Imaging in neuroblastoma: An update

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Abstract

Neuroblastoma is the third common tumor in children. Imaging plays an important role in the diagnosis, staging, treatment planning, response evaluation and in follow-up of a case of Neuroblastoma. The International Neuroblastoma Risk Group task force has recently introduced an imaging-based staging system and laid down guidelines for uniform reporting of imaging studies. This review is an update on imaging in neuroblastoma, with emphasis on these guidelines.

Key words: Image-defined risk factor; international neuroblastoma risk group staging system; metaiodobenzylguanidine; neuroblastoma

Introduction

Neuroblastoma (NB) is the most common extracranial solid tumor in children.[¹] It has a perplexing behavior with varied range of presentation and outcome. Some NBs can show spontaneous regression (without any therapy), while some cannot be salvaged even with aggressive therapies including bone marrow transplant (BMT). In order to administer the right treatment to such variedly behaving tumor, NBs need to be assigned a risk status. The risk status is dependent on age of the patient, stage of the disease, histopathology, and multiple biological factors. There has been a recent update in the staging and risk stratification of NB, published in the year 2009, by the International Neuroblastoma Risk Group (INRG) task force.[²] This new staging system is based on imaging and is called the INRG Staging System (INRGSS). The task force has also proposed guidelines to standardize the use of various imaging techniques and reporting.[¹,³,⁴] In this article, we will review the role of imaging in NB, with emphasis on INRGSS and these new guidelines.

Background Information

NB arises from the primordial neural crest cells that form the sympathetic nervous system. The exact etiology of this disease is not yet known. It usually occurs sporadically, only 1-2% of the cases being familial.[⁵,⁶] The most common site of NB is the adrenal gland (40% of the tumors), followed by the paraspinal ganglia in the retroperitoneum (25%), mediastinum (15%), neck (5%), and pelvis (3%).[⁷] Approximately 60-70% of the cases are metastatic at presentation.[⁷] The median age at diagnosis is 22 months.[⁷] About 81.5% cases are diagnosed by the age of 4 years and another 15% by the age of 9 years.[⁹]

A child with NB can present with symptoms, which may be in the form of a lump, or its related mass effects like lower limb weakness due to compression of spinal cord or difficulty in breathing due to an enlarged liver. Symptoms can also be caused by metastatic disease, e.g., skeletal metastases leading to bony pain, orbital wall metastases presenting as Panda sign or Raccoon eyes (due to orbital ecchymoses causing darkening of periorbital tissues).[⁸] Less than 2% of the patients present with paraneoplastic syndrome like profuse diarrhea (due to secretion of vasoactive intestinal peptide) or opsoclonus-myoclonus-ataxia.[⁹]

The treatment and outcome of NB is dependent on risk assessment and stage of the disease. For a long time, the International Neuroblastoma Staging System (INSS) [Table 1] has been routinely used for staging.[¹⁰] This is a post-surgical staging system; hence, it

Table 1: International neuroblastoma staging system

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Localized tumor with gross total resection with or without microscopic residual disease, and identifiable bilateral lymph nodes negative microscopically</td>
</tr>
<tr>
<td>2A</td>
<td>Unilateral tumor with incomplete resection, and identifiable bilateral lymph nodes negative microscopically</td>
</tr>
<tr>
<td>2B</td>
<td>Unilateral tumor with complete or incomplete resection, and microscopically positive ipsilateral nodes but contralateral regional lymph nodes negative</td>
</tr>
<tr>
<td>3</td>
<td>Crosses midline with or without positive regional lymph nodes, or unilateral tumor with positive contralateral regional lymph nodes. Midline tumor with positive bilateral regional lymph nodes</td>
</tr>
<tr>
<td>4</td>
<td>Metastatic disease to distant lymph nodes, bone, bone marrow, liver and/or other organs (except as in 4S)</td>
</tr>
<tr>
<td>4S</td>
<td>Stage 1 or 2 primary tumor with metastases limited to liver, skin, and/or bone marrow (with &lt;10% tumor) in a child less than one year of age</td>
</tr>
</tbody>
</table>

