Neuroblastoma: a 1990 overview

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Abstract. Neuroblastoma is the most common solid tumor in infancy. This tumor is of neural crest origin and occurs in the neck (3%), mediastinum (20%), pelvis [3], adrenal medulla (50%), and paraspinal sympathetic ganglia (24%). The tumor may produce catecholamines, vasoactive intestinal polypeptide, and ferritin. More than 50% of cases have metastases at the time of diagnosis. Radiologic (CT scan, scintigraphy) examinations, bone-marrow aspirate and biochemical testing (urinary VMA) often pinpoint the diagnosis and permit initiation of therapy. Treatment is based on the extent of disease according to staging criteria. Stages I and II reflect localized disease that is resectable and frequently requires no other therapy. Stage III and stage IV disease represent advanced and metastatic disease, respectively, and require aggressive combined treatment, including multiagent chemotherapy, total-body irradiation, and rescue with bone-marrow transplantation using autologous marrow purged of tumor cells with monoclonal antibodies. Delayed primary and second-look resection of tumor is an integral part of this therapy. Infants under 1 year of age and those with stages I, II, and IV-S disease have an improved prognosis. Aneuploid flow cytometry, low serum ferritin and NSE levels, few or no copies of the N-myc oncogene, favorable histology and primary tumors affecting the neck, pelvis and mediastinum have an improved prognosis. The survival in 266 cases was 44.5%.

Keywords: Neuroblastoma – N-myc oncogene – DNA flow cytometry – Bone-marrow transplantation – Total body irradiation

Introduction

During the past two decades, there has been a significant improvement in the survival rate of children with cancer. This has been related to the development of multidisciplined efforts in cancer care following prospective protocols designed by large, multicenter co-operative study groups. The dramatic increase in tumor-free survival in children with Wilms' tumor and acute lymphocytic leukemia highlight this trend. In contrast to these improved results, infants and children with neuroblastoma still have a relatively dismal outcome. The purpose of this minisymposium is to update the reader regarding the evaluation and management of children with this highly malignant lesion.

Pathophysiology of neuroblastoma

Neuroblastoma is an embryonal tumor of neural crest origin that may arise at any site in the sympathetic nervous system including the brain, neck (3%), mediastinum (20%), para-aortic sympathetic ganglia (24%), pelvis (3%), and adrenal medulla (50%). This neoplasm is the most common solid tumor of infancy and childhood. More than 50% of cases present in the first 2 years of life, and 90% are diagnosed by 8 years of age [8]. This lesion has been noted to occur in patients with other neural crest-related conditions (neurocristopathies) including Hirschsprung's disease, Klippel-Feil Syndrome, Von Waardenburg's syndrome, Ondine's curse, as well as cases of Beckwith-Weideman syndrome, fetal alcohol syndrome, and in mothers taking phenylhydantoin for seizure disorders [9]. Neuroblastoma occurs more frequently in boys (2:1) and the reported incidence is 1:7,000–10,000 children.

Neuroblastoma cells secrete a number of products including hormones such as vasoactive intestinal polypeptide (VIP) and other vasoactive substances, including the catecholamines and their byproducts – homovanillic acid (HVA), vanillmandelic acid (VMA), 3-methoxytryamine (3-MT), metanephrines, and dopamine – and rarely, a parasympathetic neuroblastoma may occur and secrete acetylcholine. Since it is a neural crest tumor with hormonal capacity, this neoplasm should be classified in the family of APUD tumors [9]. Presenting symptoms in cases of neuroblastoma vary according to the location of the pri-
primary lesion and whether or not tumor metastasis has occurred. The most common sites of metastasis are the bone cortex, bone marrow, and regional and/or distant lymph nodes.

An abdominal mass is palpable in more than 50% of patients due to a primary adrenal or paraspinal tumor. The mass is often nodular and tender on palpation [8, 9]. Respiratory distress may herald the presence of a posterior mediastinal lesion, while Horner’s syndrome (ptosis, meiosis, anhydrosis, and heterochromia) may indicate a primary tumor affecting the stellate ganglion. Proptosis or bilateral orbital ecchymosis (“panda eyes”) is a common presenting finding and usually is indicative of metastases to the orbit. Systemic manifestations such as anemia, failure to thrive, weight loss, and malnutrition are often noted in advanced cases. Children with bone metastases affecting the lower extremities may refuse to walk because of severe leg pain. Hypertension may accompany this lesion in up to 35% of cases due to release of catecholamines from the tumor. Paraplegia or cauda equina syndrome may occur as a result of tumor extension through an intervertebral foramen into the extradural space. More unusual manifestations include opsoclonus/nystagmus (“dancing-eye syndrome”), which is probably due to an antigen-antibody complex affecting the cerebellum (not a metastasis), and hypokalemic watery diarrhea syndrome (HWDS) due to release of VIP from the tumor [8, 9, 29]. Some very young infants may present with hepatomegaly related to tumor infiltration and multiple subcutaneous tumor nodules [8, 9, 15].

