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Neuroblastoma and Other Neuroendocrine Tumors

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Neuroblastoma is the most common extracranial solid tumor of childhood. It commonly presents in children younger than 2 years of age, with 90% being younger than 5 years of age. There is marked variability in clinical behavior ranging from spontaneous regression or differentiation into benign tumors to rapid and progressive fatal disease. Approximately 50% of patients will have metastases at presentation. The management is dependent on age, stage of disease, and biological and biochemical markers. Nuclear medicine plays an important role in the initial staging, as a prognostic indicator, for assessment of response to treatment, and also in therapy. The most common nuclear medicine diagnostic studies are ^{99m}Tc-disphosphonate bone scintigraphy and ^{123}I-MIBG (metaiodobenzylguanidine) scintigraphy. Bone scintigraphy has been the main investigational modality to diagnose skeletal metastases. Whole body imaging with ^{123}I-MIBG has become the preferred diagnostic test because this agent accumulates in neuroblastoma in 90% to 95% of cases and will accumulate in the primary tumor and metastases particularly in bone, bone marrow, lymph nodes, and soft tissues. MIBG can be used to assess therapy response and is a significant prognostic indicator. Other diagnostic techniques include positron emission tomography (PET)/computed tomography, mainly using ^{18}F-fluorodeoxyglucose. Other more experimental PET agents, as well as radiolabeled antibodies and octreotide, also are being investigated. Therapy has mainly focused on palliation and has been used alone or in combination with chemotherapy in high-risk refractory or relapsed patients. Major attention is being placed on stratification of patients to try and reduce the side effects associated with intensive megatherapy in the low to intermediate risk patients. Neuroendocrine tumors (NETs) are rare in childhood, but nuclear medicine techniques, mainly using MIBG and somatostatin receptor agents, have a role in diagnosis, staging, and a limited role in therapy. Newer radiopharmaceuticals, including PET agents, are being evaluated for the assessment of NET. Nuclear medicine techniques play a major role in the management of neuroblastoma and NET.
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Neuroblastoma is the most common extracranial solid tumor of childhood, accounting for 8% to 10% of pediatric malignancy and is responsible for approximately 15% of all childhood cancer deaths. It is an embryonal malignancy arising from the sympathetic nervous system. The incidence is 10 per million in white children and 8 per million in black children in the United States. Neuroblastoma occurs more commonly in young children with 50% of them presenting before 2 years of age and more than 90% before 5 years of age. There is marked variability in the clinical behavior of neuroblastoma, ranging from spontaneous regression, differentiation into benign ganglioneuromas, to rapid and progressive fatal disease.[1,2] This variable natural history of neuroblastoma is linked to the age at presentation. Patients younger than 12 months of age have a better prognosis, even with metastatic disease, than those older than 12 months of age.[3-6] Approximately 50% of patients will have metastases at presentation.[1,2,7] The prognosis for neuroblastoma is based on stratification into low-, intermediate-, or high-risk disease.[7-9] Most

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infants younger than 12 months of age even with metastatic disease can have a favorable outcome with chemotherapy and surgery. There is a small subset aged up to 18 months with metastatic disease whose disease is not MYCN oncogene (MYCN) amplified who also have a favorable prognosis.[3,4,6] However, the majority of children older than 12 months of age at presentation with advanced disease will die from progressive disease. Treatments are based on the subtype classification which depends not only on the clinical and imaging stage of the disease but also on biological and biochemical parameters.[6-8]

Clinical Presentation

Neuroblastoma may present in many ways depending usually on the location and extent of the primary tumor and presence of metastatic disease. The most common primary site is the retroperitoneum: adrenal glands (35%) or paraspinal ganglia (35%), with the other sites being posterior mediastinum (20%), pelvis (<5%), and neck (<5%). Rarely no primary site is detected. The symptoms or signs may relate to the primary tumor or metastatic disease.[1,2,7,8]

- Abdominal mass is the commonest presentation[1]
- Newborns may present with abdominal distension due to an intra-abdominal mass or liver enlargement from metastatic disease[1,7]
- Bruising particularly around the eyes or proptosis is not uncommon. It is caused by the frequent metastatic involvement of the bones and soft tissues around the orbits[1,7]
- Some children may present with symptoms similar to leukemia, with pallor, anemia, fever, and bone pain, whereas older children may also present with a limp or joint pain suggesting arthritis[1,7]
- Primary tumors arising in the apical thorax or neck may be detected on a routine chest x-ray[1,7]
- Tumors in this area also may present with Horner's syndrome[1,7]
- Paraspinal tumors may encroach on the spinal canal, causing cord compression[1,7]
- Large abdominal and pelvic tumors may cause obstruction to urinary outflow and cause hypertension because of catecholamine secretion[1,7]
- Subcutaneous nodules or soft-tissue masses may be the presenting sign, particularly in neonates[1,7]
- A paraneoplastic syndrome, ie, opsoclonus–myoclonus–ataxia syndrome,[10,11] is a rare presentation of neuroblastoma (2-3% of cases), but in as many as 50% of patients with this syndrome, neuroblastoma is the cause[12]
- Diarrhea may occur as the result of catecholamine excess[13]
- Antenatal ultrasound may suggest neuroblastoma in utero[1,7]

Staging of Neuroblastoma

The prognosis and treatment of neuroblastoma depends on the age and stage of the disease at presentation. The most common staging in neuroblastoma is the International Neuroblastoma Staging System (INSS).[14] This system uses the clinical stage, radiographic and nuclear medicine results, surgical findings, and bone marrow examination. In general, the staging is defined as follows:

Stage 1: Localized tumor without regional lymph node involvement.
Stage 2: Unilateral tumor with either incomplete gross resection or ipsilateral nodal involvement.
Stage 3: Tumor that crosses the midline or has contralateral nodal involvement.
Stage 4: Tumor disseminated to distant lymph nodes, bone, bone marrow, liver, etc.
Stage 4S: Special category: age <1 year, localized primary tumor, dissemination only to liver, skin, or bone marrow.

Biological and Clinical Subtypes

Biological Markers

The biological hallmarks of neuroblastoma relate to acquired genetic abnormalities, some of which have significant prognostic features. The main genetic markers are amplification of MYCN, ploidy changes (DNA content), and partial deletions of chromosome 1 and 11 and gains of chromosome 17.[2,15-22] These markers are useful for risk stratification of patients at presentation and allow more informed selection of the most appropriate and intensive treatments. This is beneficial in sparing patients with low- and some intermediate-risk disease, the deleterious effects of chemotherapy, radiotherapy, and bone marrow transplantation.

Biochemical

Biochemical markers associated with poor prognosis include high serum levels of lactate dehydrogenase, neuron-specific enolase, and ferritin levels. Urinary catecholamines are not predictive of outcomes. However, low vanillylmandelic acid and high homovanillic acid levels have been associated with shortened survival.[1,8]

Histology

Shimada and colleagues reported a classification for neuroblastoma, which related the histopathologic features with clinical behavior.[23] Cellular differentiation determines the favorable or unfavorable classification. There is a strong association of unfavorable histology with MYCN amplification.[22,24] Because the Shimada classification includes age as well as histology, it detracts from its power as an independent prognostic factor and so is being replaced by a histological only grading scale.

