
Iodine-131-Metaiodobenzylguanidine and Bone Scintigraphy for the Detection of Neuroblastoma

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The purpose of this study was to compare the utility of bone and metaiodobenzylguanidine (MIBG) scintigraphy for the detection of primary and metastatic deposits of neuroblastoma. ^{99m}Tc methylene diphosphonate (MDP) bone and ^{131}I -MIBG scans performed within 1 mo of each other in 85 patients with known or suspected neuroblastoma were evaluated for evidence of skeletal and extraskelatal disease. In 77 of 77 patients with confirmed neuroblastoma, the MDP and MIBG scans were concordant for the presence or absence of skeletal disease. A nearly twofold greater number of skeletal lesions were evident on MIBG scanning. No patients with normal bone scans had MIBG studies indicating bone involvement. In patients with histologic evidence of bone marrow involvement, each study suggested skeletal lesions in approximately 70%. In patients with extraskelatal disease demonstrated by CT, there was soft-tissue uptake of MIBG in 80% and MDP in 39%. We conclude that both MIBG and MDP are useful for the detection of skeletal neuroblastoma. MIBG is the better agent for characterizing the extent of disease, and MDP is a valuable adjunctive agent that provides skeletal landmarks for comparison. MIBG is clearly superior for the detection of extraskelatal neuroblastoma.

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Neuroblastoma is the most common extracranial malignancy of childhood. It frequently metastasizes to bone, and patients often present with disseminated disease. Skeletal scintigraphy has long been used as the procedure of choice to assess bony involvement (1-5). However, the skeletal manifestations of metastatic neuroblastoma can be subtle and interpretation of the bone scan requires high quality images obtained with great attention to technique. In addition, soft-tissue deposits of neuroblastoma also frequently accumulate bone-seeking agents (6-10).

The detection of neuroblastoma deposits has been greatly facilitated by the development and application of the radiopharmaceutical metaiodobenzylguanidine (MIBG), an in-vivo radiotracer for the sympathetic nerv-

ous system and tumors derived from it. MIBG, labeled with either ^{131}I or ^{123}I , has been shown to be highly sensitive and specific for the localization of neuroblastoma (11-17).

Controversy persists as to the need for both MIBG and bone scanning in routine evaluation (18,19). Recent studies suggest that the use of ^{123}I -MIBG alone would somewhat underestimate the number of patients with skeletal involvement (18,19). The purpose of our study was to compare the utility of the more widely available ^{131}I -MIBG scintigraphy with bone scanning for the detection of skeletal and extraskelatal deposits of neuroblastoma.

METHODS

Patients

The subjects of this study were 85 patients with known or suspected neuroblastoma who underwent bone and MIBG scans within 1 mo of each other. Patients were classified into stages using the Evans criteria (20).

Scintigraphy

1. Bone scans were performed 2 hr following the intravenous injection of 15 mCi ^{99m}Tc -MDP per 1.7 square meters, adjusted to body surface area. Whole-body images and/or spot views were acquired using a Technicare Omega gamma camera interfaced to a portable computer.
2. MIBG scintigraphy was performed as previously described (21,22). Images were obtained one, two and three days following the intravenous administration of 0.5 mCi ^{131}I -MIBG per 1.7 square meters and adjusted to total surface area. Overlapping views from the skull to the feet were acquired for 20 min or 100,000 counts, whichever came first.

Images were reviewed by two observers (BLS, BS). All lesions were marked on standardized body maps for subsequent comparison.

Bone Marrow Examination

Bone marrow aspirates and biopsies were done from posterior iliac sites using standard procurement techniques. Smears of the aspirated marrow were immediately prepared and then stained with Wright-Giemsa stain. Two to four of the stained coverslips were scanned for tumor clumps in each patient. Biopsy specimens were fixed in B5 fixative, decalcified, sectioned at three levels and stained with hematoxylin and eosin. Multiple sections from each level were reviewed for evidence of tumor infiltration.

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RESULTS

Of 85 patients examined, 77 were ultimately shown to have neuroblastoma. Eight were eventually shown to have neoplasms other than neuroblastoma. These were adenocarcinoma of unknown primary, rhabdomyosarcoma, primitive neuroectodermal tumor (three subjects), myofibroma, Hodgkin's disease and non-Hodgkin's lymphoma. Forty patients were examined more than once. In such cases, only the first set of studies was included in this evaluation.

