypertension, tachycardia, sweating and irritability as an adrenergic storm due to the release of catecholamines. A broad differential diagnosis should be made that includes cardiac and metabolic pathology (hypoglycemia) and/or poisoning.

Abstract

The most common clinical presentation of neuroblastoma is an abdominal mass, but it can present with uncommon symptoms, such as adrenergic storm due to catecholamine release. **Objective**: To describe an unusual presentation of neuroblastoma and the wide differential diagnosis that exists in an infant with adrenergic symptoms. **Clinical Case**: A 7-week old female infant was evaluated due to a 3-week history of sweating and irritability associated with a 24-hour fever and respiratory distress. At admission, she presented poor general condition, irritability, sweating, facial redness, tachypnea and skin paleness, extreme sinus tachycardia, and high blood pressure (HBP), interpreted as adrenergic symptoms. The study was completed with abdominal ultrasound and magnetic resonance imaging that showed a large retroperitoneal mass compatible with neuroblastoma. Plasma and urinary catecholamines tests showed high levels of dopamine, adrenaline, and noradrenaline, probably of tumor origin. We started antihypertensive treatment with alpha-blocker drugs, showing a good blood pressure control. The tumor was surgically resected without incidents and adequate subsequent recovery. The patient presented a favorable evolution after three years of follow-up. **Conclusions**: In an infant with adrenergic symptoms such as irritability, redness, sweating associated with HBP, it should be ruled out pathology heart or metabolic (hypoglycemia) pathology, intoxications, and/or adrenal pathology. Within this last one, neuroblastoma is the first diagnostic possibility, since it is one of the main tumors in childhood and, although this presentation is not usual, it can produce these symptoms.

Keywords:
Nephrology;
Arterial Hypertension;
Oncology;
Neoplasms;
Neuroblastoma

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How to cite this article: Rev Chil Pediatr. 2020;91(5):767-772. DOI: 10.32641/rchped.v91i5.1828

Introduction

Neuroblastoma is the most common extracranial solid tumor in pediatrics, which accounts for 6%-8% of all pediatric cancers[1-6] and can appear along the entire sympathetic nerve chain[1-4]. The male-female ratio is 1.2:11.2. The mean age of patients at the time of diagnosis is 2 years, and 90% of cases are detected in children under 5 years of age[1-3]. Its etiology is unknown, and to date, no pre or postnatal environmental trigger has been identified[3]. Most cases are sporadic but there are 1-2% of them with previous family history[3,4].

It usually occurs in isolation, but can be associated with other syndromes such as Hirschsprung's disease, Ondine syndrome, von Recklinghausen's disease, and hypomelanosis of Ito[4]. It is characterized by a very heterogeneous behavior, ranging from tumors diagnosed by chance in childhood with a survival of more than 90%, better prognosis in children under one year, in contrast to those that have highly aggressive behavior, its onset is with metastasis, and have a low survival[1-6].

Adrenal tumors have been found during autopsies of fetuses and premature infants[3,4]. For some reason the tumor spontaneously returns in most survivors, becoming clinically unnoticeable while in other cases differentiating into benign tumors later on, once they are born[1,3].

The symptoms of presentation are usually quite nonspecific and can be caused by the primary tumor, by metastasis, or by metabolic alterations[1-6]. In 60% of cases, the primary tumor is found in the abdomen, and in more than half of the cases, it is located in the adrenal gland[1-6]. The second location in frequency is the thorax, which represents 14% of all cases, followed by the pelvis with 6%, and the cervical region with 2%[1-6]. Up to 18% are in other regions[1-6].

The most frequent clinical presentation of abdominal tumors is an abdominal mass that can cause abdominal pain, distension, or, rarely, intestinal obstruction[1-3]. Thoracic tumors can cause coughing, dysphagia, shortness of breath, superior vena cava syndrome, or Horner's syndrome[1-3]. The latter can also be caused by tumors in the cervical region. Tumors in the pelvis can cause urinary obstruction or constipation[1-3].

The most common areas of metastasis are lymph nodes, liver, skin, bones, and bone marrow[1-3,5]. They can appear with diverse symptoms such as bone pain, limp, spinal cord compression, periorbital ecchymosis, and ocular proptosis, which are called "raccoon eyes" and can present on physical examination a fast-growing hepatomegaly[1-3,5]. In addition, they can associate different paraneoplastic syndromes such as opsoclonus-myoclonus syndrome which causes ataxia, myoclonus, and erratic eye movements; severe secretory diarrhea, redness, sweating, and high blood pressure (HBP) due to increased production of vasoactive intestinal peptide, or, more infrequent, in the form of HBP, tachycardia, and sweating due to catecholamine release[1-3,5]. In the latter situation, irritability can also occur and be equivalent to headache in older children as part of the adrenergic symptomatology[1-3,5].

