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Clinical manifestations of neuroblastoma with head and neck involvement in children

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ABSTRACT

Objective: The purpose of our study is to review our 15-year experience with pediatric patients who have been diagnosed with neuroblastoma, and to determine their most frequent head and neck manifestations and symptoms.
Study design: Retrospective chart review of electronic medical record.
Setting: An academic, tertiary care pediatric hospital.
Subjects and Methods: IRB approval from the Office of Research Integrity at Children's Mercy Hospital was obtained. The hospital tumor database was analyzed to identify patients with neuroblastoma, ganglioneuroblastoma, and esthesioneuroblastoma diagnosed between 1997 and 2012. We recorded the various clinical signs and symptoms these patients displayed at their initial presentation, focusing on patients with head and neck involvement. We then determined the relative incidence of these various findings.
Results: Our review yielded 118 patients diagnosed with neuroblastoma, ganglioneuroblastoma, or esthesioneuroblastoma over our 15 year study period. 7 of the 118 patients were diagnosed with primary tumors of the head and neck. Another 19 patients had metastatic head and neck involvement. For those with primary disease, presence of a neck mass and signs of Horner's syndrome were the most common findings. For metastatic disease, craniofacial bony metastasis was the most frequent finding in our study.
Conclusions: Based on our data, there are a handful of findings that occur frequently in pediatric head and neck neuroblastoma. Any persistent neck mass, unexplained Horner's syndrome, or periorbital ecchymosis should be carefully evaluated. This study should serve as an aid for the otolaryngologist to be aware of the possible manifestations of this malignancy in children.

1. Background

Neuroblastoma is the most common extracranial soft tissue tumor in infants less than 12 months of age, and the second most common in childhood after rhabdomyosarcoma [1,2]. At 1 year of age, the incidence of neuroblastoma is approximately 35 cases per 1 million in the United States [3]. Neuroblastoma accounts for approximately 8–10% of all childhood malignancies and 15% of cancer mortality in children [1,4]. The median age of presentation is approximately 18 months, and males are slightly more often affected than females. 50% of cases are diagnosed before 1 year of age, and 80% are diagnosed before 5 years [5]. Most cases are sporadic, but in 1–2% of cases there is a familial component and these tend to present even earlier, at a mean age of 9 months [5].

The tumor arises from primitive neuroectodermal cells, which are derived from neural crest cells. Thus, the tumor can develop anywhere along the sympathetic chain, wherever sympathetic nervous tissue is found. Previous studies report the breakdown of primary locations of the tumor as 47% in the adrenal glands, 24% in the abdomen, 15% in the thoracic cavity, 3% in the pelvis, and 3% in the head and neck [6,7]. Neuroblastoma (NB),

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ganglioneuroblastoma (GNB), and esthesioneuroblastoma (ENB) are all within the spectrum of sympathetic neuroectodermal tumors. NB and GNB differ in terms of maturation, with NB being composed of primarily undifferentiated neuroblasts and GNB having a significant component of mature differentiated ganglion cells [8]. They are grouped together for the purposes of cancer staging, survival, and prognosis. ENB is a neuroblastoma originating in the olfactory neuroepithelium, and thus involves the nasal cavity and frequently the paranasal sinuses [9].

In our review of the literature, we found only isolated case reports and small case series regarding the various symptoms and presentations of head and neck neuroblastoma in children. Most series focus on esthesioneuroblastoma and cervical tumors [10,11]. Our goal is to create a comprehensive reference to aid the otolaryngologist in recognizing the most common head and neck manifestations of this disease.

2. Materials & methods

The setting of our study is an academic tertiary care pediatric hospital. We conducted a 15 year retrospective chart review, from January 1, 1997 to January 1, 2012 of the hospital tumor base with the aid of our Hematology/Oncology division. IRB approval from the Office of Research Integrity at Children's Mercy Hospital was obtained prior to initiating this study. Our inclusion criteria were all patients diagnosed with NB, GNB, and ENB in that time period. Medical records, diagnostic imaging studies, and other related data were reviewed on these patients. There were no exclusion criteria.

For each patient we included the history and physical exam on presentation as well as baseline demographics. As mentioned, we also reviewed the results of imaging studies; including CT, MRI, bone scan, and metaiodobenzoguanidine (MIBG) scan. MIBG scanning utilizes a compound similar to norepinephrine (with radiolabeled iodine) to identify adrenergic tissue. This diagnostic study has become a prominent tool in neuroblastoma evaluation in the past 10–15 years [12].