Of the 77 patients with neuroblastoma, 41 were seen at the time of diagnosis (D group) before therapy was initiated, and 36 at various times of follow-up from 1 wk post-resection to 11 yr after the original presentation (F group). Of the 41 seen at the time of diagnosis, 1 patient had Stage I disease, 9 Stage II, 10 Stage III and 21 Stage IV. In the follow-up group of 36 patients, at the time of initial presentation, there were 2 patients with Stage I disease, 6 with Stage II, 6 with Stage III, 21 with Stage IV and 1 with Stage IVs.

Skeletal Lesions

Patients with Tumors Other than Neuroblastoma. Abnormal skeletal deposits of MDP consistent with metastatic disease were found in three patients (12 foci). None of these accumulated MIBG.

D Group (Fig. 1). Of 41 patients, 24 had both normal bone and MIBG studies upon presentation. In the other 17 subjects, the bone scan was abnormal in 17, and the MIBG was abnormal in 16. In the single patient with an abnormal bone scan yet normal MIBG study, the abnormal accumulation of MDP was due to a recent bone marrow biopsy. In 16 patients, both the MIBG and MDP scans indicated skeletal involvement. The MIBG studies tended to show greater numbers of lesions and more widespread disease (Fig. 2). When >10 lesions were present, precise quantitation was subject to greater interobserver variability and is thus not reported. There were seven patients with >10 MIBG deposits. In two of these seven, the number of abnormal foci on bone scan was >10 (Fig. 3). In the other 5 patients whose MIBG studies showed >10 skeletal lesions, there were 4, 6, 6, 8 and 9 abnormal foci depicted by bone scanning. There were no patients with >10 abnormal MDP deposits who had 10 or fewer on MIBG. In the remaining 9 patients with 10 or fewer lesions on both bone and MIBG scans, there were 51 abnormal deposits of MIBG and 27 abnormal deposits of MDP. Then, excluding the 2 patients with >10 abnormal deposits on both MIBG and bone scans, more lesions were found on MIBG scan than bone scan in 10 patients, more on bone than MIBG in 3 patients, and equal numbers of lesions in both studies in 1 patient.

Thus, in 41 of 41 patients, bone and MIBG scanning were in agreement for the presence or absence of skeletal disease, but more lesions were depicted by MIBG.

F group (Fig. 4). Of 36 patients, 23 had both normal

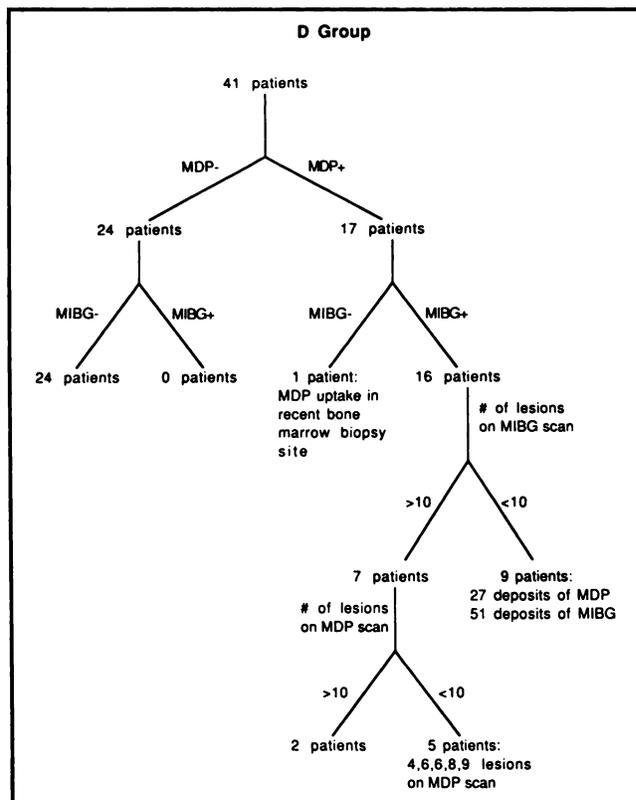


FIGURE 1. Diagram of patients studied at the time of diagnosis (D group). Patients are initially classified by the results of the bone scan (either negative or positive for bone disease), and then by the results of the MIBG scan. Although more lesions were detected by the MIBG scan, both studies were remarkably congruent for determining the presence or absence of bony metastases.

