Malignant Paraganglioma Presenting With Hemorrhagic Stroke in a Child

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ABBREVIATIONS CT—computed tomography
FDG PET—fluoro-2-deoxy-D-glucose positron emission tomography
MIBG—metaiodobenzylguanidine
MRI—magnetic resonance imaging
SDHB—succinate dehydrogenase subunit B

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abstract

Sympathetic paragangliomas are rare catecholamine-secreting tumors of extra-adrenal origin, and their diagnosis in children is even more infrequent. They usually manifest as hypertension, palpitations, headache, sweating, and pallor. Malignant paragangliomas are identified by the presence of metastasis. Hemorrhagic stroke in the pediatric population is a life-threatening condition with several etiologies. We report here the case of a 12-year-old boy with malignant sympathetic paraganglioma presenting with hemorrhagic stroke. Severe hypertension was found and the patient evolved into a coma. Brain computed tomography scan showed right thalamus hemorrhage with intraventricular extension. After clinical improvement, further investigation revealed elevated catecholamine and metanephrine levels, and 2 abdominal tumors were identified by computed tomography. Resection of both lesions was performed, and histologic findings were consistent with paraganglioma. Multiple metastatic involvement of bones and soft tissues appeared several years later. Genetic testing identified a mutation in succinate dehydrogenase subunit B gene, with paternal transmission. 131I-metaiodobenzylguanidine therapy was performed 3 times with no tumoral response. Our patient is alive, with adequate quality of life, 25 years after initial diagnosis. To our knowledge, this is the first pediatric case of paraganglioma presenting with hemorrhagic stroke. Intracerebral hemorrhage was probably caused by severe hypertension due to paraganglioma. Therefore, we expand the recognized clinical spectrum of the disease. Physicians evaluating children with hemorrhagic stroke, particularly if hypertension is a main symptom, should consider the possibility of catecholamine-secreting tumors. Metastatic disease is associated with succinate dehydrogenase subunit B mutations and, although some patients have poor prognosis, progression can be indolent. Pediatrics 2013;132:e1709–e1714
Pheochromocytomas and paragangliomas are rare neuroendocrine tumors, with an estimated prevalence of 1.6500 to 1.25000, and an annual incidence of 1.5 to 9 cases per 1 million people.1,2 Although pheochromocytomas are defined as tumors arising from catecholamine-producing chromaffin cells in the adrenal medulla, closely related lesions of extra-adrenal sympathetic and parasympathetic paraganglia are known as paragangliomas.3

Pheochromocytomas and sympathetic paragangliomas are classified as catecholamine-secreting tumors. They are diagnosed in the pediatric population in ~10% to 20%. Most cases are sporadic but in children they are part of hereditary syndromes in 40% to 70%.4,5 Main signs and symptoms include hypertension, palpitations, headache, sweating, and pallor.1 Malignancy is identified by the presence of metastasis, and corresponds to 2% to 47% of childhood tumors.3,5

Hemorrhagic stroke in the pediatric population is a life-threatening condition and accounts for half of all stroke cases. It usually presents with headache and focal neurologic signs. Initial investigation is made by brain computed tomography (CT); cerebral angiography is usually done to rule out vascular pathology. Neurosurgical intervention is sometimes required.6–8

We report here the case of a child with malignant sympathetic paraganglioma presenting with hemorrhagic stroke, and we perform a review of the related literature.

**CASE REPORT**

A 12-year-old boy presented with sudden onset of headache, diaphoresis, weakness on the left side of the body, and altered mental status that evolved into a coma. He complained of frequent episodes of headaches in the previous 4 years, without seeking medical advice.

On examination, he had a Glasgow Coma Scale score of 7, severe hypertension (blood pressure 280/140 mm Hg), left hemiparesis, and papilledema. Brain CT scan showed intracranial hemorrhage located in the right thalamus with intraventricular extension (Fig 1). Cerebral angiography revealed no vascular anomaly, and no neurosurgical intervention was performed.