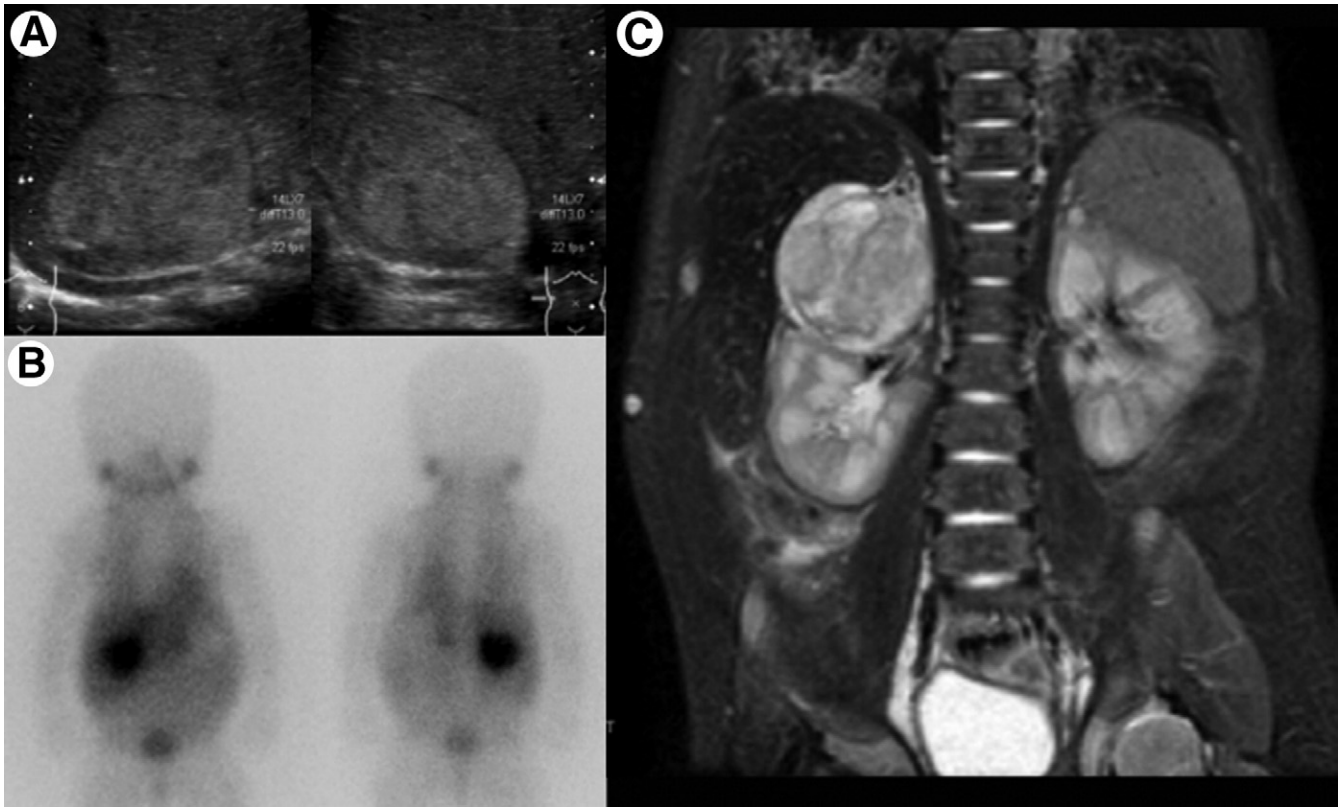

Figure 1 Neuroblastoma in a newborn. Postnatal ultrasound (A) confirms a solid mass in the right adrenal gland. ^{123}I-MIBG scan (B) confirmed avid uptake in the mass consistent with neuroblastoma. MRI (short-TI inversion-recovery) (C). The tumor was removed completely at surgery.

Age

Independent of the stage of the disease, age is a major prognostic indicator regarding response to treatment and survival.[3,25] All stages of neuroblastoma in infants younger than 12 months including stage 4 disease have a better disease-free survival than patients older than 12 months of age. More recent data extend a more favorable prognosis for patients 12 to 18 months who have stage 4 nonamplified MYCN neuroblastoma.[4,6,20,21] Children older than the age of 2 years with stage 4 disease have a very poor prognosis.[3,4,6,25] Age has been shown to be a continuous independent variable though its impact decreases in children older than 2.[3,25]

Management and Treatment

Before any treatment strategies are planned, patients are assigned into risk categories: low, intermediate, and high. These are based on age at diagnosis (<365 days vs >365 days), INSS stage (1, 2, 3, 4, 4S), histopathology (Shimada favorable versus unfavorable), MYCN amplification, and tumor cell ploidy.[1,8,15] Management is tailored to risk and will vary widely. Significant effort is now made to stratify patients as accurately as possible thus reducing the need for more aggressive chemotherapy regimens and bone marrow transplantation.[25-31]

Low-Risk Disease

Low-risk disease usually requires surgery alone and results in survival rates of more than 95% for stage 1 disease.[1,8,29,31] Newborns with small adrenal masses have a good prognosis (Fig. 1), and spontaneous regression may occur in adrenal neuroblastomas detected antenatally.[1,8,31] There is a high rate of spontaneous remission in infants with stage 4S disease, and high survival rates are observed in patients with stage 4S disease with no MYCN amplification. However, Tonini and colleagues have reported favorable outcomes in infants with MYCN amplified stage 4S disease.[19] Very good outcomes have been reported in stage 2 disease. Several studies have shown good results supporting the concept of a reduction in therapy in these groups.[8]

Intermediate-Risk Disease

Patients with regional disease are stratified by MYCN amplification and tumor cell ploidy. Patients with no MYCN amplification have better 3-year survival rates (93 ± 4%) compared with those with amplified MYCN (10 ± 7%). Also, patients with hyperdiploid tumors show higher survival rates (94 ± 5%) compared with diploid tumor patients (52 ± 16%).[6] These studies suggest that in patients with biologically favorable regional tumors, chemotherapy can be reduced or possibly eliminated in some cases.[6,8,26,27,31]

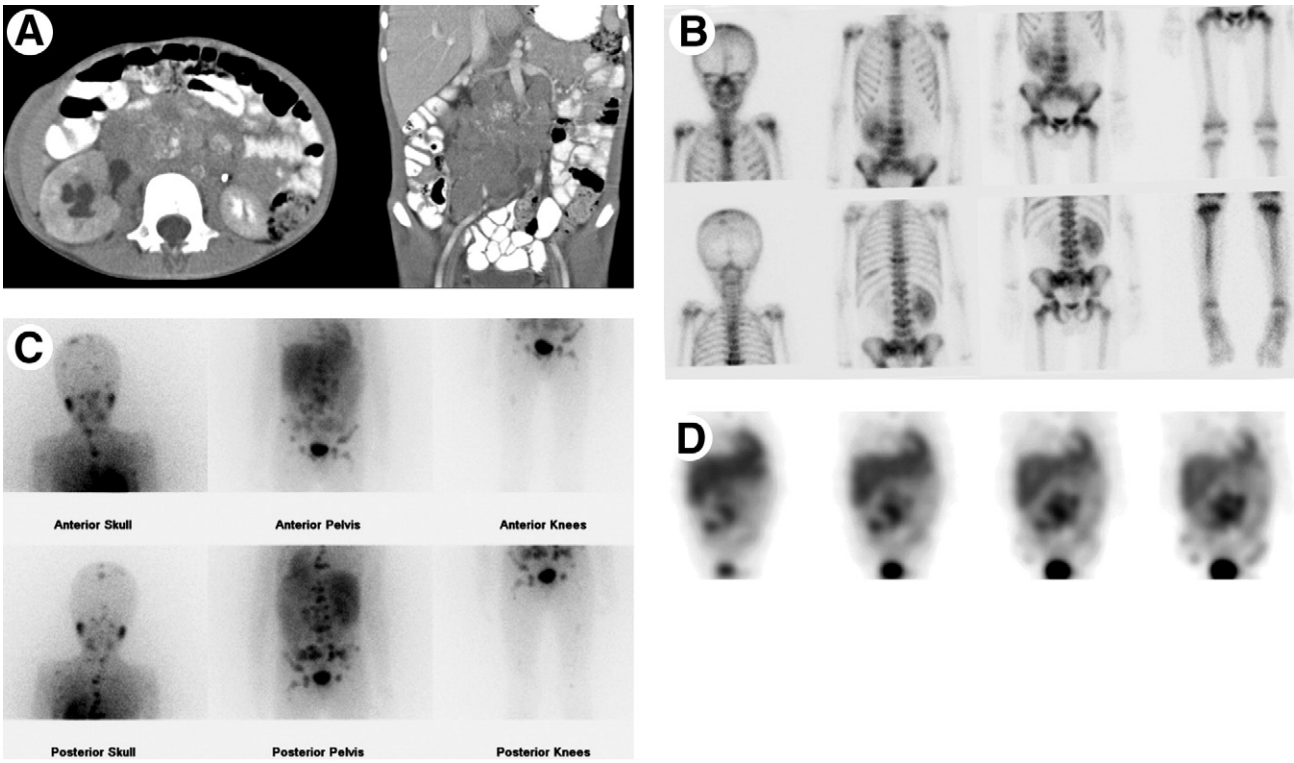

Figure 2 The abdominal examination in a 5-year-old boy revealed a large mass which on CT (A: transaxial, coronal) shows a large solid calcified mass in the midabdomen, causing obstruction to the right kidney, encasing the main intra-abdominal vessels and with focal areas of calcification. A total body bone scan (B) shows multiple skeletal metastases. The ^{123}I-MIBG study shows multiple focal osteomedullary metastases (C). There is heterogeneous uptake in the primary tumor consistent with necrosis. This was more obvious on the SPECT study (coronal; D).