bone and MIBG studies. Of the remaining 13 patients, each had abnormal skeletal scintigraphy. In one of these, MIBG scintigraphy was negative and MDP accumulations were due to prior surgery. Of the other 12 subjects with abnormal MDP scans, 2 had >10 lesions on MIBG scanning, one of which also had >10 abnormal foci on bone scan, and the other only 2. Considering the 10 patients with bone disease due to neuroblastoma and in whom both MIBG and bone scintigraphy showed 10 or fewer lesions, there were 45 skeletal deposits of MIBG and 31 of MDP. In these same 10 subjects, MIBG scanning showed more abnormal foci than MDP in 6, MDP showed more than MIBG in 2, and equal numbers in 2. Thus, in 36 of 36 patients, MIBG and MDP studies agreed as to the presence or absence of skeletal disease. As before, MIBG tended to show more widespread involvement.

Bone Marrow Involvement by Aspiration/Biopsy

Both studies were relatively ineffective in assessing bone marrow involvement.

D Group. Of the 21 patients with Stage IV disease, 14 had histologic evidence of bone marrow disease. In these 14 patients, MIBG and MDP scans showed bony involvement in 12 (sensitivity 86%). However, there were two

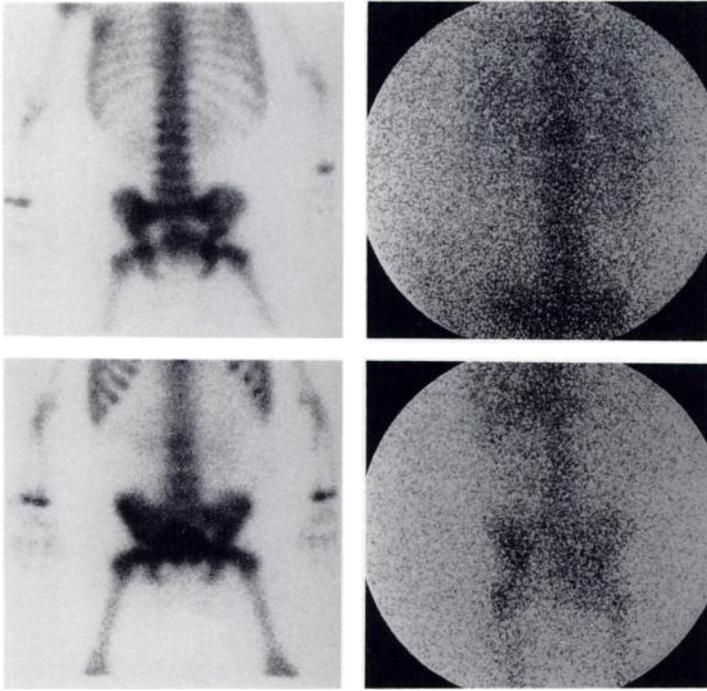


FIGURE 2. Posterior (upper panels) and anterior views (lower panels) of the bone scan (left) and 48-hr MIBG scan (right) of a 2-yr-old girl with Stage IV neuroblastoma and bone marrow involvement. The bone scan shows mildly increased uptake in the iliac wings and effacement of the proximal femoral growth plates bilaterally, but the spine appears unremarkable. The MIBG scan shows uptake throughout the spine, pelvis, and femurs. The extent of bony disease in this patient is considerably underestimated by the bone scan.

patients with bone marrow disease in whom both MIBG and MDP scintigraphy were normal. Of the seven patients with Stage IV neuroblastoma, three had normal MIBG and bone scans, while the other four had bony involvement depicted by both studies (specificity 43% in Stage IV, overall 85% in D group).