After clinical improvement, a search for possible secondary causes of hypertension was undertaken. Total catecholamines and total metanephrines in a 24-hour urine collection were increased, 1997.6 μg (normal: 10–100 μg/24 hours) and 3100 μg (normal: 250–800 μg/24 hours), respectively. Fractionated catecholamines in plasma revealed a very elevated norepinephrine level of 16 393 pg/mL (normal: < 450 pg/mL), an increase in epinephrine measurement of 312.8 pg/mL (normal: < 70 pg/mL), and a normal dopamine level of 83.3 pg/mL (normal: < 130 pg/mL).

Abdominal CT scan was performed and revealed 2 lesions: a tumor in the organ of Zuckerkandl, extending from the left renal artery to the aortic bifurcation, with 9 cm of maximal dimension, and a retroperitoneal mass extending to the right side of the inferior vena cava, with 2 cm of maximal dimension. After preoperative medical treatment, the patient was subjected to median laparotomy and resection of both lesions. Histologic findings were consistent with the diagnosis of paraganglioma. One month after surgical intervention, a significant decrease in catecholamine and metanephrine levels was noticed but remained above the upper limit of normal. Abdominal CT scan and 131I-metaiodobenzylguanidine (MIBG) scintigraphy were normal. The patient had full motor recovery, and his blood pressure was controlled with phenoxybenzamine and atenolol.

At age 14, he was admitted with right lumbar pain and motor disability in the lower limbs. Spastic paraparesis was present on physical examination. Spine magnetic resonance imaging (MRI) revealed a tumor at T2-T3 level, a pathologic fracture of T3 vertebral body, and spinal cord compression. Laminctomy and removal of the tumor were performed. Histologic results were compatible with bone metastasis of paraganglioma (Fig 2). After surgery, the patient had an almost complete clinical recovery, and the 131I-MIBG scan was unremarkable. The patient abandoned hospital appointments for a long period, returning at the age of 26. At that time 125I-MIBG scintigraphy revealed multiple metastatic involvement of bones and soft tissues. Genetic testing identified a missense point mutation in succinate dehydrogenase subunit B (SDHB) gene: c.725G→A in exon 7, which alters an arginine at amino acid position 242 to a histidine (R242H). His parents were submitted to genetic analysis, and the R242H mutation was identified in his father.

Therapeutic 131I-MIBG was performed 3 times (at 26, 27, and 36 years of age), with a cumulative dose of 580 mCi. After the third session, repeated scintigraphy was similar to the examination performed before the first treatment (Fig 3). 18F-fluoro-2-deoxy-D-glucose positron...
emission tomography (FDG PET) combined with CT was recently performed and revealed multiple lesions located in bones and lymph nodes, without visceral involvement (Fig 4). The patient is now 37 years old, is independent in daily activities, has good general condition, but complains of osteoarticular pain associated with mild motor disability. Blood pressure is controlled with phenoxybenzamine 10 mg/day and atenolol 50 mg/day. Metanephrines had always been high and recent urinary measurements revealed the following: total metanephrines 3050 μg/24 hours (normal: 329–1263 μg/24 hours), normetanephrine 2803 μg/24 hours (normal: 162–527 μg/24 hours), and metanephrine 103 μg/24 hours (normal: 64–302 μg/24 hours). His father has been submitted to periodic measurement of fractionated metanephrines in plasma and urine, with normal results. He is currently 71 years old and has no typical signs and symptoms of the disease.

**DISCUSSION**

Hemorrhagic stroke in childhood is associated with rupture of intracranial vascular anomalies in approximately half of the cases, namely arteriovenous malformations, aneurysms, and cavernous malformations. Hypertension is an infrequent cause and accounts for only 1% to 2%. In our patient, intracerebral hemorrhage was probably caused by severe hypertension due to paraganglioma. Hemorrhagic stroke is a very rare complication of catecholamine-secreting tumors, and few cases have been reported in adults. In the pediatric population, we found a case of a 6-year-old boy presenting with left occipital spontaneous lobar hematoma and hypertension and whose additional investigation revealed a left adrenal pheochromocytoma. To our knowledge, we report the first pediatric case of paraganglioma presenting with hemorrhagic stroke.