High-Risk Disease

High-risk disease relates to patients with stage 4 neuroblastoma irrespective of the biology in children older than 18 months of age and MYCN amplified unresectable disease in all age groups.[8,30] There has been a modest improvement during the last 20 years in event-free survival, although cure rates remain low. This improvement is the result of intensification of chemotherapy, local radiotherapy, and improved supportive care.[30] More intensive chemotherapeutic regimens are typified by megatherapy consolidation requiring hematopoietic stem cell rescue, with bone marrow or more recently peripheral blood stem cell support. Other treatments include biologic response modifiers, such as cis-retinoic acid. Autologous peripheral blood stem cell support is now the routine in management. Several studies have indicated improved survival with intensification of consolidation therapy with autologous bone marrow transplantation (ABMT) with or without total body irradiation.[30-35] Targeted radiotherapy using metaiodobenzylguanidine (^{131}I-MIBG) and ^{131}I-labeled monoclonal antibodies has been used in various protocols often combined with chemotherapy.[36] Unfortunately even with such dose intensive consolidation therapies approximately 50% of children with high risk disease will relapse with drug resistant disease.[8]

Imaging

Medical imaging plays a vital role in the investigation of patients with neuroblastoma. This is at initial staging, in assessing response to therapy and in long-term surveillance for detection of recurrence of cancer.[7,31]

Computed Tomography

Computed tomography (CT) has been the main initial anatomical investigation of masses in patients with possible neuroblastoma for many years.[31,37,38] CT defines the site and extent of tumor, evidence of regional invasion, vascular encasement, adenopathy, and calcification (Fig. 2). Calcification in the tumor is highly suggestive of neuroblastoma and occurs in 80% to 90% of patients. CT has been the main method of differentiating between Wilms' tumor and neuroblastoma, the 2 main malignant causes of an abdominal mass in childhood.[39,40] Abdominal and pelvic tumors may be very large with areas of necrosis and hemorrhage. Invasion of tumor into the neural foramina and epidural space may occur. Neuroblastoma may metastasize to lymph nodes in the renal hila, porta hepatis, and retroperitoneum. CT scans of the thorax should be performed for pulmonary metastases and pleural involvement although this is uncommon. Bone involvement may be detected on CT particularly involving the skull and orbital regions. Brain involvement is uncom-

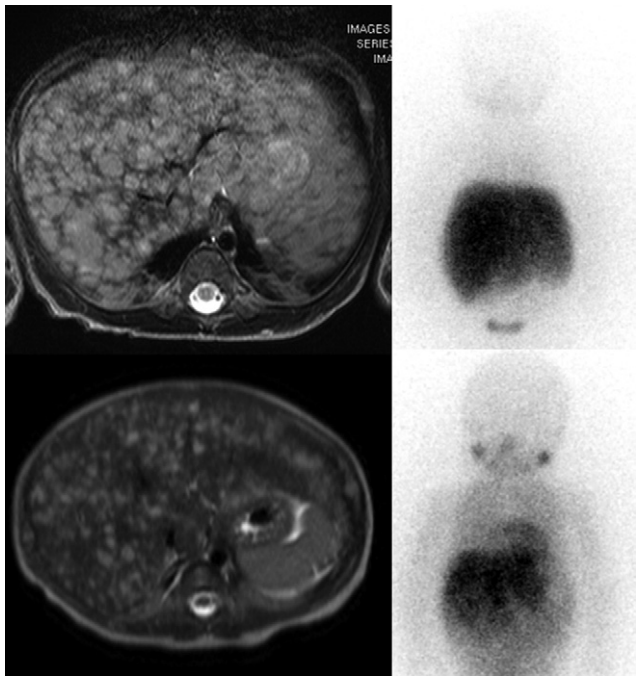

Figure 3 Neuroblastoma stage 4S. MRI (top left) in a 3-month-old infant confirms a markedly enlarged liver with multiple solid lesions. The initial ^{123}I-MIBG study (top right) shows marked increased uptake of tracer in the liver, confirming neuroblastoma. Note almost no distribution of MIBG in the normal distribution areas, including the myocardium. After chemotherapy, there was marked shrinkage of the liver. MRI (lower left) shows marked improvement but still abnormal. The ^{123}I-MIBG study (lower right) shows patchy increased uptake in the liver and the biodistribution of the tracer now shows normal uptake in the myocardium and salivary glands. Later follow-up studies were within normal limits.

mon and detected on CT or MRI. Involvement of the liver may occur in neuroblastoma and is part of stage 4S disease (Fig. 3).[31,37,38]

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a major anatomical imaging modality in neuroblastoma and has supplanted CT in many centers (Figs. 1 and 3). Its advantages include lack of ionizing radiation, excellent definition of the primary tumor with high intrinsic soft-tissue contrast resolution, depiction of internal structure, exact definition of intraspinal tumor extension, or diaphragmatic involvement. MRI is the preferred modality for determining spinal cord involvement and can detect extension into the epidural space. Bone marrow and cortical involvement can be detected and MRI is useful for defining MIBG avid foci within soft tissues or bone and bone marrow. However, false-positive studies on MRI for bone marrow involvement after treatment have been described.[47] Primary neuroblastoma on MRI is typically heterogeneous with gadolinium enhancement. Calcification may not be detected on MRI but necrotic, cystic and hemorrhagic areas are readily seen. Hepatic involvement is better visualized with MRI than CT. Small lymph nodes (<13 mm) are difficult to define on MRI.[41-46]

Ultrasound

Ultrasound often is used initially to investigate an abdominal mass or other soft-tissue masses that are evident clinically. Infants with large livers or abdominal or pelvic masses are readily examined by ultrasound. In most cases however, more cross sectional anatomic imaging, ie, CT or MRI are preferred to fully examine and stage the patient.[7,31]

Nuclear Medicine

Bone Scintigraphy

Total body radionuclide bone scintigraphy (BS) using ^{99m}Tc-disphosphonate compounds has been the main diagnostic investigation for detection of cortical skeletal metastases since the late 1970s.[48,49] BS is more sensitive than conventional skeletal radiography for detection of skeletal metastases. Howman-Giles and coworkers described the metastatic pattern of neuroblastoma in bone and highlighted the often symmetrical pattern of skeletal metastases in the metaphyseal areas of the long bones.[48] There has often been comment on the difficulty of determining metastatic disease in the metaphyseal regions of long bones because of the normal epiphyseal uptake of tracer on BS. The normal growth plate has a well-defined linear appearance on scan with clear demarcation between the plate and metaphysis. Symmetrical flaring and blurring of the growth plate with extension into the metaphysis should be considered abnormal and in a patient with neuroblastoma is highly suggestive of metastatic disease.[48] This is usually abnormal also on the blood pool phase of bone scintigraphy (Fig. 4). Early metastatic involvement within or adjacent to the growth plate may be missed. MIBG scans usually will detect these abnormal areas. Focal abnormalities on bone scintigraphy involving the orbits, skull, particularly parasagittal area, and multiple focal "hot" and "cold" lesions in the spine are highly suggestive of skeletal metastatic disease from neuroblastoma (Figs. 2 and 5). In as many as 60% of patients, the ^{99m}Tc-disphosphonate compounds would also accumulate into the primary tumors, but there is no prognostic significance in this finding.[50] If this is seen on bone scintigraphy, the most likely diagnosis is a tumor of neural crest origin. Rarely other primary tumors in childhood may accumulate the bone agent. Most pediatric centers managing patients with neuroblastoma perform total body BS at initial diagnosis to stage the disease. BS can be used to differentiate cortical from bone marrow metastases, the former having a worse prognosis. In recent years, there has been a trend to follow-up the patients with MIBG studies alone because the bone scan adds little extra information over the MIBG study.[31,51-53] Gordon and coworkers in a review comparing bone with ^{123}I-MIBG scintigraphy showed that ^{123}I-MIBG may miss abnormalities suggestive of metastatic disease and advised that ^{123}I-MIBG should not be substituted for BS in the staging of neuroblastoma.[54] However, Shulkin and coworkers did not miss any sites on ^{131}I-MIBG when compared with the BS.[55]

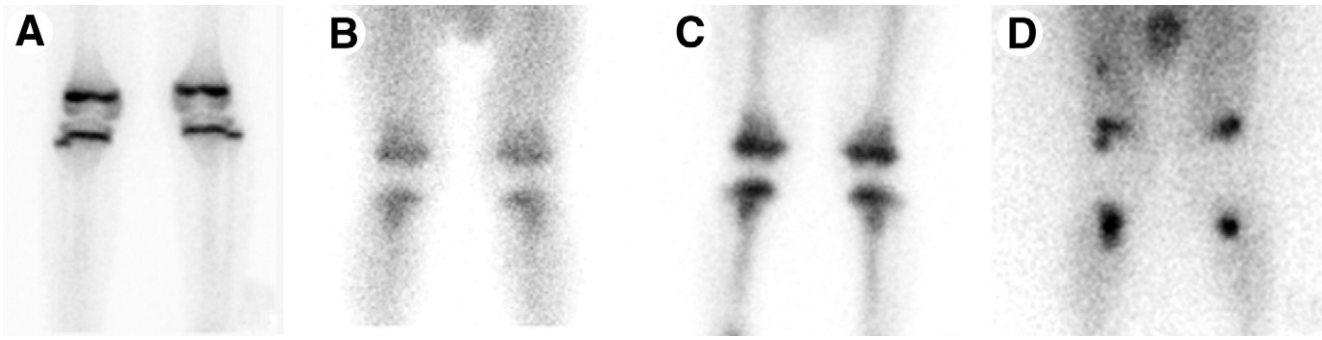

Figure 4 Bone and ^{123}I-MIBG scintigraphy epiphyseal plate appearance (knees): in a normal bone scan the epiphyseal plates are flat and well defined with no extension into the metaphysis (A). Bone scintigraphy with metastatic neuroblastoma may have a symmetrical pattern. In an abnormal study for metastases the blood pool is usually abnormal (B) with increased vascularity in the metaphyses, the delayed scan shows loss of the linear flat plate with extension into the metaphysis of both distal femora and proximal tibia in this patient (C). The ^{123}I-MIBG confirms metastatic disease in these areas (D).