F Group. Of 22 patients with Stage IV or IVs disease on original presentation, 19 had bone marrow examinations at the time of the MIBG and bone scans. Eight showed neuroblastoma in the bone marrow. In these eight, both the MIBG and MDP scans showed bone involvement in three (sensitivity 38%). In the 11 patients whose bone marrow did not show neuroblastoma, both bone and MIBG scans indicated bony metastases in five, while in the other six neither study found bone involvement (specificity 55% in Stage IV, overall 80% in F group).

Soft Tissues

Patients with Tumors Other than Neuroblastoma. Each of the eight patients had soft-tissue masses, only one of which faintly accumulated MIBG and none accumulated MDP (23).

D Group. Forty of the 41 patients studied at the time of diagnosis had concurrent CT scans for comparison. Each of these 40 subjects had one or more extraskelatal deposits of neuroblastoma visible on CT scanning. In 34 (85%), MIBG scanning detected soft-tissue involvement, while bone scanning showed extraskelatal uptake in only 19 (47%) (Fig. 5). Overall, there were 39 soft-tissue deposits on MIBG scanning and 20 on bone scanning.

F Group. Twenty-nine of the 36 patients studied at follow-up had concurrent CT scans for comparison. In seven patients, there was no evidence for residual or re-

current extraskelatal disease by CT, MIBG, or bone scintigraphy. In 22 of the 29 patients, there was residual/recurrent neuroblastoma seen by CT scanning. One of the patients with CT evidence of recurrence, whose MIBG and bone scans did not show soft-tissue uptake, was ultimately found to have a mature ganglioneuroma rather than neuroblastoma. In 15 of the remaining 21 patients, MIBG scanning also showed the extraskelatal neuroblastoma (71%), while in only 5 patients (24%) did bone scanning locate the extraskelatal disease. Overall, there were 32 soft-tissue deposits of MIBG and 9 of MDP.

DISCUSSION

Scintigraphy has long played a critical role in evaluating the extent of disease in patients with neuroblastoma. Multiple bone-avid agents have been shown to localize in neuroblastoma deposits in quantities sufficient to permit imaging. These include ^{18}F , $^{99\text{m}}\text{Tc}$ -polyphosphate, $^{99\text{m}}\text{Tc}$ -diphosphonate, $^{99\text{m}}\text{Tc}$ -pyrophosphate, $^{99\text{m}}\text{Tc}$ -methylenediphosphonate and ^{67}Ga -citrate (1-10,17,24). Bone scans were shown subsequently to be significantly more sensitive than radiologic skeletal surveys for the detection of osseous metastases (2,4,5).

MIBG was first used to detect neuroblastoma in 1984 and its use has become increasingly widespread (25). MIBG localizes in both primary and secondary (most often bone and bone marrow) deposits. MIBG uptake is relatively specific for tissues of the sympathetic nervous system and related tumors, and MIBG scintigraphy provides the opportunity to evaluate primary and metastatic deposits by means of a single procedure. The normal uptake of MIBG in the extremities is faint and reflects the distribu-

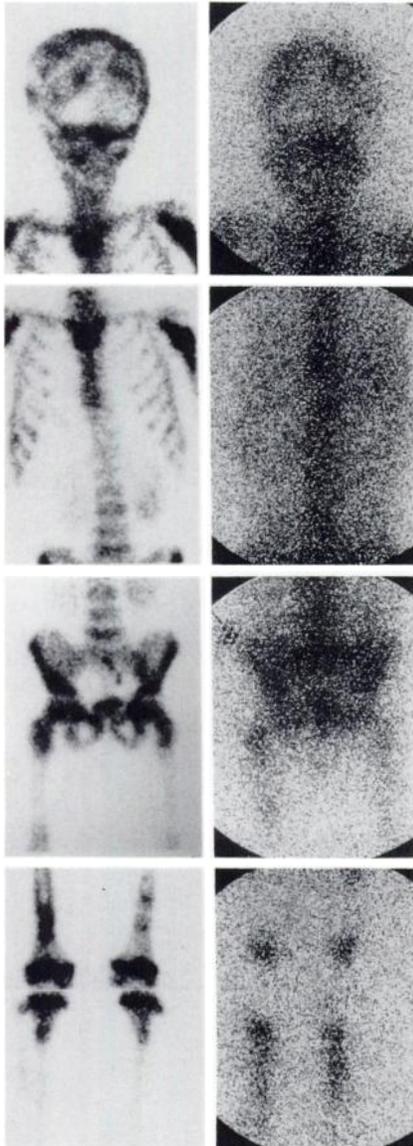


FIGURE 3. Anterior views from the bone scan (left) and 48-hr MIBG scan (right) of a 1-yr-old girl with Stage IV neuroblastoma and bone marrow involvement. Patchy, irregular uptake of MDP is evident in the skull, proximal humeri, ribs, pelvis, femurs and tibia. There is diffuse uptake of MIBG within most of the axial and appendicular skeleton. The extensive bony metastases are well illustrated by both studies.

