Imaging Findings of Patients with Metastatic Neuroblastoma to the Brain

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Rationale and Objectives: Metastatic involvement of brain is rare in neuroblastoma (NB). We retrospectively evaluated conventional and advanced imaging and clinical findings of seven patients with secondary intra-axial brain NB metastases.

Materials and Methods: Magnetic resonance imaging and computed tomography examinations of patients with metastatic brain NB were reviewed. Recent iodine-123 metaiodobenzylguanidine (^{123}I-MIBG) scans were also reviewed. A medical record review was performed for relevant clinical, laboratory, histopathologic, and genetic data.

Results: Mean age at the time of primary tumor diagnosis was 35 months, and all were considered high-risk NB at diagnosis. Mean time interval between diagnosis and brain involvement was 23.2 months. Extensive prior extra-central nervous system (CNS) disease was present in all patients, but concomitant extra-CNS disease at the time of brain involvement was absent in three (43%) patients. Various forms of disease, including intraparenchymal, intraventricular, and leptomeningeal lesions were detected.

Most intraparenchymal lesions were supratentorial and hemorrhagic; however, hemorrhage was absent in multiple leptomeningeal nodules in one patient. Contrast enhancement of lesions was present on all contrast-enhanced studies. Restricted diffusion of lesions was present in two patients. Arterial spin labeling (ASL) perfusion in two patients also revealed increased cerebral blood flow. Recent ^{123}I-MIBG scans were available in four patients and showed lesions in two patients with larger metastases but failed to demonstrate lesions in another two patients with smaller lesions.

Conclusions: Brain metastases of NB are often supratentorial and hemorrhagic and demonstrate contrast enhancement. Diffusion-weighted imaging can show restricted diffusion. ASL images may reveal increased perfusion. MIBG scans may not show smaller brain metastases.

Key Words: Neuroblastoma; brain; metastasis; pediatric.

Neuroblastoma (NB) is the most common pediatric extracranial neoplasm after leukemia. Metastases are present in up to 70% of patients with NB, frequently involving bone, bone marrow, and liver at the time of diagnosis (1) and confer a poor prognosis. Metastatic involvement of the head and neck is also commonly seen both at presentation and recurrence and manifests most often as osseous metastases involving the calvarium, orbit, or skull base (2). However, metastasis to the brain (parenchymal, intraventricular, or leptomeningeal) is rare and a serious complication indicating poor prognosis (3). Recently, the survival of patients with advanced stage NB has improved because of novel treatment protocols that include aggressive chemotherapy, surgery, radiation, autologous stem cell transplantation, and immunotherapy (4,5). As life expectancy has increased, brain metastases may be diagnosed more frequently (4,6). A single-center study from Memorial Sloan-Kettering Cancer Center revealed a low but increasing incidence of central nervous system (CNS) NB as a complication of stage IV metastatic disease (4) and showed that CNS NB can be the sole site of disease recurrence in 64% of patients, and therefore CNS may represent a sanctuary site for NB (4). Some recent reports have also suggested that the incidence of CNS recurrence may be increasing (4,6,7), although the increasing incidence of NB metastasis has not been confirmed in all studies (3).

In this study, we retrospectively evaluated the conventional and advanced imaging findings of seven NB patients with secondary intra-axial brain recurrence, which were diagnosed, treated, or referred to our institution in the last 8 years. Relevant clinical findings of these patients will also briefly described.

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METHODS AND MATERIALS

Patients

A radiology information system query was performed on all magnetic resonance imaging (MRI) and computed

tomography (CT) examinations of the brain and spine during the past 8 years to find patients with secondary intra-axial brain NB. The review yielded 12 pediatric patients with metastatic brain involvement by NB. Four patients had brain involvement secondary to metastatic disease in adjacent structures including the dura, skull, orbit, face, paranasal sinuses, and paraspinal disease and were excluded from the study. A 7-day-old patient with an intra-abdominal mass and multiple intraparenchymal brain metastases was also excluded because the fresh frozen diagnosis was consistent with NB; however, the final diagnosis was consistent with primitive neuroectodermal tumor. Thereafter, a chart review was performed to find the relevant clinical, laboratory, and genetic data.