MIBG Scintigraphy

MIBG is an aralkylguanidine analog of catecholamine precursors and was first developed in 1979.[56] MIBG is concentrated within the secretory granules of catecholamine producing cells. The uptake mechanism of MIBG into adrenomedullary tissue is by the type 1 amine uptake mechanism. MIBG remains both in the cytoplasm and norepinephrine storage granules of the neuroblastoma cells.[57,58] In phaeochromocytoma the MIBG is predominantly stored in the granules. During a 24-hour period, the majority of the MIBG is excreted in the urine (40-50%) and approximately 70% to 90% will be excreted over the course of 96 hours.[59-61] MIBG can be labeled with ^{123}I or ^{131}I. ^{123}I is a gamma emitter with energy of 159 keV and a half life of 13 hours, which makes ^{123}I-MIBG very suitable for imaging with a gamma camera. Compared with ^{131}I, ^{123}I has better imaging characteristics with greater sensitivity, better image quality, and only 5% of the ionizing radiation exposure. Single-photon emission computed tomography (SPECT) is also a major factor for ^{123}I-MIBG imaging as it allows more precise anatomical location of disease and coregistration with anatomical modalities such as CT and

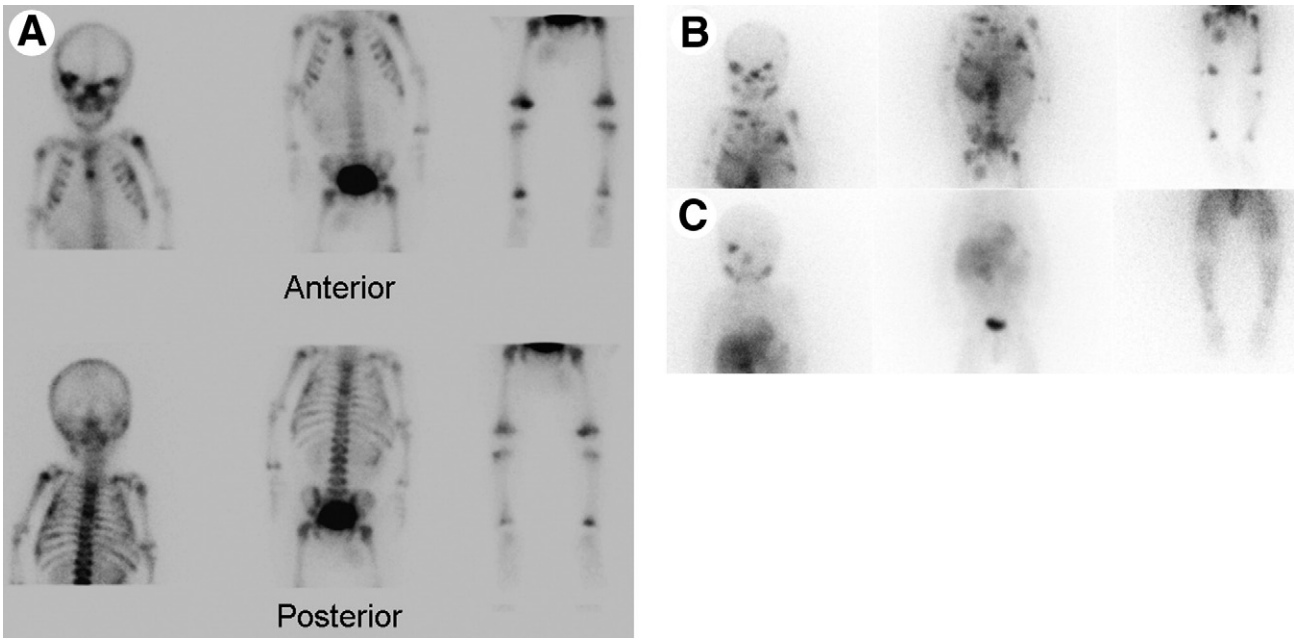

Figure 5 Neuroblastoma stage 4: A 12-month-old boy presented with a hard mass over the right orbit. A radionuclide bone scan (A) shows multiple skeletal metastases. Note the metastatic pattern in the orbits, metaphyseal regions of the long bones, and the abnormal areas of increased and decreased uptake in the spine. ^{123}I-MIBG studies at presentation (B, anterior planar views) shows extensive disease in the orbits, the skeleton, the right upper abdominal mass with central photopenia (necrosis), and in a soft-tissue mass in the upper right medial thigh. The response study (C) with ^{123}I-MIBG after intensive chemotherapy including ^{131}I-MIBG therapy shows a good response but persisting activity in the right orbit and the primary tumor.

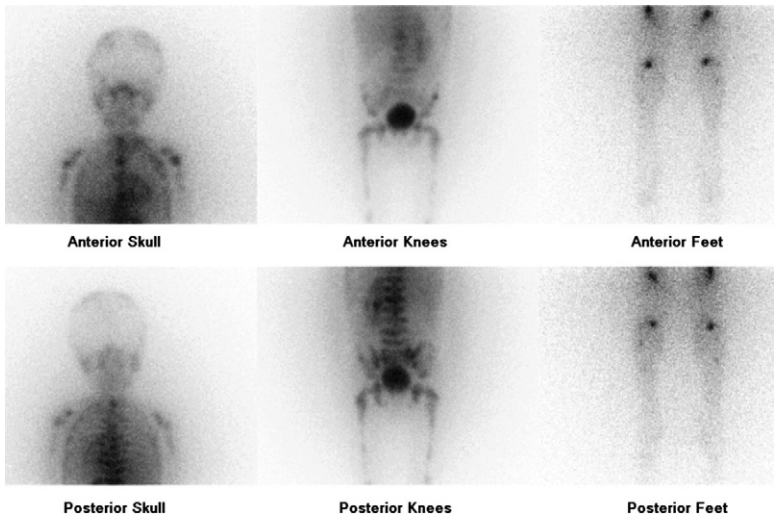

Figure 6 ^{123}I-MIBG study showing a diffuse metastatic pattern throughout the bone and bone marrow.

MRI. The first report of clinical applications of ^{131}I-MIBG in phaeochromocytoma was in 1981[62] and in neuroblastoma in 1985.[63] ^{131}I-MIBG can also be used for therapy. ^{131}I emits beta particles and high-energy gamma rays, with the main energy at 364keV and has a half life of 8.05 days. Although ^{131}1-MIBG has been used for diagnosis particularly in the United States, ^{123}I-MIBG is the preferred diagnostic agent.[31,64]

The normal physiological biodistribution of MIBG includes liver, myocardium, salivary glands, intestines, renal, and thyroid, and a mild uptake may be seen in normal adrenal glands.[31,59] Occasionally, some hold up may be viewed in the pelvicalyceal systems, which is physiological. Increased fluids or a diuretic will clear this activity. After adrenalectomy, the remaining adrenal gland often appears to have increased uptake of MIBG. Occasionally, particularly in infants, uptake may be seen in a symmetrical pattern in the upper chest and supraclavicular areas corresponding to brown fat uptake.[65] Also a mild diffuse increase may be seen in the lungs in small infants (Fig. 1).