tion of skeletal muscle (26). Skeletal involvement of neuroblastoma may be focal, diffuse or both. Differing patterns of uptake of MIBG within bone distinguish discrete skeletal metastases and bone marrow infiltration (18,24,27).

It has been suggested that MIBG scintigraphy may obviate the need for routine skeletal scintigraphy in neuroblastoma due to the ability of MIBG to detect both soft-tissue and skeletal lesions (16). Gordon and colleagues using ^{123}I -MIBG, however, showed that MIBG scintigraphy without bone scintigraphy may underestimate the prevalence of bone involvement (18). The current study, using ^{131}I -MIBG, revealed that for patients studied at the time of diagnosis, MIBG scintigraphy and bone scanning are remarkably equally effective in determining the presence or absence of bone involvement. When bone involvement was present, MIBG scanning detected nearly twice as many skeletal lesions as did bone scanning. On the other hand, the precise documentation of individual foci

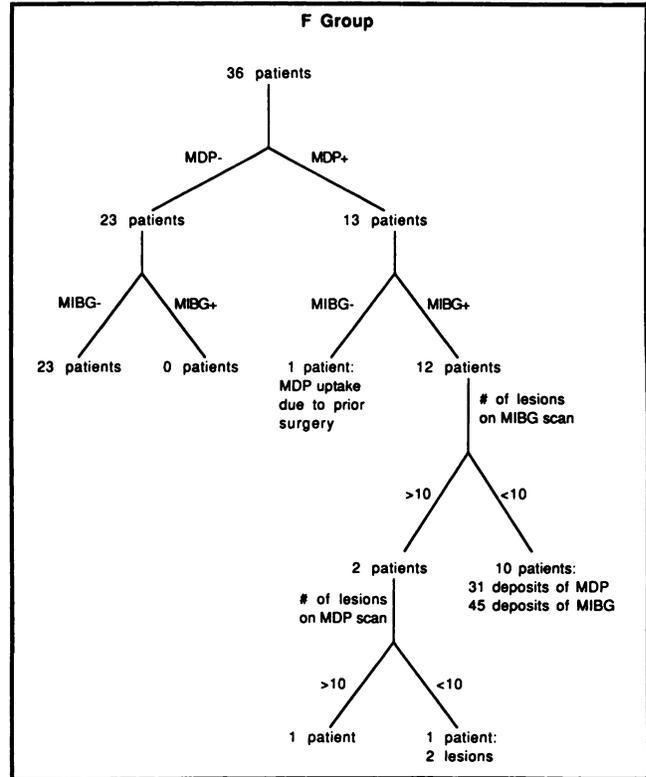


FIGURE 4. Diagram of patients studied at various intervals of follow-up (F group). Patients are initially classified by the results of the bone scan (either negative or positive for bone disease), and then by the results of the MIBG scan. As also shown for patients studied at diagnosis, both studies were remarkably congruent for determining the presence or absence of bony metastases.

of disease in this context is less important for staging purposes than whether or not a study demonstrates *any* abnormal skeletal deposits. In this group, either study was sufficient for staging purposes. In patients seen at various stages of follow-up, similar results were obtained.