Diagnosis

The diagnosis of neuroblastoma is usually achieved by obtaining a series of radiologic and chemical studies. Plain roentgenograms of the involved area (neck, chest, abdomen, etc.) often show stippled calcifications within the tumor mass, which is highly suggestive of neuroblastoma. Paraspinal widening is commonly observed in tumors that arise in the lower mediastinum and in proximity to the celiac axis. A CT scan with intravenous contrast can separate a Wilms’ tumor from a neuroblastoma in cases of retroperitoneal tumors, as the latter usually depresses the kidney and displaces it downward (adrenal tumor) and/or laterally (paraspinal tumor) without intrinsic distortion of the renal collecting system. Although an intravenous urogram was the mainstay of diagnosis in the past, this study is no longer necessary. Magnetic resonance imaging (MRI) is the most useful test to document whether extradural tumor extension has occurred and, in addition, may also demonstrate the presence of bone marrow involvement and major blood vessel encroachment [9]. Isotope bone scans (sodium pertechnetate Tc 99 m) and long-bone X-rays will usually document the presence of bone cortex metastases. The bone-seeking isotope is also picked up by the primary tumor as well. 123I-labeled metaiodobenzylguanidine (MIBG) is also useful in identifying both primary tumor and metastases. Bone marrow aspirate may show rosettes of metastatic foci of neuroblastas. A 24-h sample of urine is collected to evaluate for VMA, HVA, metanephrine, etc., and is useful both in achieving a diagnosis and as a tumor marker. Additional preoperative studies include serum neuron-specific enolase (NSE), serum ferritin, coagulation profile, and a complete blood count and platelet count.

Treatment

Treatment of neuroblastoma depends on the stage of the disease at diagnosis as determined by preoperative clinical and operative staging criteria (see the accompanying article on staging in this issue). We have used the Evans et al. staging system as advocated by the Children’s Cancer Group in the United States, as our Children’s Hospital is a member institution [6]. In the 266 children studied, 14 were classified as stage I, 52 stage II, 62 stage III, 117 stage IV, and 21 stage IV-S. For stage I tumors, complete surgical excision is the only therapy required. Operative staging determines the presence or absence of tumor extension to local tissues or lymph nodes, liver metastases, the feasibility of complete tumor resection, evaluation of tumor histology into favorable and unfavorable categories, and permits sampling of the tumor tissues for DNA-flow cytometry studies (aneuploidy or diploidy), the number of copies of the amplified N-myc oncogene, and response to monoclonal antibodies, which all may have prognostic significance [14, 16, 22, 23, 28].

Patients with stage II tumors characterized by small foci of gross or microscopic residual disease, favorable histology, negative lymph nodes, normal serum NSE and ferritin levels, less than ten copies of the N-myc oncogene, and DNA aneuploidy (especially in infants <1 year of age) are probably adequately treated by excision of the tumor alone. However, if the tumor has unfavorable histology, lymph nodes are positive, and the tumor markers (serum NSE, ferritin) are elevated (particularly in children >1 year), we treat the local field with low-dose irradiation 1000 R and strongly consider the use of multimodal chemotherapy if the tumor tissue is diploid on DNA-flow cytometry and has over ten copies of the N-myc oncogene.

In stage III patients with a completely resectable tumor that has favorable histology, is node negative, and has normal tumor markers, surgery alone may be a reasonable method of management. The technique of surgical resection of neuroblastoma in various sites has been described in detail elsewhere [8, 10]. However, most stage III cases have an unresectable lesion with positive tumor markers indicative of advanced disease. This requires an aggressive multimodal chemotherapy program, which aims to shrink the primary tumor and allow subsequent resection that may favorably affect the child’s survival prior to the development of distant metastases [11]. Cis-platinum, (etoposide), VP-16, adriamycin, and melphalan are the current drugs being used in a combined therapy program that includes attempts at delayed primary tumor resection, total body irradiation (TBI), and rescue with autogenous or allogeneic HLA-identical bone marrow transplantation (BMT) [8, 9].

In stage IV patients with distant metastases the diagnosis of neuroblastoma can often be achieved by obtaining urinary VMA studies, a positive bone marrow aspirate, and an isotope bone scan. Accurate tumor cell histology, DNA-