Staging for our patients was based on the International Neuroblastoma Staging System (INSS). The INSS is a staging classification developed by a multidisciplinary consensus group. The patient's classification depends on the resectability of the primary tumor as well as metastasis to local lymph nodes and distant tissues. Tumor histopathology and genetics do not factor in to INSS staging, however they are included in risk stratification [12].

We also looked at the results of histology, tumor biopsy, and bone marrow aspirates. Other studies included testing for urine catecholamine metabolites such as vanillylmandelic acid (VMA) and homovanillic acid (HVA). For tumor genetics, we reviewed MYCN gene amplification and DNA index. MYCN is an oncogene, the amplification of which is associated with advanced stage and poorer prognosis. MYCN status is a mainstay in neuroblastoma evaluation [13,14]. Other tumor markers such as ferritin, lactate dehydrogenase (LDH), and ganglioside GD2 have helpful in disease monitoring in the past, but now have been largely replaced by genetic markers.

3. Results

We identified a total of 118 patients diagnosed with neuroblastoma, ganglioneuroblastoma, or esthesioneuroblastoma in the hospital tumor base over our 15 year study period. Seven of the 118 (6%) patients had primary tumors of the head and neck. This figure is similar to what has been reported in previous literature regarding the relative incidence of head and neck neuroblastoma. Another 19 (16%) patients had metastatic involvement to the head and neck. These patients all had primary disease sites outside of the head and neck, such as in the adrenal glands or elsewhere in the abdomen.

3.1. Patients with primary head and neck involvement

Table 1 is an overview of the 7 patients with primary head and neck involvement. One of these 7 patients was diagnosed with esthesioneuroblastoma, and the other 6 were diagnosed with neuroblastoma. In the 6 neuroblastoma patients, the tumor presented as a palpable neck mass. On imaging, 4 of these masses were unicentric, and 3 had significant extension of disease to the thoracic inlet. The sizes of the primary masses ranged from 3.2 to 8.0 cm in largest diameter. These patients presented from 2 to 28 months of age, with a mean age of 15.5 months. Of note, one patient (patient E) also had metastasis to contralateral cervical lymph nodes and to the mandible. No other patient in the primary head and neck group had additional metastatic involvement of the head and neck.

Table 2 is a summary of the different signs that patients with primary head and neck neuroblastoma exhibited on presentation. Three of the 7 patients (43%) with primary head and neck disease presented with Horner's syndrome. All 3 exhibited miosis and ptosis on the affected side. One of these 3 patients with Horner's syndrome also displayed heterochromia iridis. Of note, 3 separate patients developed signs of Horner's syndrome post-operatively after surgical resection of superior mediastinal tumors. Two of these iatrogenic cases of Horner's syndrome resolved spontaneously. In addition, we report that 1 of the primary head and neck patients presented with vocal cord paralysis (patient C). Another patient presented with metastasis to a contralateral cervical lymph node and contralateral mandible, as previously mentioned. These metastatic foci were identified on MIBG scan.

Fig. 1 represents patient C from our primary head and neck group. This patient presented at 10 months of age to an outside physician with symptoms of upper respiratory infection. CXR was

Table 1
Primary neuroblastoma of the head & neck.

Patient	Age (months)	Primary tumor location	Tumor size	Description	Metastasis
A	28	R neck, submandibular	8 cm	Unicentric, extension to retropharynx	No
B	131	R maxillary sinus (Esthesioneuroblastoma)	6 cm	Unicentric, extension to R nasal cavity and R ethmoid air cells	No
C	10	R lower neck	3.2 × 3.4 x. 4.3 cm	Unicentric, extension to thoracic inlet, L tracheal shift, involving great vessels	No
D	10	L neck, submandibular	3.7 × 6.6 × 8.3 cm	Multicentric conglomerate of elarged lymph nodes	Liver
E	20	L neck, carotid body	2.5 × 1.3 × 1.6 cm (largest node)	Multicentric enlarged lymph nodes, mass involving cervical chain	R cervical, Right mandible, shoulder, inguinal
F	2	R lower neck	3.5 × 5 cm	Unicentric, extension to thoracic inlet, L tracheal shift, extension to spinal canal	No
G	23	L lower neck	3.5 × 4.3 × 4.3 cm	Unicentric, extends into thoracic inlet, R tracheal shift	No