Uptake of MIBG will occur at sites of neuroblastoma in 90% to 95% of patients, including the primary tumor, metastases in bone, bone marrow, and lymph nodes (Figs. 5 and 6).[31,66-72] Metastatic disease in the central nervous system is not common and MIBG does not appear to be as accurate here for the detection of metastases.[73] Those tumors that are MIBG negative have very poorly differentiated cellularity and are unable to metabolize the MIBG. This group can effectively be studied with ^{18}F-fluorodeoxyglucose positron emission tomography PET (FDG-PET).[75,76] The size of the tumor will reflect whether the uptake is uniform or irregular with focal areas of reduced uptake, indicating central necrosis. In some of these tumors, the areas of reduced uptake may reflect areas of de-differentiation, ie, more malignant clones of neuroblastoma. There is a commonly held belief that well differentiated tumors show a lower MIBG uptake in vivo, although it could not be confirmed by Brans and coworkers.[77] As the uptake of MIBG is dependent on cathecholamine transporters, care must be taken that the patient is not taking medications that may block the uptake mechanism. Several agents, in particular tricyclic antidepressants, phenylpropanolamine, pseudoephridine (often in over the counter cough medicine), and labetolol, will block the uptake.[60,78-80]

The initial response of neuroblastoma to therapy can be assessed, and MIBG uptake has been used as a prognostic indicator.[31,81-85] The risk of failing to achieve complete remission correlates with a higher number of MIBG-avid lesions. Several MIBG scoring systems have been devised to define both the number and extent of disease. Absolute and relative MIBG scores correlated with overall pretransplantation response and event-free survival (EFS). Suc and coworkers described a scoring system in which patients with MIBG scores lower than 4 had a higher probability of achieving complete response after induction therapy. However, there was no long-term difference in survival for these patients compared with those with a score greater than 4. Sequential MIBG scans performed at the beginning, midcourse, and end of induction showed that the midcourse score strongly correlated, with complete remission at end of induction.[81] Matthay and coworkers used a similar scoring system and looked at both the overall response and bone marrow response after pretransplantation therapy but before final myeloablative therapy. The probability of a complete response after transplantation was significantly greater if the score was less than 0.5 after 2 cycles of chemotherapy or less than 0.24 after 4 cycles. There was a significant correlation to EFS.[83]

Since the introduction of more dose-intensive induction protocols, there are improved response rates and MIBG is being used more effectively in patient management.[81-86] Katzenstein and coworkers reported the MIBG score (>3) correlated and identified a subset of ultra high-risk patients who were more likely to relapse after therapy. There was a strong correlation between EFS and the postinduction MIBG score. In contrast, uptake on bone scans after induction therapy did not correlate with EFS. Osteomedullary uptake before myeloabalative therapy and bone marrow transplant was asso-

ciated with poor outcome.[84] These studies indicate that an early response to therapy is highly prognostic in neuroblastoma.[85] Kushner and coworkers comment that to assess reliably for major disease response, that extensive bone marrow testing and MIBG scintigraphy are prerequisites for the accurate determination of disease status.[86] Measuring the osteomedullary response using the scoring systems provides additional information that helps distinguish high likelihood of long term remission with intensive multimodality therapy from those who are destined to fail. Alternative therapies such as ^{131}I-MIBG therapy, retinoids, tyrosine kinase inhibitors, antiangiogenic agents, immunotherapy, and novel chemotherapeutic drugs should be considered for this group.[8,31]

Tumors with False-Positive MIBG: Specificity

Several rare pathological conditions also may show MIBG uptake. These are infantile myofibromatosis, neuroendocrine tumors, pancreaticoblastomas, and neuroectodermal tumors. Only 4% of nonsympathomedullary tumors (nonphaeochromocytoma, nonneuroblastoma) showed MIBG uptake.[87]

Somatostatin Receptor Scintigraphy (SRS)

Somatostatin receptors (SRs) have been described on neuroblastoma cell lines and tumors.[59,88,89] Several studies compared ^{111}In-pentetreotide scintigraphy, a radiolabeled form of octreotide with MIBG scintigraphy.[89-91] The sensitivity of ^{111}In-pentetreotide ranged from 55% to 70% compared with MIBG, which had a range of 83% to 94%. Most of the octreotide studies used only planar imaging, which probably reduced their sensitivity. More recent studies using SPECT have shown improved sensitivity. There also appears to be a more favorable prognosis in those patients with a positive octreotide study. These patients usually have low-stage disease and have favorable biological factors, ie, nonamplified MYCN, hyperdiploid, and intact chromosomal 1p36.[31,59,90,91] Also, SR expression is downregulated in more aggressive tumors and can be variable within a tumor. However, in our opinion, the use of octreotide imaging adds no extra information, which changes patient management. Currently, there is no routine role for octretoide imaging in neuroblastoma management.

Radiolabeled Antibodies

As radiolabeled antibodies bind to specific cell surface proteins that may be expressed on both mature and immature tumor cells, highly sensitive and specific diagnostic and therapeutic agents are possible. Goldman and coworkers described radiolabeled antibody detection of neuroblastoma in 1984 using an IgG1 monoclonal antibody (^{131}I-UJ13A).[92] Other centers used ^{131}I-labeled anti-G_{D2} IgG3 antibody (^{131}I-3F8) and showed excellent tumor targeting of neuroblastoma. The ^{131}I-3F8 was more sensitive and specific than ^{131}I-MIBG and MRI imaging.[93] Other anti-G_{D2} antibodies (^{131}I-1gG2a and ^{99m}Tc-Ch14.18) have shown positive scans in neuroblastoma.[94,95] A comparison study of ^{123}I-MIBG and ^{99m}Tc-Ch14.18 reported that ^{99m}Tc-Ch14.18 studies were more sensitive than MIBG in the detection of local tumor recurrences and skeletal metastases. In sequential studies assessing response to treatment, metastases were detected earlier by ^{99m}Tc-Ch14.18 than by MIBG.[95] However, few centers are routinely using radiolabeled antibodies for scanning due to the complexity of using antibodies, although they are being used for treatment (see below). Also from a practical clinical perspective ^{123}I-MIBG is more readily available, easier for detection of neuroblastoma, and images can be readily coregistered with CT or MRI. PET/CT scanning with FDG and newer PET agents also are becoming more readily available.

Positron Emission Tomography

FDG has been shown to reflect the increased glycolytic rate of tumor cells and uptake is proportional to tumor cell burden and tumor cell proliferation.[96] The data on FDG-PET in neuroblastoma is very limited. Shulkin and coworkers reported FDG uptake in 16 of 17 neuroblastoma patients. Neuroblastoma primary tumors and metastases avidly accumulated FDG before chemotherapy and radiation therapy. This report concluded that the majority of neuroblastomas are metabolically active and can be detected by FDG-PET imaging but that MIBG was overall superior to FDG-PET imaging.[74,75] Kushner reported using FDG-PET in 51 patients with neuroblastoma and documented complete and partial remission, stable disease, and progressive disease. The standardized uptake values ranged from 1.8 to 8.4, with a mean of 5.3. Serial FDG studies documented treatment response. The FDG studies correlated well with disease status and with ^{123}I-MIBG studies and conventional imaging; however, the FDG studies detected more abnormal areas. FDG PET missed lesions in the skull because of the high-but-normal FDG uptake in the brain. The assessment of treatment response was accurate. FDG-PET appears better for analysis of the liver, where there is a significant uptake on MIBG scans.

PET showed more osteomedullary abnormalities than bone scintigraphy and MIBG scans. With the use of PET/CT systems, better definition of FDG abnormalities in bone and bone marrow is possible (Fig. 7).[76] Detection of minimal bone marrow disease is not possible, and reactive marrow after chemotherapy is common on FDG studies. Other false-positive abnormalities may cause some difficulty in FDG-PET imaging, but the use of PET/CT enables most physiological variants to be recognized. The role of FDG-PET is still uncertain; however, there is definitely a role in the small percentage of neuroblastoma patients who are MIBG negative at presentation. We have also found PET/CT to be useful in those patients, particularly in the neck region, where the resolution and coregistration of the FDG study with CT allows a better evaluation of the lesion and response to treatment (Fig. 8). The uptake of ^{123}I-MIBG into salivary glands may obscure the neuroblastoma lesions in that area. Shulkin comments that it is unlikely that FDG-PET will replace MIBG scanning in the management of neuroblastoma patients; however, more data