The signs and symptoms of sympathetic overactivity produced by a rise in vascular resistance, increased oxygen consumption, and a hyperdynamic state with increased afterload are very unusual and can go unnoticed, causing these patients to develop heart failure, shock, and even death[2,4]. It is vitally important to early identify these patients to avoid their metabolic decompensation, the spread of the tumor to other organs, and thus improve their prognosis.

The objective of this work is to describe an unusual presentation of neuroblastoma and the wide differential diagnosis that exists in an infant with adrenergic symptoms.

Clinical Case

7-week old female infant taken to the emergency department due to a 24-hour history of fever and respiratory distress. Parents reported that approximately three weeks earlier they noticed the child was more irritable and sweating almost constantly, without any obvious trigger. The child was fed with adapted milk formula from the beginning, without changes from birth, with adequate weight increase. She was a full-term newborn with adequate weight for gestational age (3910 grams). Pregnancy and birth without complications. Her metabolic tests (TSH and PKU) were normal. Non-consanguineous parents. Father with history of coarctation of the aorta in the neonatal period. No other relevant history.

In the initial evaluation, she presented with fair general condition due to respiratory difficulty with marked sub and intercostal retraction, irritability, and poor distal perfusion. Initial saturation was 97%, respiratory rate 68 rpm, heart rate 231 bpm, blood pressure (BP) 119/84 mmHg, blood glucose 112 mg/dl, and axillary temperature 39.5 ºC. The airway was permeable and pulmonary auscultation was normal. Cardiac auscultation showed sustained tachycardia with gallop rhythm. When checking the pulse, it was palpable in all four extremities, and capillary refill was slow (3 seconds) with coldness in the extreme of the lower limbs. Isochoric and normally reactive pupils. Facial redness without skin lesions. On examination, the abdomen was soft and non-tender without apparent masses or visceromegalies. The rest of the examination showed no alterations. The patient had symmetrical and spontaneous

movements in all four extremities, good muscle tone, and no focal neurological signs.

It was started oxygen therapy with a non-rebreather mask. Two peripheral venous lines were placed for blood test extraction (Table 1) and 10 ml/kg of physiological saline was infused. An antipyretic and a dose of broad-spectrum antibiotic IV were administered.

The electrocardiogram showed inappropriate sinus tachycardia with a frequency of 225 bpm and an echocardiogram showed a structurally and functionally normal heart ruling out heart pathology. Analysis of sediment and toxins in urine without alterations.

During her stay in the emergency department, her heart rate and BP continued to be above the 99th percentile for her age, and the shortness of breath that initially presented did not improve despite initial stabilization measures. She was admitted to the pediatric intensive care unit (PICU) for close monitoring to complete her study.

At the PICU, the patient presented BP figures compatible with a hypertensive crisis. Tachycardia, sweating, HBP, and peripheral vasoconstriction were considered as adrenergic symptoms. The study was completed with an abdominal ultrasound to dismiss a tumor secreting catecholamines, in addition to assessing the renal affectation and ruling out alteration in that area.

The abdominal ultrasound (Figure 1) showed a large retroperitoneal mass of right perivertebral location with well-defined borders measuring approximately 4 x 4.3 x 5.4 centimeters that was compatible with neuroblastoma, which was confirmed by MRI (Figure 2). Subsequently, the catecholamine count in blood and urine (Table 2) showed high levels of dopamine, adre-

Table 1. Blood tests performed in the initial evaluation

Analytical values	Results	Normal values
Leukocytes	14,280/mm^3	4,000-11,000
Neutrophils	6,420/mm^3	
Lymphocites	7,190/mm^3	
Hemoglobin	10.1 g/dl	10.4-12.5 g/dl
Platelets	685,000/mm^3	150,000-400,000/mm^3
Glucose	94 mg/dl	64-100 mg/dl
Urea	38.4 mg/dl	8-35 mg/dl
Creatinine	0.34 mg/dl	0.24-0.42 mg/dl
Sodium	143 mEq/l	134-145 mEq/l
Potassium	4.8 mEq/l	4.3-6.2 mEq/l
Chlorine	108 mEq/l	95-111 mEq/l
C-reactive protein	0.57 mg/dl	0.01-1 mg/dl
Procalcitonin	0.11 ng/ml	0.1-0.5 ng/ml

Table 2. Catecholamines in blood and urine

Catecholamines in urine	Patient values	Reference values
Adrenalin	6.12 mcg/24 h	0-3.5 mcg/24 h
Noradrenaline	18.36 mcg/24 h	0-15 mcg/24 h
Dopamine	139.46 mcg/24 h	3-85 mcg/24 h
Vanylmandelic acid	4.8 mg/24 h	1-2.6 mg/24 h
Homovalinic acid	13.24 mg/24 h	0-4.3 mg/24 h

