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Case Report

How Reliable are Urine Catecholamines in the Workup of Neuroblastoma Associated with Opsoclonus Myoclonus Ataxia?

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Abstract

We report a rare case of neuroblastoma with Opsoclonus Myoclonus Ataxia (OMA) and Horner's syndrome in a previously healthy 17-month-old female who presented with titubations and a wide based gait. The patient had an initial negative workup including urine catecholamines. After further investigation, including a Magnetic Resonance Imaging (MRI) of the spine, neuroblastoma was revealed. This case emphasizes the importance of having a high suspicion for neuroblastoma despite negative urine catecholamine metabolites, especially when associated with OMA and Horner's syndrome. Prompt treatment along with consultation with oncology is imperative to improve survival outcomes.

ABBREVIATIONS

OMA: Opsoclonus Myoclonus Ataxia; MRI: Magnetic Resonance Imaging; HVA: Urine Homo Vanillic Acid; VMA: Urine Vanillyl Mandelic Acid

INTRODUCTION

Neuroblastoma is the most common extracranial solid malignancy in childhood and prevalence is about 1 in 7,000 live births [1]. More than 90% of cases are diagnosed before the age of 5 years old. The median age of diagnosis is 17 months [2]. The incidence of neuroblastoma is 10.2 cases per million children under 15 years of age. It is the most common cancer diagnosed during the first year of life [3]. Opsoclonus Myoclonus Ataxia (OMA) is a rare neurological disorder, often found in children to be associated with neuroblastoma. It is a movement disorder characterized by chaotic saccadic, high amplitude, multidirectional and involuntary eye movements. It is usually associated with myoclonus affecting the head, trunk and limbs. Signs of cerebellar ataxia are seen, especially the inability to stand and walk [4]. In children, the symptoms also include irritability, and, over a long-term course, learning and behavioral disturbances [5]. It is thought to develop through an immunologically driven response that rapidly progresses and precedes an oncological disease. When OMA is present, the differential diagnosis of neural crest cell origin tumors, such as neuroblastoma must be high. Catecholamine metabolites, urine homovanillic acid (HVA) and vanillylmandelic acid (VMA) are routinely used to support this diagnosis. The purpose of this case is to emphasize the importance of imaging and an oncological consultation in a child that manifests with OMA with negative urine catecholamine markers when there is a high index of suspicion.

CASE PRESENTATION

A 17-month-old previously healthy female presented to the Emergency Department from neurology clinic due to one month of intermittent wide based ataxic gait and titubations of the head. The symptoms were worse in the morning, with improvement throughout the day. Review of systems was otherwise negative including no recent upper respiratory symptoms, no history of fever, no weight loss, and no change in bowel or bladder function. Further history from the mother revealed a child who had met

all her developmental milestones. However, she was having more temper tantrums over the last month and regression of speech. Her family history was unremarkable. On physical examination she was alert and in no acute distress. She had a wide based gait with abnormal balance, resting head tremor worse with tracking, and intermittent fluttering of the eyelids. Remaining physical examination was unremarkable. Vitals signs were within normal limits for age. Differential diagnosis at that time included an intracranial tumor, cerebellar ataxia, acute disseminated encephalomyelitis, neural crest cell tumor, meningitis, metabolic disorder, Wilson's disease, and non-accidental head trauma. An urgent brain magnetic resonance image (MRI) without contrast was performed to rule out intracranial mass or lesion which revealed an incidental 6 mm low lying cerebellar tonsil from the level of the foramen magnum with no flow restriction. Despite a negative brain MRI, the patient was admitted to the hospital for further investigation of her ataxic gait. Due to the age of the patient along with symptoms consistent with OMA, complex diagnostics for neuroblastoma were performed. Biochemical markers, as well as imaging examinations including ultrasound and computed tomography (CT) of the abdomen and the mediastinum were performed with no pathological findings. Urine HVA and VMA were negative. A tumor lysis panel was also done which was negative. Laboratory testing for metabolic and genetic causes disclosed normal levels of serum copper, urine and serum organic acids, serum ceruloplasmin, 24-hour urinary copper, lactate, pyruvate, free carnitine and total carnitine.

Due to continued concerns for neuroblastoma for persistent symptoms of OMA, hematology-oncology was consulted. It was recommended to obtain an MRI of the spine to rule out a mass not visualized by ultrasound. The MRI demonstrated a right paraspinal enhancing lesion at the level of T1-T2, suspicious for a small neuroblastoma. However, a meta-iodobenzylguanidine (MIBG) scan was done after the MRI which showed no abnormal focus. The patient subsequently underwent a thoracoscopic excision biopsy of the right paraspinal tumor. The greatest dimension of the mediastinal mass was 1.1x1.0x0.2 cm. The initial immunohistopathologic examination was consistent with a diagnosis of neuroblastoma. A bilateral bone marrow aspiration and biopsy were performed and were negative for metastasis and displayed normocellular marrow. The patient was diagnosed with stage 1 neuroblastoma.