Our patient had severe hypertension, headache, and diaphoresis, which are typical of paraganglioma, with right hemiparesis due to intracerebral hemorrhage. The complaining of frequent episodes of headaches for a period of 4 years suggests that the disease was already present.
Diagnosis of endocrine active paragangliomas is made by measurement of fractionated metanephrines in plasma, urine, or both. In patients discovered by clinical signs and symptoms, an elevation of more than fourfold above the upper reference limit is associated with close to 100% probability of the disease. In contrast, patients with a known SDH mutation, who are screened at regular intervals, may have only slight biochemical elevations indicative of endocrine activity of a paraganglioma. CT scan or MRI of the adrenal glands and abdomen should be performed initially to localize the tumor. PET is recommended for metastatic SDHB-associated paragangliomas; in a patient with malignant disease, the main purpose of 123I-MIBG scan is to determine if 131I-MIBG therapy is an appropriate choice for treatment.

Inherited mutations in SDHB gene are defined as familiar paraganglioma type 4 and have an autosomal dominant pattern. Mean age at diagnosis of SDHB-related tumors is 34 years, but several cases have been reported in children. By the age of 40 years, 65% of mutation carriers develop the disease. Penetration increases to 77% by age 50. This genetic change is mainly associated with abdominal paragangliomas (50% to 59%) and less frequent locations include the adrenal glands, head and neck, thorax, and pelvis. Tumors are often multiple (12% to 28%), metastatic (34% to 71%), and usually secrete noradrenaline and dopamine. Malignant disease is found at presentation in 22% to 28% of patients with SDHB disorders. Most common sites of secondary involvement are bones, lymph nodes, liver, and lungs. Genetic testing for this mutation is mandatory in cases...
of extra-adrenal, multiple, or metastatic disease. In patients with malignancy secondary to a paraganglioma, almost 50% have SDHB abnormalities.\textsuperscript{1,11,20,21}  

King et al\textsuperscript{22} stated that most patients with metastatic pheochromocytoma/paraganglioma who presented with a primary lesion in childhood/adolescence have a SDHB mutation (71.9%) and primary extra-adrenal disease (78.1%). Of the 27 patients who had pediatric tumors and harbored the referred mutation, 23 (85.2%) developed metastasis.

Clinical characteristics found in our patient are typical of SDHB-related disorders, and the mutation was identified by genetic testing. Paternal transmission was noticed, but his father is still free of the disease.

Surgery is the primary treatment.\textsuperscript{23,24} Long-term periodic management remains recommended for all cases of paraganglioma, as tumors can recur many years after the initial diagnosis. Our patient abandoned hospital appointments for 14 years and, during that period of no follow-up, he developed multiple metastatic involvement.

The therapeutic approach of malignant disease is often palliative and focuses on assuring quality of life. \textsuperscript{131}I-MIBG therapy is performed in case of positive \textsuperscript{123}I-MIBG scan (>1% uptake of the injected dose). It has limited efficacy, with tumor responses in approximately one-third of cases.\textsuperscript{25} In our patient, therapeutic MIBG was performed 3 times (cumulative dose of 580 mCi) with no tumoral response. Our intention is to continue performing that treatment modality, as needed, for a cumulative dose of 1000 mCi or more, before starting chemotherapy.

Prognosis of metastatic disease is variable. Short-term survivors tend to be individuals with metastasis in the liver and lungs, whereas long-term survivors are those with lesions in bones.\textsuperscript{11} Our patient has disseminated bone and soft tissue disease with no visceral lesions and is alive, with adequate quality of life, 25 years after the diagnosis of paraganglioma. Few cases with such a long survival have been reported in the literature.\textsuperscript{26}

CONCLUSIONS

We report here, to our knowledge, the first pediatric case of paraganglioma presenting with hemorrhagic stroke. Intracerebral hemorrhage was probably caused by severe hypertension due to paraganglioma. Therefore, we expand the recognized clinical spectrum of the disease. Physicians evaluating children with hemorrhagic stroke, particularly if hypertension is a main symptom, should consider the possibility of catecholamine-secreting tumors. Prompt diagnosis, adequate treatment, and long-term follow-up are mandatory. Metastatic disease is associated with SDHB mutations, and its treatment should focus on palliative approaches; although some patients have poor prognosis, progression can be indolent.

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