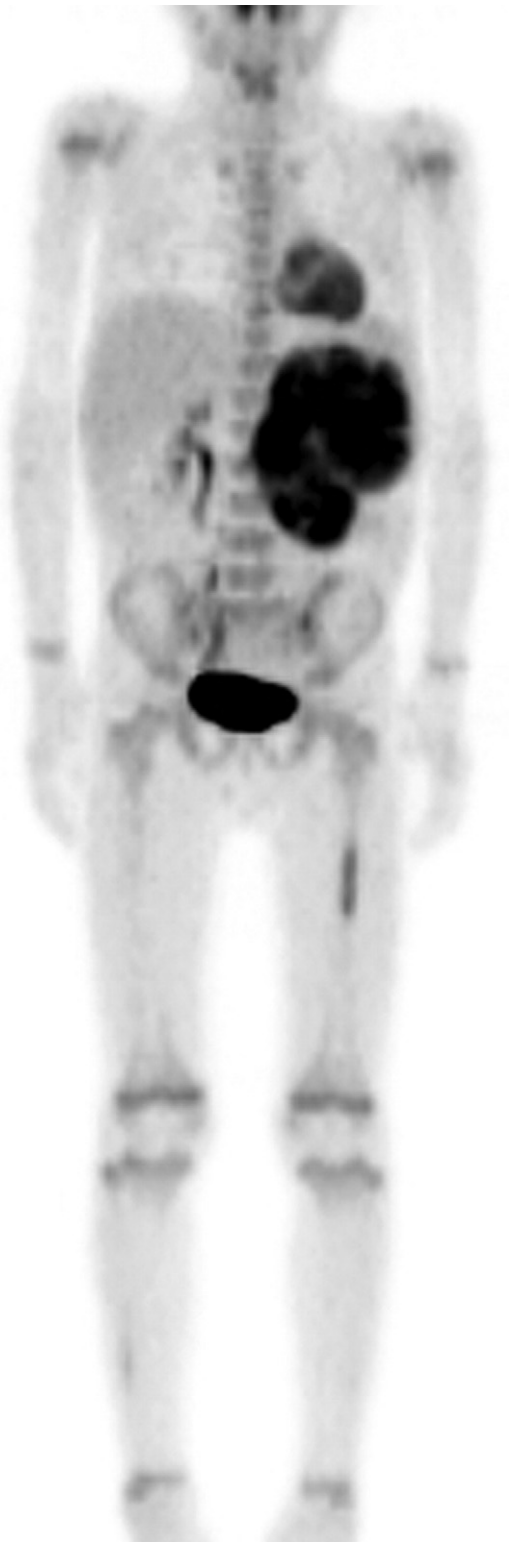

Figure 7 A 6-year-old boy presented with pain in the left leg and a mass was found on examination in the left abdomen. Bone scan and ^{123}I-MIBG studies confirmed neuroblastoma with metastatic disease in the skeleton. The ^{18}F-FDG study (MIP image) showed marked metabolic activity in the mass and metastatic disease in the left mid femur, mid right fibula and left iliac crest.

are required to adequately determine the role of PET/CT in the management of neuroblastoma.[97]

^{11}C-hydroxyephedrine (HED) also has been used to image neuroblastoma.[98,99] HED accumulated in all sites seen on MIBG.[98] Franzius and coworkers also reported the feasibility of use and biodistribution of HED and its clinical application in tumors of the sympathetic system including 6 patients with neuroblastoma.[99] There was some variation in the detection of different lesions when compared with ^{123}I-MIBG however HED detected more lesions than MIBG. The overall sensitivity for HED was 99% whereas ^{123}I-MIBG was 93%. The major drawback on HED is the short half life. ^{11}C-epinephrine also has been studied in neuroblastoma and phaeochromocytoma; however, because only between half and two thirds of neuroblastomas accumulated ^{11}C-epinephrine its application is limited.[97] Other experimental agents include 4-^{18}F-flouro-3-iodobenzylguanidine, 6-^{18}F-fluorodopamine, and ^{18}F-dihydroxyphenylalanine (DOPA).[97]

Therapy

^{131}I-MIBG has been used for targeted radiotherapy since the mid-1980s. MIBG has a specific tissue uptake and has prolonged intracellular retention when compared with normal tissues.[101-104] ^{131}I-MIBG therapy remains controversial because of a large variation in response rates in the published literature and the potential side effects. Response rates vary between 20% and 60% in newly diagnosed and relapsed or refractory patients.[104] Good pain relief has been well documented for palliation.[105] MIBG therapy is well tolerated but in high doses can lead to significant bone marrow depression, often requiring ABMT. The application of ^{131}I-MIBG therapy has been extensively reported in adults with phaeochromocytoma and carcinoid tumors but in pediatric patients has been mainly used in neuroblastoma.[101] In a review on MIBG therapy by Tepmongkol and Heyman in 1999 the cumulative results of the literature for MIBG therapy in neuroblastoma in 276 patients was complete remission (17), partial remission (70), stable disease (88), progressive disease (74), not evaluable (27), and an objective response was observed in 34.9%.[105] Pooled results in 229 patients from the European Association Nuclear Medicine in 1999 reported an objective response of 51%.[106]

Single-Agent Therapy: Progressive or Recurrent Disease

The most frequent application of ^{131}I-MIBG in neuroblastoma is as single agent therapy in patients with metastatic neuroblastoma who have failed to respond to conventional chemotherapy or have recurrent relapsed disease after all other treatment programs have failed. A retrospective review in 2006 reported a 3-year EFS of 28 ± 4% and a 3 year overall survival of 48 ± 5%. Patients who underwent MIBG therapy had a better EFS (46 ± 8%) and 3-year survival (58 ± 9%) than patients without MIBG therapy. However, there was no independent advantage of MIBG therapy.[107] A further multimodal therapy trial (NB2004) is currently underway. Other

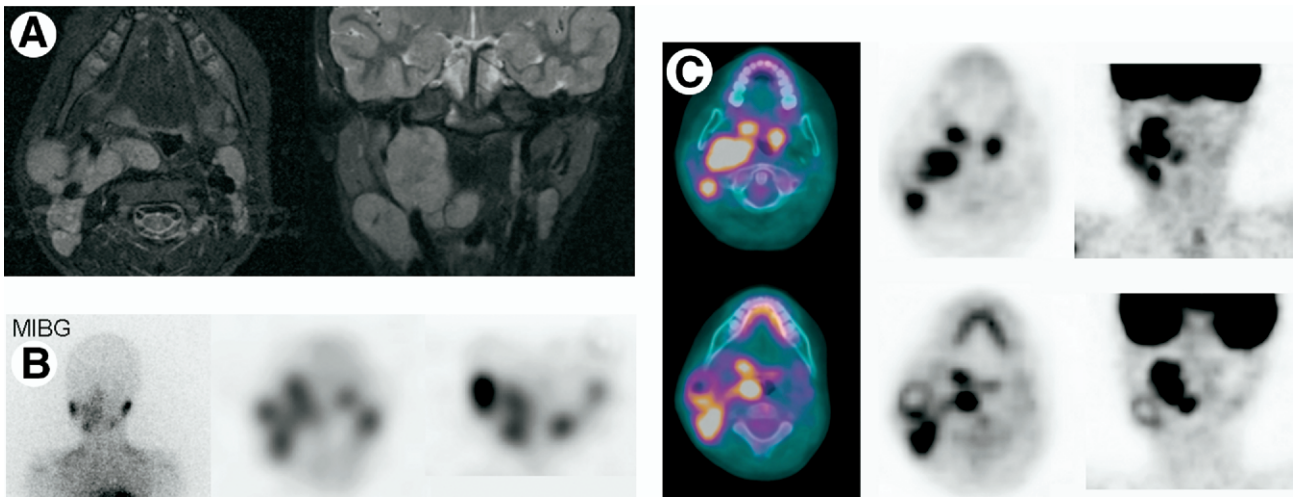

Figure 8 (A) MRI (left transaxial, right coronal) short-TI inversion-recovery image in a 4-year-old girl shows a large mass with abnormal lymph nodes in the right side of the neck with displacement of the right tonsil and possibly abnormal nodes in the left neck. (B) ^{123}I-MIBG anterior planar image (left) shows abnormal uptake in the mass. The SPECT images (center, transaxial; right, coronal) shows uptake within the mass; however, there is difficulty in differentiating the tumor mass from salivary glands and lymph nodes on the right and left side. (C) The coregistered PET/CT FDG study shows clear demarcation of the mass, lymph nodes and tonsils. The mass shows marked metabolic activity, and there is necrosis in one of the enlarged lymph nodes in the right neck. No abnormal nodes were detected on the left side. This allowed more accurate staging to stage 2 with no involvement on the left side of the neck.

techniques use multiple infusions of high-dose ^{131}I-MIBG in refractory neuroblastoma.[108]

Hyperbaric Oxygen-Enhancement MIBG Therapy

Hyperbaric oxygen has been used to enhance the radiation effect in children undergoing ^{131}I-MIBG therapy.[101,102] Voute and coworkers reported the cumulative probability of survival as 32% for the group with hyperbaric oxygen and MIBG treatment.[109] No further significant data have been reported to support this treatment method.

Low Recurrent-Dose MIBG Therapy

Recent data have been presented using low recurrent doses of ^{131}I-MIBG. This technique limits toxicity, and the patient can be treated as an outpatient. Doses from 0.5 mCi (18.5MBq)/kg to a maximum of 25mCi (925MBq) were administered every 4 to 6 weeks and continued until efficacy was not seen. This method has resulted in an excellent palliative effect (A. McEwan, personal communication, 2006). Further studies are needed to confirm this treatment method.