Medical records were reviewed for patient age, sex, time interval between disease onset and brain involvement, type of treatment prior and after brain involvement, and presence or absence of extra-CNS disease at the time of brain involvement. Iodine-123 metaiodobenzylguanidine (^{123}I-MIBG) scintiscans were also reviewed if they had been performed within a short time frame (1 month) before or after the diagnosis of brain NB.

CT and MR Imaging Protocol

CT imaging was performed on 16- or 64-detector CT scanners (Siemens, Erlangen, Germany). All CT scans were done with 120 kV and varying current milliampere based on patient age groups. Axial CT slices had been reconstructed at 3 or 5 mm thickness. MR studies were performed either with 1.5 or 3 Tesla MR systems (Siemens, Erlangen, Germany). MR sequences slightly varied among patients but generally included pre- and postcontrast T1-weighted, T2-weighted, fluid attenuation inversion recovery; diffusion-weighted and T2* gradient echo; or susceptibility-weighted sequences. In addition, pulsed arterial spin labeling (ASL) perfusion imaging had also been performed in two patients using proximal inversion with control for off-resonance effects (PICORE) with quantitative imaging of perfusion using a single subtraction (QUIPSS II) and thin-slice TI1 periodic saturation (Q2TIPS) labeling scheme (8,9). Parameters included field of view, 200 mm; matrix, 64 × 64; echo time/repetition time, 13/5000 ms; bandwidth, 2230 Hz/pixel; slice thickness, 8 mm; 11 slices; TI1 = 700 ms; TI2 = 1800 ms; and generalized autocalibrating partially parallel acquisitions with a factor of 2.

Image Analysis

The CT and MR studies of these patients were reviewed by two neuroradiologists (with 1 and 9 years experience) by consensus. For each scan, data were recorded on tumor size, numbers, anatomical location, density/signal intensity of lesions on different imaging sequences, and presence or absence of hemorrhage. Diagnosis of hemorrhage was based on hyperdensity on noncontrast CT scan or expected MR imaging findings (hyperintensity on T1, hypointensity on T2, and increased susceptibility on gradient echo or susceptibility-weighted images).

For analysis of diffusion-weighted images, the imaging data were transferred to a research server in which it was analyzed by in-house software written in Interactive Data Language. The data were transformed into a four-dimensional array. A region of interest (ROI) drawn over the diffusion-weighted images was placed in the lesion. Mean signal intensity within the ROI was plotted against the b value. A nonlinear least squares fitting algorithm, the Levenberg–Marquardt algorithm, was used to fit the data to a mono exponential decay function. The mean apparent diffusion coefficient (ADC) values in each of these lesions were obtained. Absolute cerebral blood flow was measured by drawing an ROI on the region of the tumor in such a way to spare areas with hemorrhage. In addition, ROI of equal size was positioned exactly in the contralateral healthy hemisphere.

Histopathology and Genetic Analysis

Histopathology was available in five patients that had been operated at our institution. Microscopic examination was performed on hematoxylin and eosin stained sections. Immunohistochemical stains with neuron specific enolase, synaptophysin, chromogranin, tyrosine hydroxylase, and glial fibrillary acidic protein, NB84, and CD56 had also been performed. Results of cancer cytogenetic study were also reviewed when available.

The study was performed following approval of the institutional review board of the Children's Hospital of Philadelphia and was compliant with guidelines of the Health Insurance Portability and Accountability Act.

RESULTS

Seven patients (five male, two female) with direct intra-axial brain involvement were identified. Mean age of the patients at the time of primary tumor diagnosis was 35 months (standard deviation [SD] = 10.9; range, 21–50 months). Mean time interval between initial tumor diagnosis and brain involvement was 23.2 months (SD = 9.6; range, 11–32 months) (Table 1).

Imaging Findings

In three patients, both noncontrast CT scan and contrast-enhanced MRI had been performed. CT was the imaging modality in another three patients (one with contrast and two without contrast), and in one patient only contrast-enhanced MRI had been performed. Most patients (five out of seven, 71%) had only one mass lesion (four intraparenchymal, one intraventricular). One patient presented with two (14%) intraparenchymal lesions, and finally, one patient