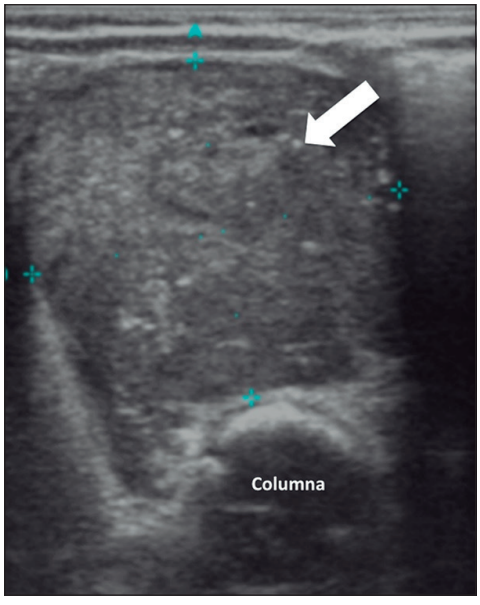

Figure 1. Abdominal ultrasound, transverse section. Large solid retroperitoneal paravertebral mass, discretely lateralized to the right with well-defined borders (arrow). The lesion is solid, slightly heterogeneous with scattered punctate hyperechoic images (calcifications).

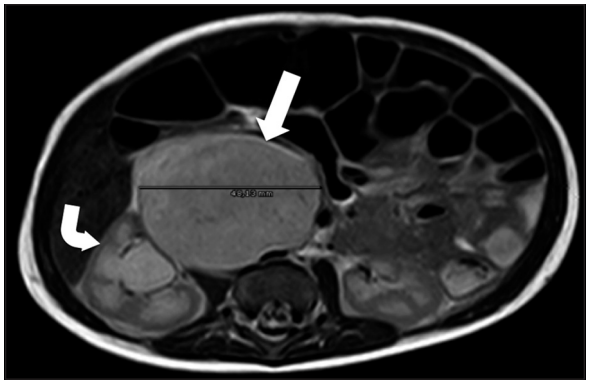

Figure 2. Abdominal magnetic resonance imaging. T1-weighted image with contrast. Axial image at the level of the lower renal poles. Well-defined solid retroperitoneal mass, right paravertebral, that crosses the midline. The lesion is slightly heterogeneous impregnated after the use of contrast (arrow). It has a mass effect on the right pyeloureteral region causing obstructive hydronephrosis (curved arrow). There are no signs of invasion of the spinal canal.

Table 3. Episodes of adrenergic crisis during admission before surgery

Days since your initial care (treatment established)	Maximum HR	Maximum BP	Adrenergic symptomatology
0	231	149/104	++++
+1 (phenoxybenzamine every 24 h)	218	126/81	++++
+4 (phenoxybenzamine every 12 h)	170	122/60	+++
+6 (phenoxybenzamine every 6 h)	206	110/70	++
+10 (phenoxybenzamine every 6 h)	158	102/53	-

HR: heart rate; BP: blood pressure; ++++: severe; +++: moderate; ++: mild; -: no symptoms.

naline, and noradrenaline, presumably of tumor origin. The extension studies of aspiration, bone marrow biopsy, and chest X-ray were negative. The MIBG scan showed metabolic activity in the retroperitoneal region without metastatic disease.

Oral antihypertensive treatment with amlodipine was initiated together with the alpha-blocking drug phenoxybenzamine, which progressively reduced the BP to figures around the 90th percentile for the patient's age (BP 90/50 mmHg), and controlled the episodes of adrenergic storms which had increasingly less hemodynamic repercussions (Table 3) until their complete disappearance on day +18 of admission. Before surgery, no beta-adrenergic blockade was performed, given the patient's age, clinical stability, and the absence of reflex tachycardia.

On day +25, the patient underwent surgery without incident. A macroscopic resection of more than 90% of the tumor was performed. In the macroscopic anatomopathological examination, it showed a brownish coloration, with areas of necrosis and calcification, presenting a heterogeneous general aspect, and in the microscopic analysis, there were few signs of differentiation towards ganglion cells, with a favorable prognosis group. After 24 hours of the intervention, the sedation was suspended and the patient was extubated without incidents with adequate recovery.

She evolved favorably in the postoperative period. In the oncological evaluation, we chose a watchful waiting approach since it was a localized neuroblastoma with favorable histology, almost complete resection, and without amplification of the N-Myc oncogene. After discharge, the patient was in follow-up during the next three years on an outpatient basis with very good evolution.