Bone involvement is more readily recognizable on MIBG studies than with bone scintigraphy. The normal distribution of MIBG about bony structures is low, diffuse muscle background activity. There is no discrete accumulation of MIBG by the bone. The detection of bone involvement by bone scanning is more challenging due to the normal, intense uptake of bone seeking agents in the bone, in particular the growth plates of children who do



FIGURE 5. Bone (left), 48-hr MIBG (center) and CT scans (right) of a 1.5-yr-old girl with Stage II neuroblastoma. There is intense accumulation of both tracers by the posterior mediastinal neuroblastoma, depicted by the arrow on the CT image.

not have marrow disease. The symmetry of bone infiltration by neuroblastoma makes the detection of subtle involvement by bone scintigraphy especially difficult. Indistinctness of the epiphyses and increased uptake in the diaphysis often indicate bone metastases. Great attention to patient position and other technical details are necessary for accurate evaluation of the growth plates and diaphyses. The MIBG study is somewhat more tolerant to the problems of precisely positioning ill, sometimes uncooperative children, since "hot" spots against a cold background are much more readily recognized than against the warm, nonuniform background of the developing skeleton.

In patients with Stage IV disease, neither study was reliable in determining bone marrow involvement. This may be due in part to the sampling errors introduced by using only two sites to histologically assess bone marrow. In addition, bone marrow involvement does not necessarily indicate cortical bone involvement, nor does cortical bone involvement always indicate bone marrow infiltration. Although not examined as part of this investigation, marrow scintigraphy with ^{99m}Tc -colloids may be helpful in cases with equivocal or normal bone scintigraphy (5). The presence of tumor deposits in the marrow may also be revealed by abnormal signal characteristics on magnetic resonance imaging (28). The latter modality is expensive and impractical for routine screening.

Despite the specificity of the underlying mechanism for tumor localization, there are disadvantages to the use of ^{131}I -MIBG for the detection of neuroblastoma. These include long imaging times due to low photon flux and low detection efficiency for the highly energetic emitted gamma photon, leading to poor image quality and the necessity for serial imaging over several days. The poor dosimetry limits the dose to 0.5–1.0 mCi/1.7 square meters. Nonetheless, we have found this agent to be as effective as bone scanning for determining the presence or absence of bone disease, more effective in defining the extent of disease and superior for detecting extraskelatal involvement. MIBG labeled with ^{123}I provides high quality images but, as shown previously, results in an important number of false-negative examinations. Indeed, the approach with longer imaging times and delayed images is likely responsible for the good results we have observed using ^{131}I -MIBG, despite its suboptimal physical and dosimetric characteristics. Iodine-131-MIBG is readily available, may be stored for up to two weeks before administration and permits prolonged imaging up to seven days (29). Disadvantages of bone scanning include its relative insensitivity for determining the extent of disease, the propensity for neuroblastoma to metastasize to the region of the MDP-avid growth plates, the necessity for meticulous attention to detail and scanning technique in patients who may be unable to cooperate or understand the procedure and the lack of specificity. The latter was well illustrated by the positive bone scans observed in patients who proved to have tumors other than neuroblastoma and

in the two patients with false-positive findings due to prior surgery or marrow biopsy.

For the detection of soft-tissue disease, MIBG is clearly superior to MDP. Previous studies have shown the incidence of extraskelatal neuroblastoma accumulating ^{99m}Tc bone-seeking tracers ranges from 60% to 74% (4,9,10). Although uptake of MDP into a soft-tissue mass in a child is highly suggestive of neuroblastoma, absence of uptake does not rule out neuroblastoma. We found that of patients with soft-tissue masses visible on CT scanning, 85% studied at initial presentation and 71% at follow-up had lesions which accumulated MIBG, while only 41% and 24%, respectively, had MDP-avid extraskelatal neuroblastoma. MIBG is thus clearly superior to bone-seeking agents for the localization of extraskelatal neuroblastoma. Nevertheless, there was a small but important number of cases with false-negative findings by MIBG scintigraphy for neuroblastoma in whom CT revealed soft-tissue deposits clinically believed to represent neuroblastoma. Although MIBG may not replace anatomic techniques, it does permit the noninvasive characterization of suspected neuroblastoma with a high specificity.

We conclude that in the evaluation of neuroblastoma, scintigraphy using ^{131}I -MIBG is superior to ^{99m}Tc -MDP. Iodine-131-MIBG studies depict more bone lesions than do conventional bone scans and far more soft-tissue deposits. Nonetheless, bone scintigraphy remains valuable in the routine evaluation of neuroblastoma and provides skeletal landmarks for better localization of abnormal foci of MIBG accumulation.

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