Single-Agent Therapy in Combination With Myeloablative Therapy Before ABMT

High-dose ^{131}I-MIBG therapy has also been combined with high dose chemotherapy.[111-113] This method is based on the hypothesis that the risk of tumor cell drug resistance is decreased by rapid cyto-reduction combined with a non cross-resistant drug. ^{131}I-MIBG has been added to myeloablative chemotherapy in combination or without radiotherapy. This is often supported by ABMT or peripheral stem cell infusion. Small numbers of patients have been treated with these protocols with varying results. In 2006, Matthay and coworkers reported that the combination of ^{131}I-MIBG and high dose chemotherapy followed by ABMT is feasible and effective therapy in patients with refractory neuroblastoma. The estimated probability of overall survival at 3 years was 58%.[114] Two new trials are being undertaken commencing in 2007 within a consortium of pediatric centers in the United States. In a Phase II study ^{131}I-MIBG will be administered with intensive chemotherapy and autologous stem cell rescue for high-risk patients. Also in a Phase I study Irinotecan and Vincristine in combination with ^{131}I-MIBG will be administered to determine safety and tolerability in patients with resistant / relapsed high-risk neuroblastoma (www.nant.org/trials.shtml). There have been reports of second malignancies in children after high-dose MIBG therapy and in combination with intensive chemotherapy.[115,116]

At Diagnosis Before Chemotherapy

Preoperative MIBG therapy in children with advanced or inoperable neuroblastoma is based on the objective to reduce tumor volume enabling better tumor resection without inducing early drug resistance or toxicity. Preoperative MIBG therapy was given in 33 patients with untreated advanced stage neuroblastoma.[117,118] There were 18 partial responses, 1 complete response, 11 patients had stable disease and 3 had progressive disease. Seventeen of 21 patients having surgery had tumor resection of >95%. There was a significant palliative effect with a dramatic improvement in quality of life. Hoefnagel reported a higher objective response (>70%) and less toxicity with this method compared with initial chemotherapy followed by MIBG therapy.[106]

Combined Radiotherapy

Recent data has shown that combined ^{131}I-MIBG and ^{90}Y-DOTOTOC can significantly increase the delivered tumor dose over the dose of either agent alone.[110] Further evaluation is required.

Radioimmunotherapy

Various radiolabeled antibodies have been assessed for therapy. These include the anti-G_{D2} antibody (^{131}I-3F8) which shows excellent targeting in neuroblastoma. In data from the Memorial Sloan Kettering using ^{131}I-3F8, the overall survival at 18 months post therapy was approximately 40%. The antibody localized in the primary tumor and metastatic sites in lymph nodes, bone marrow and bone in 42 patients. Severe side effects maybe associated and induction of HAMA response limits this therapy.[119] Other antibodies (eg,^{131}I-Ch14.18) are being assessed for radioimmunotherapy in neuroblastoma and initial results are encouraging. Severe myelosuppression frequently occurs and requires autologous bone marrow rescue or treatment with granulocyte macrophage colony stimulating factor.[120] The initial results have been sufficiently promising that the addition of Ch14.18 antibody to standard therapy is being tested in a prospective, randomized trial ANBL0032 (http://clinical trials.gov/show/NCT00026312).

Neuroendocrine Tumors

Neuroendocrine tumors (NETs) are rare, forming only a small subset of all endocrine tumors which themselves only account for 4% to 5% of childhood neoplasms.[121] Recently, the imaging of NETs has been extensively reviewed in this journal[122] and a comprehensive clinical review has also been published elsewhere.[123] This smaller section aims to highlight some aspects relevant to pediatric nuclear medicine. NET arise from cells that are able to produce, store and use biogenic amines and peptide hormones. This encompasses neuroblastoma, but it is traditional to discuss neuroblastoma and neoplasms of the pituitary and parathyroid separately. NET were formerly characterized as being from neuroectodermal origin and the amine precursor uptake and decarboxylation (ie, apud) group. However, this definition is considered dated because of more recent insight indicating almost any epithelial stem cell is capable of differentiating into a neuroendocrine cell.[124] Therefore, NETs can arise in neural elements and endocrine organs, cell clusters (eg, pancreatic islets) and single cells (eg, thyroid C-cells).[125] The amine synthetic pathways and increased cell surface receptors (especially SR) of NET are convenient targets for radionuclide tracers, securing important roles for nuclear medicine in aspects of diagnostic imaging and therapy.

Neuroendocrine tumor classification requires details of organ of origin, tissue type, secretory product, and grade of differentiation. A practical clinicopathological classification is presented:

1. Carcinoid tumor
2. Gastroenteropancreatic neuroendocrine tumors
3. Phaeochromocytoma
4. Medullary carcinoma of thyroid (MCT)
5. Multiple endocrine neoplasia (MEN)

Carcinoid Tumors

Carcinoid tumors arise from the enterochromaffin or Kulchitsky cells, which are found in the epithelia of diverse locations in the body. The incidence is 0.1 to 0.14 per 100,000 in the less than 15-year age group and is more often in girls.[126] However, histopathological finding of carcinoid is found in 1 in 200 postappendicectomy specimens.[127] This is one of the most common childhood presentations. These tumors secrete a variety of vasoactive peptides responsible for the carcinoid syndrome of flushing, diarrhea, bronchospasm, and endocardial fibrosis. Serotonin is a characteristic product, hence biochemical diagnosis based on urinary levels of its metabolite, 5-hydroxy-indoleacetic acid.

Gastroenteropancreatic NET

NETs of the pancreas are not confined to the islet cells. They originate from pluripotent pancreatic ductal cells and may arise from extrapancreatic sites, hence consideration of the gastroenteropancreatic region as a whole. Sporadic tumors are found in an older age group. Those associated with multiple endocrine neoplasia (up to 10% with MEN I) are more relevant to pediatrics. They may secrete a mixture of peptide hormones and are named after their dominant product. Only in about two-thirds of cases is the hormone secreted in enough quantities to cause a clinical endocrinopathy, when they are classified as functional. The most common is insulinoma, which is included in the differential diagnosis of hyperinsulinaemic hypoglycemia.[128] Less common are gastrinoma and the much rarer glucagonoma, VIPoma and somatostatinoma. The majority of these tumors are malignant (up to 77%), except for insulinomas (10%).[129] Although not classified as a NET, congenital hyperinsulinism is an important cause of recurrent hypoglycemia in infancy. This condition requires aggressive treatment to prevent severe neurologic complications. Histopathologically there are focal and diffuse forms. In the focal form pathologic pancreatic β cells are gathered in a focal adenoma. The diffuse form involves the whole pancreas with disseminated β cells showing enlarged abnormal nuclei. Focal involvement may be cured by limited pancreatectomy whereas diffuse requires subtotal pancreatectomy.[130]

Phaeochromocytoma

Phaeochromocytomas arise from chromaffin cells of the adrenal medulla and paragangliomas from chromaffin cells in extra-adrenal sympathetic nervous elements. These have an incidence of 0.1 to 0.8 per 100,000, of which only about 10% occur in childhood.[123] They are predominantly found between the ages of 6 to 15 years and more often in boys.[121] They secrete catecholamines characteristically, accounting for sustained or paroxysmal hypertension as the presenting sign in up to 80% of childhood cases. Biochemical diagnosis

is by finding raised serum or urinary levels of catecholamines and their metabolites.[123]

Medullary Carcinomas of the Thyroid

MCTs arise from the parafollicular C-cells and account for 3% to 10% of all thyroid cancers but are very rare in children.[131] The majority are sporadic cases occurring in the fourth and fifth decades of life. About one-third are familial, either in isolation or associated with MEN IIA and IIB.[121] These hereditary forms are the only ones that occur in childhood, and nearly all patients with MEN II eventually develop MCT. Because C-cells secrete calcitonin normally, they are a useful tumor marker. Because increased calcitonin secretion does not cause any manifest clinical syndrome, MCT usually presents as a thyroid nodule or with mass effect. Close follow up after surgery is necessary as approximately 50% may develop recurrences.[121,123]

Clinical diagnosis is based on a consistent clinical history and examination, followed by either biochemical confirmation of elevated secretory products or immunohistochemical confirmation of neuroendocrine markers.[132] Although they may have a dominant or characteristic secretory product, NET tend to secrete multiple amines and peptides. Hence, for any one tumor there is a panel of serum and histochemical markers available.[123]

Multiple Endocrine Neoplasia

MENs are disorders in which multiple glands undergo neoplastic transformation and are preceded in their development by endocrine cell hyperplasia. Three distinct patterns have been described. About half of these cases are sporadic, the rest are autosomal dominant and a gene defect has been characterized.[121] MEN I syndrome consists of hyperplasia or neoplasia of the pituitary, parathyroids and pancreatic islet cells. It is the most common form with an incidence of 2 per 100,000. The MEN I susceptibility gene is on chromosome 11q13 and encodes a protein, menin. MEN IIA syndrome consists of hyperplasia or neoplasia of the thyroid C-cells, parathyroids and adrenal medulla. The responsible gene is *ret* proto-oncogene on chromosome 10q11.2 that encodes a tyrosine kinase. MEN IIB syndrome consists of hyperplasia or neoplasia of the thyroid C-cells and adrenal medulla with characteristic mucosal neuromas. It is more commonly sporadic. However, most with autosomal dominant inheritance also have a *ret* mutation. In addition, neuroendocrine tumors are part of other multiple endocrine neoplastic syndromes, eg, von Hippel-Lindau syndrome (gastroenteropancreatic NET and phaeochromocytoma) and neurofibromatosis type I (phaeochromocytoma).[123]

Imaging

Because these tumors occur rarely, much of the nuclear medicine literature is based on retrospective clinical series dominated by adult patients. However, similar principles can be applied to pediatrics. Nuclear imaging has a central role in the diagnostic workup. Tumor localization and staging of the extent of disease allows decisions about the appropriateness and aggressiveness of surgery; in general, for NET, resection of all evidence of the tumor is the only chance of cure. The two main single photon emitting radiopharmaceuticals are ^{123}I-MIBG and SRS with ^{111}In-pentetreotide. Imaging with these tracers also assesses the potential for radionuclide therapy.