The patient was treated according to Children's Oncology Group (COG) protocol ANBL00P3 due to concurrent neuroblastoma with OMA which includes intravenous immunoglobulin, cyclophosphamide, and prednisone. It is presumed that combining chemotherapy and steroid therapy with immunoglobulin may be effective in treating abnormal muscle movement associated with OMA. Due to early recognition of neuroblastoma in this patient, the patient had early resection of the tumor. She did have post surgical complication of Horner's Syndrome with right sided ptosis and miosis. The patient did well after resection of the tumor and continues to show improvement in her speech, behavior, and development. Currently, she is able to stand without assistance, walk, run, and climb up stairs. She continues to have some signs of titubations and ataxia in the morning but significantly improved from prior to resection. Additionally, the miosis and ptosis from Horner's syndrome continues to improve.

DISCUSSION

The presenting symptoms of neuroblastoma are often vague which makes the diagnosis difficult. There are certain clinical findings that raise suspicion for neuroblastoma, including: fever, joint pain, loss of appetite, and fatigue. Patients usually present with symptoms that arise as a direct result of a primary or metastatic tumor, including: abdominal distention, back pain, limp, palpable bony masses, lymphadenopathy, paraparesis, irritability, headache, anemia, or thrombocytopenia [6]. The most common location of a mass is the retroperitoneum, adrenal glands, the sympathetic ganglia of the abdomen, or the mediastinum [2]. As in this case, the patient was found to have a neuroblastoma in the sympathetic ganglia at the level of T1-T2. However, the patient did not have typical symptoms that would be concerning at first glance for neuroblastoma. Instead, the continued concern and high probability of neuroblastoma was secondary to the presentation of OMA. This led to further investigation for neuroblastoma as OMA is the most common paraneoplastic syndrome of childhood and when seen in children approximately 50% of cases are associated with neuroblastoma [7].

Neuroblastoma has neuroendocrine properties which have the potential to secrete catecholamines, causing paraneoplastic syndromes. According to Erdelyi et al. when there is low suspicion for neuroblastoma the probability of positive urine catecholamines is only 63%. However, when there is a distinct suspicion for neuroblastoma then the probability of elevated urine catecholamines increases to 99%. Similarly, when there is a paraspinal mass and a strong suspicion for neuroblastoma then urine catecholamines are positive 99.9% of the time [8]. However, in our patient there was a high suspicion for neuroblastoma due to the closely likely association with OMA and a paraspinal mass, yet urine catecholamines were negative. Likewise, De Bernardi et al. presented a cohort of 144 patients with stage 1 and stage 2 neuroblastoma in which only 68% of the cases had urine VMA and HVA greater than two standard deviations above the normal limit [9]. According to the International Neuroblastoma Staging System, the sensitivity of abnormal VMA or HVA is 78-85% in stage 1 neuroblastoma. Therefore, although urine catecholamines are important in the workup for neuroblastoma, there are subsets of patients who will be negative despite a high pre-test probability.

Additionally, the patient's initial abdominal ultrasound revealed no mass in the adrenal gland or the abdomen. Abdominal ultrasound is often the first modality for diagnosing neuroblastoma as it is a relatively accessible and cheap diagnostic tool. In addition to ultrasound, MRI and CT are used for staging of neuroblastoma. However, which image modality to use depends on the institution and availability of resources. Our patient was able to obtain an MRI of her brain and subsequently an MRI of her abdomen due to the fact she was at a tertiary children's hospital with available resources. Similarly, an MIBG scan is used to identify the location of the neuroblastoma and whether it has spread to the bones and/or other parts of the body. MIBG has 90-95% sensitivity for neuroblastoma [12]. However, MIBG was negative in our patient. Due to difficulty of diagnosing neuroblastoma, 50-60% of all neuroblastomas present with

metastases. Fortunately, the patient in this case was diagnosed early and was able to have a resection prior to metastasis. This is a case that shows the importance of having a high index of suspicion despite having a negative abdominal ultrasound, urine catecholamines, tumor lysis panel, and a MIBG scan.

CONCLUSION

We present a case of a patient who presented with ataxia and titubations and found to have neuroblastoma with OMA and subsequently Horner syndrome. In a patient who has characteristic findings of OMA, ataxia, Horner's syndrome, transverse myelopathy and/or hypertension, it is important to keep a high index of suspicion of neuroblastoma despite negative initial laboratory findings and imaging. The use of urine VMA and HVA remain an important part of the workup for neuroblastoma; however, the clinician should not rule out neuroblastoma based off of negative values. It remains imperative that pediatricians are able to recognize the signs and symptoms associated with neuroblastoma to ensure prompt consultation with an oncologist and ensure proper imaging is carried out.

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