Source: Modified from reference 10

is dependent on the surgical skill set and the infrastructure available at a given hospital. Using this system, the same tumor can be labeled as stage I in a center with good surgical expertise or stage III in another center where such facilities are not available. Hence, INSS can neither be uniformly applied across the globe nor be used in pre-treatment risk stratification. In 2004, NB investigators from the major cooperative groups from North America (Childrens’ Oncology Group (COG)), Europe (Society of Pediatric Oncology European Neuroblastoma Network (SIOPEN)), Australia–New Zealand, Germany, Japan, and China formed the INRG task force and proposed a pre-treatment staging system called the INRGSS. This staging is primarily dependent on cross-sectional imaging, metaiodobenzylguanidine (MIBG) scan, and bone marrow biopsy results, and is discussed further in detail. The risk assessment is further dependent on the INRG stage, age of the patient and biological factors; it segregates the patients into very low, low, intermediate, and high-risk categories. Assessment of risk is not only essential for planning of appropriate treatment but also helps in predicting the outcome of patients - the 5-year event-free survival is more than 85% in very low-risk disease and less than 50% in high-risk disease. INRGSS is not meant to replace INSS but to be used in addition for pre-surgical risk stratification.

Detection and Diagnosis

Screening

Like most cancers, detection of the disease at an early stage has a bearing on the outcome of NB. In addition, the outcome is likely to be even better if the child is younger at the time of diagnosis (less than 18 months). Hence, trials for screening of NB using urinary catecholamine levels were initiated many years ago, Japan being the pioneering country for the same. However, it was found that the NBs detected by this method had good biologic features and probably would have undergone spontaneous regression without manifesting clinically. Two subsequent prospective screening studies showed that screening for NB did not reduce mortality. Hence, currently, screening for NB is not routinely advocated.

Detection

Neuroblastic tumors are usually detected in a symptomatic child, but may sometimes be seen incidentally. For example, one may detect such a tumor on a chest radiograph ordered in a child with suspected pneumonia, when there is posterior mediastinal widening caused by a mass. In a child presenting with a palpable abdominal mass (most common site), the investigation of choice is ultrasound (USG). On USG, NBs are seen as heterogeneous solid masses that often show calcification. When in the adrenal, the mass displaces the kidney inferiorly. The neighboring vessels are also generally encased, stretched, and displaced, rather than infiltrated. There can be associated adenopathy and/or liver lesions. Once a provisional diagnosis of NB is made, a cross-sectional imaging study, computed tomography (CT) or magnetic resonance imaging (MRI), needs to be performed. There is no clear evidence as to which modality is superior, as each comes with its own inherent pros and cons. MRI may be preferred as it is free of ionizing radiation and superior in evaluation of intraspinal and marrow involvement, while CT scan is more widely available and a rapid technique (can avoid sedation) which is superior for detection of calcification within the tumor.

On CT or MRI scan, NB is often seen as a large, lobulated, heterogeneous solid mass displacing the adjacent organs [Figure 1]. When NB occurs in the adrenal, the most important differential diagnosis is Wilms’ tumor (WT). The presence of stippled calcification favors NB and is seen in 85% of abdominal NBs. While NB is likely to displace the kidney inferiorly, WT arises from the kidney. NB tends to be a mass crossing the midline, encasing and displacing vessels, rather than infiltrating them, while a tumor thrombus in the renal vein or inferior vena cava is highly predictive for WT. Conglomerate nodal masses with calcification or a paravertebral mass with intra-spinal extension are suggestive of NB. The other differential diagnosis is that of an adrenocortical carcinoma (ACC), which is rather rare tumor having bimodal distribution with one peak in the first decade of life. It may be difficult to distinguish ACC from NB on imaging; however, ACC often secretes steroids leading to clinical presentation with virilization, Cushing’s syndrome, etc.
in infants. Liver involvement in NB can be in the form of focal lesions or diffuse infiltration causing hepatomegaly and respiratory distress. Lung and central nervous system metastases are extremely rare and show non-specific and varied appearances.[3]

International Neuroblastoma Risk Group Staging System

The INRGSS broadly classifies NB into localized and metastatic cases.[3] The localized disease is further divided into L1 and L2 stages, depending upon the absence or presence of one or more image-defined risk factors (IDRFs, described later), respectively. The type of metastases and the age of the child define the metastatic stages. The presence of special sites of metastases - only liver, skin, or less than 10% of the sampled bone marrow in a child less than 547 days of age (18 months) - classifies the disease as stage MS (the bone marrow involvement should not be appreciable on MIBG scan), while all other types of metastases like the bone/bone marrow or non-regional nodes make the disease stage M. This has been summarized in Table 2.