Discussion

In a patient with tachycardia, HBP, sweating, and peripheral hypoperfusion, we should consider an adrenergic storm produced by the increased release of catecholamines that stimulate alpha and beta-adrenergic receptors[7]. Different diagnostic entities can cause these symptoms.

The intense sweating and peripheral vasoconstriction presented by the patient could be signs of heart failure secondary to congenital heart disease not diagnosed during pregnancy, such as coarctation of the aorta[8]. Palpation of all pulses and BP measurement in all four limbs are essential for diagnosis[8]. The echocardiogram is the indicated complementary test when there is suspicion[8]. The father of this patient had presented coarctation of the aorta in childhood, and it is known that the risk of having a child with congenital heart disease increases when one of the parents has had it[9].

Since the patient's heart rate was extremely high, a tachyarrhythmia had to be ruled out, through an electrocardiogram with all the leads. Paroxysmal supraventricular tachycardia is the most frequent tachyarrhythmia in pediatrics[10]. It has a regular heart rate of 150-300 beats per minute and P waves are not always present[10].

Another pathological condition to be ruled out is hypoglycemia since it is one of the most frequent metabolic disorders in pediatrics, and its early diagnosis and treatment are essential for the prevention of neurological sequelae[11]. The symptomatology is caused both by the direct effects of the decrease in energy supply to the central nervous system and by the adrenergic response[11]. The symptoms are nonspecific, occurring lethargy, apathy, apnea, weak crying, tremor, irritability, seizures, coma, sweating, tachycardia, vomiting, and pallor[11]. In neonates and small infants, most of the causes are transitory, due to decreased production or increased use of glucose[11], but other causes produce persistent hypoglycemia such as hyperinsulinism, hypopituitarism, or metabolic diseases[11].

Also, it is important to screen for drug abuse in urine such as amphetamines or cocaine that produce HBP, tachycardia, and sweating[12].

In the initial monitoring of this patient, very high figures of BP compatible with a hypertensive crisis were found[13]. An abdominal ultrasound with Doppler

was performed to evaluate the renal affectation and rule out alteration in renal flow rate or stenosis of the renal arteries, finding an adrenal mass that explained the adrenergic symptoms.

The main tumors derived from the neural crest cells are pheochromocytoma, paraganglioma, and neuroblastoma[14,15]. Within these, pheochromocytoma and paraganglioma appear similarly to our patient, but are very rare in the neonatal period and the first years of life[14,15], while neuroblastoma, which is the most frequent solid extracranial tumor in childhood[1-6,14,15], does not usually produce symptoms related to catecholamine release[1-6,17-19]. It is not a frequent cause of HBP and, when it occurs, it is usually secondary to renal compression by the tumor mass in most cases and not due to catecholamine release[16-19]. As occurred in this case, catecholamine-producing neuroblastomas and especially those with predominantly dopamine excretion can produce facial redness, tachycardia, and HBP[1-3,5].

Catecholamine-secreting tumors require specific control of adrenergic symptoms, since the excessive release of catecholamines can cause hypertensive crises[16-21]. Preoperative pharmacological preparation is indicated for patients with catecholamine-secreting neoplasms, including those with no symptoms and normal BP[16,20,21]. The α-adrenergic blockade should be initiated 7-10 days before surgery to normalize the BP while attempting volume expansion by appropriate adjustment of fluid therapy and/or transfusion of red blood cell concentrate if necessary[16,20,21]. Phenoxybenzamine is the most commonly used drug in the preoperative preparation to control HBP and arrhythmias. After achieving an adequate α-adrenergic blockade, the β-adrenergic blockade is initiated usually 2 or 3 days before surgery[16,20,21]. Treatment with β-blockers should not be started earlier, since the blocking effect on the β2 receptors, whose stimulation produces peripheral vasodilation, could lead to increased arterial vasoconstriction and cause severe HBP or cardiopulmonary decompensation[16,20,21]. Other drugs used in the management of HBP associated with catecholamine release are calcium antagonists[19-21], which block noradrenaline-mediated transport of calcium to vascular smooth muscle. The main function of these drugs is to complement the combined alpha and beta-adrenergic blocking protocol when HBP control is not adequate or to replace it, in patients with severe side effects[20-22].

Conclusions

In infants who present adrenergic symptoms such as irritability, redness, sweating associated with HBP, there is a varied differential diagnosis such as cardiac pathology, metabolic (hypoglycemia), intoxications, and/or adrenal pathology. Within the latter, neuroblastoma is usually one of the main tumors in childhood and, although this presentation is not the most common, it can cause these symptoms when they have an increased release of catecholamines.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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