Carcinoid Tumors and Gastroenteropancreatic NET

SRS with ^{111}In-pentetreotide is the initial functional imaging of choice (Fig. 9). Because insulinomas have a lower expression of somatostatin receptors, CT, MRI, or endoscopic ultrasound of the pancreas are more appropriate first investigations. In the event of a negative SRS, ^{123}I-mIBG has been suggested as a second study for carcinoid tumors but not pancreatic NET, where the sensitivity is lower.[133,134] In general, most NET are well differentiated with low proliferative rate and PET imaging with FDG has a lower sensitivity than the first choice single photon agent. Therefore, FDG can be considered in poorly differentiated NET and is a prognostic indicator for more aggressive disease which may impact on therapeutic decisions.[135] Newer PET radiopharmaceuticals are being developed. In particular, ^{11}C-5-hydroxytryptophan shows great promise.[135] Other agents include ^{11}C-epinephrine, ^{11}C-hydroxyephedrine, ^{18}F-fluorodopamine, and L-dihydroxyphenylalanine (L-DOPA) labeled with ^{11}C or ^{18}F.[122] PET agents which label new peptides DOTA-TOC and DOTA-NOC have been developed recently and have significant potential. These can be labeled with ^{68}Ga, which can be eluted from an in house ^{68}Ga-generator. Other agents include ^{64}Cu-TETA-octreotide and ^{18}F-fluoropropionyl-Lys^0-Tyr^3-octreotate.[122] In congenital hyperinsulinism of infancy, ^{18}F-DOPA has been used to distinguish between focal and diffuse disease which allows the most appropriate surgical management.[130]

Phaeochromocytoma and Paraganglioma

Because 90% of phaeochromocytomas are intra-abdominal and of these 90% are in the adrenal glands, morphological imaging with CT or MRI are initial investigations of choice and a have high sensitivity (93-100%). ^{123}I-MIBG is the functional agent of choice, with overall 95% to 100% specificity and up to 90% sensitivity (Fig. 10).[136] In cases in which MIBG is negative, SRS can be considered.[134] PET imaging with FDG has a sensitivity of 70% for solitary benign or malignant phaeochromocytoma, whereas ^{11}C-HED had a sensitivity of 90% for primary and metastatic phaeochromocytoma. Other promising PET agents are ^{18}F-DOPA, ^{18}F-FDA, and ^{18}F-fluoro-benzylguanidine.[122]

Medullary Carcinoma of the Thyroid

Nuclear medicine procedures have a limited role in preoperative assessment. In the postoperative situation, morphological imaging with ultrasound and fine-needle aspiration biopsy of abnormal lymph nodes should be the initial imaging for detection of residual or recurrent neck disease. CT or MRI also may be used, but their sensitivity in detecting minimal residual disease is low. SRS is only 50% to 75% sensitive, and specificity is low (37%). ^{131}I-MIBG has a low sensitivity of 35

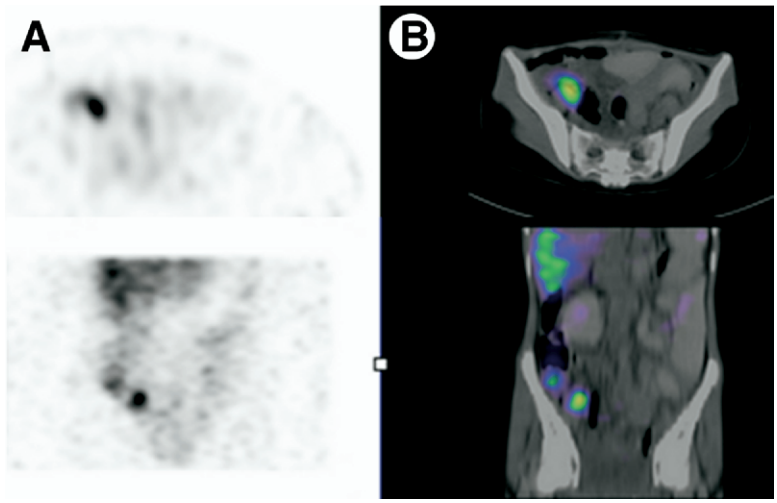

Figure 9 A 14-year-old girl presented with symptoms consistent with appendicitis. At surgery, a mass was removed from the appendix which on histology was a carcinoid tumor. (A) ^{111}In-pentetreotide scan and (B) coregistered CT (top row axial; lower row coronal) were undertaken to exclude other lesions detected a focus in the right iliac fossa. At surgery a second carcinoid tumor was removed from the mesentery.

to 50% although the specificity is high (>95%).[134] The sensitivity does not seem to improve with ^{123}I-MIBG and SPECT.[122] Pentavalent ^{99m}TcDMSA has been reported to have a high sensitivity but the results with this tracer have not been reproduced consistently.[138] Anti-CEA scintigraphy appears promising and is undergoing evaluation as are radio-labeled anticalcitonin or antichromogranin A monoclonal antibodies. Other experimental agents include cholecystokinin-B/gastrin-related peptides and ^{99m}Tc-EDDA/HYNIC-TOC.[122] PET imaging with FDG has been shown to be useful to detect metastases and improve identification of involved lymph nodes.[122,123,137]

Therapy

Once a given NET shows avidity on a diagnostic nuclear scan, radionuclide therapy becomes a potential management tool. ^{131}I-MIBG and ^{111}In-pentetreotide have been used as a palliative treatment in currently published series of NET.[123] Newer agents such as ^{90}Y-somatostatin analogs and new protocols are undergoing investigation.[138,139] Combination radionuclide therapy has potential.[123,139] A recent published series of 149 patients with NET who had both ^{131}I-MIBG and SRS, had a significant group in whom there was uptake of both agents, but where some lesions were positive for one agent but not the other agent.[140]

Besides the application of these agents at initial staging, they play an important role in follow up after operation, diagnosis of recurrences usually where there are increasing specific tumor markers and evaluating response to chemotherapy or biological therapy (eg, octreotide). The functional information from scintigraphy is complementary to morphological imaging. New imaging technologies of SPECT/CT and PET/CT improve the diagnostic application of these agents and allows more rapid total body imaging and more precise localization of NET.

Conclusion

Nuclear medicine plays a pivotal role in the management of neuroblastoma, particularly in diagnosis, assessment of treatment response, detection of residual disease, and recurrence but also in therapy. PET with FDG and newer agents also are

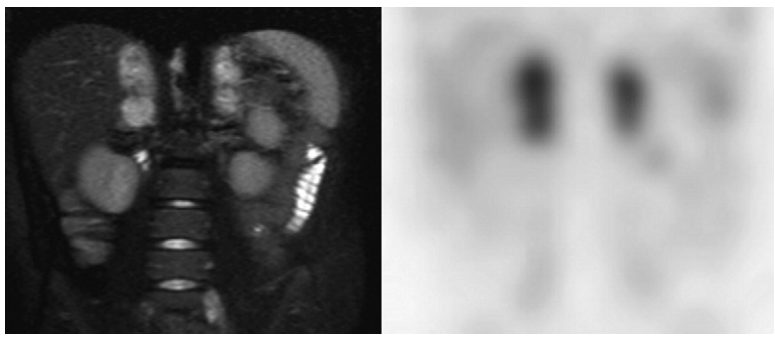

Figure 10 Bilateral phaeochromocytoma in a 10-year-old boy who presented with hypertension. MRI (A, T2 fat suppressed) shows bilateral adrenal masses. The ^{123}I-MIBG study (B, coronal SPECT) confirms marked uptake within the masses, but no other abnormalities were found within the body.

playing an increasing role. Neuroendocrine tumors in the pediatric population are very rare and nuclear medicine techniques again are central to diagnostic evaluation of the disease besides having a limited role in therapy.

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