In INRGSS, multifocal tumor (distinct primaries) needs to be staged according to the site of larger disease. Disease extending into ipsilateral contiguous body compartments is called loco-regional disease and constitutes L2 disease. Ascites and pleural effusion do not categorize as metastatic disease, but need to be mentioned in the report.

There are a few major differences between INSS and INRGSS. The loco-regional disease is divided into three stages in INSS and into two stages in INRGSS. In INSS, extension across the midline makes the disease stage III. In INRGSS, there is no specific importance for midline and even ipsilateral disease can be L2 depending upon the involvement of vital structures. Also, the nodes are categorized as regional or non-regional in INRGSS, rather than ipsilateral, contralateral, or distant. Non-regional nodes include non-contiguous nodal involvement in different body compartments, e.g. abdominal tumor with supraclavicular disease (M stage), while the presence of lower mediastinal nodes in upper abdominal tumor constitutes loco-regional disease (L2).

Local Staging and IDRFs

Twenty IDRFs have been identified based on the known locations of the primary tumor and the adjacent vital structures [Table 3 and Figures 2-5].[3] The use of standardized terminology to assess the status of the adjacent vital organ, as listed in Table 4, is recommended by the INRG Imaging Committee - this should help in reducing inter-observer variability for reporting of neuroblastic tumors.[4]
Metastatic Disease Evaluation

The routine metastatic workup of NB involves tests to identify the common sites of metastases mentioned above. Bilateral bone marrow aspiration and biopsies are mandatory for assessing the involvement of marrow. In addition, Iodine-123 MIBG scintigraphy is also essential for evaluating metastatic disease to marrow and other sites. This scan should ideally be obtained prior to tumor excision.[3]

MIBG scan

MIBG is an aralkylguanidine with a structure similar to norepinephrine (NE) and, therefore, is taken up and stored in tumors of neuroendocrine origin. MIBG uptake is seen in 90-95% of patients with NB (including the primary sites, bone, bone marrow, and lymph nodes).[3] MIBG is labeled with either Iodine-123 (I-123) or Iodine-131 (I-131). I-123 labeled MIBG is preferred over I-131 as it can be
administered in larger doses resulting in a better tumor-to-background ratio. However, I-123 is not universally manufactured, and hence, I-131 MIBG is used in smaller doses for diagnostic purposes. The INRG task force has provided guidelines for MIBG scan technique, patient preparation, drug dosage, image acquisition, and analysis to facilitate high-quality studies and to achieve consistency in interpretation.

Since MIBG is excreted in the urine, the urinary bladder and urinary tract show intense activity. MIBG is normally taken up mainly by the liver; smaller uptake is described in spleen, lungs, salivary glands, thyroid, skeletal muscles, and myocardium [Figure 6A]. Normal adrenal glands are usually not seen, but faint uptake may be visible 48-72 h after injection in up to 15% of cases. Primary tumor with high MIBG avidity appears as a region of increased tracer concentration. Single Photon Emission Computed Tomography (SPECT) may be done to improve the diagnostic accuracy. Use of SPECT-CT allows further improvement in localization because of additional CT component and, thus, increases the specificity.

One unequivocal MIBG-positive lesion at a distant site is sufficient to define metastatic disease. However, an equivocal lesion requires confirmation by another imaging modality (plain radiographs, and if negative, MRI) and/or biopsy. The INRG task force recommends the use of semi-quantitative methods for assessing the tumor burden and response on an MIBG scan. Various scoring methods have been described which basically divide the body into a different number of segments and assign a score depending upon the number of sites involved and
bone scintigraphy is required if the primary tumor does not show MIBG avidity or the tumor has been excised. The metastatic cortical lesions are generally seen as focal hot spots. Blurring at the growth plate with extension of tracer uptake into the metaphyseal region is suggestive of metastatic involvement. An isolated bone uptake should be confirmed by another imaging modality and/or biopsy. PET/CT

The role of 18-fluorodeoxyglucose (FDG) PET/CT is not well defined. Early reports confirmed that NBs are FDG avid. Sharp et al. have shown that PET is superior in depicting localized stage disease, in tumors that weakly accumulate MIBG, and at major decision points during therapy; however, MIBG is superior in the evaluation of metastatic disease. PET scan may be useful in discrepant or inconclusive findings on MIBG scintigraphy/SPECT and morphological imaging. The routine use of FDG PET/CT as a substitute to MIBG is not advocated by the INRG task force. However, it should be noted that I-123 MIBG as recommended by the task force is not universally available and I-131 MIBG is not as sensitive as I-123 MIBG as it is limited by the dose that can be administered. The role of PET/CT needs to be evaluated further in such a clinical scenario, bearing in mind that PET/CT may not be suitable for response evaluation in the bone due to reactive changes.

Somatostatin receptor scintigraphy
Some somatostatin receptors are expressed in the NB tissue. This can be explored to detect NB using radiolabeled somatostatin analogues like indium-111 labeled octreotide, pentreotide, and lanreotide. Tc or Ga labeled somatostatin receptor imaging agents are now used in SPECT or PET studies respectively. There is some evidence that NBs expressing somatostatin receptors are low-risk disease and have better prognosis. SRS may be considered in MIBG-negative tumor.

Table 5 summarizes the investigations in NB.

Response Evaluation

Response assessment to neo-adjuvant therapy is done using cross-sectional imaging for local disease and also with MIBG in high-risk/metastatic disease. The International Neuroblastoma Response Evaluation criteria are shown in Table 6. According to these criteria, the evaluation of response at local site is done using volume calculations and that at metastatic sites should be done using the MIBG scoring systems. Recent evidence suggests that response to therapy in patients with high-risk NB has prognostic significance. Though IDRFs may continue to be present in the post-chemotherapy scan, they do not represent contraindication for surgery.

Surveillance

All patients treated for NB require clinical follow-up along with urinary catecholamine levels and imaging. There is no strict guideline for imaging-based surveillance, though it is limited by the dose that can be administered. The suggested frequency of investigations in localized stage favorable biology disease is about 3 monthly in the first year, followed by 4 monthly in the second year and 6 monthly from the third year onwards. It is more intensive in the high-risk disease, where in addition to cross-sectional imaging, MIBG scan also needs to be performed every 3 monthly for 2 years and 4 monthly in the third year. Bone marrow aspiration and biopsy are usually performed if relapse is suspected.

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Table 5: Imaging work-up in a case of NB\textsuperscript{3,4}

<table>
<thead>
<tr>
<th>Mandatory</th>
<th>Problem-solving</th>
<th>Needs further evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT/MRI (evaluation of loco-regional disease extent)</td>
<td>Bone scan (MIBG non-avid tumor or primary has been excised)</td>
<td>Somatostatin receptor studies</td>
</tr>
<tr>
<td>123I MIBG scan (to look for avidity in the primary and screen for metastatic disease- ideally done prior to excision of primary)</td>
<td>Radiographs/MRI (equivocal focus of metastatic disease on MIBG or bone scan)</td>
<td>Whole body MRI (radiation free tool for marrow metastases)</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>FDG-PET/CT (MIBG non-avid tumors, equivocal lesions especially in soft tissues)</td>
<td>Other radionuclides</td>
</tr>
<tr>
<td>CT chest: For suspected pleural or pulmonary metastases</td>
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<td></td>
</tr>
</tbody>
</table>

Table 6: International neuroblastoma response evaluation criteria\textsuperscript{10}

<table>
<thead>
<tr>
<th>Response</th>
<th>Primary tumor</th>
<th>Metastatic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>No tumour</td>
<td>No tumour, normal catecholamines</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>Decreased by 90%-99%</td>
<td>No tumour, normal catecholamines, Improved bone scan</td>
</tr>
<tr>
<td>Partial response</td>
<td>Decreased by &gt;50%</td>
<td>All sites decreased by &gt;50%, no &gt;1 positive bone marrow sites</td>
</tr>
<tr>
<td>Mixed response</td>
<td>No new lesions; &gt;50% decrease of any measurable lesion (primary or metastatic) with 50% decrease in any other; 25% increase in any existing lesion</td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>No new lesions, &lt;50% decrease but &lt;25% increase in any existing lesion</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>Any new lesion, increase of any measurable lesion by &gt;25%</td>
<td></td>
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Conclusion

Imaging plays a central role in the diagnosis, staging, response evaluation, and follow-up of NB. A thorough knowledge of imaging, use of appropriate scanning technique, and reporting using correct terminology and specific criteria are essential for a radiologist to guide clinical colleagues.

References


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