

# Does I-131-MIBG underestimate skeletal disease burden in neuroblastoma?

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## ABSTRACT

**Background:** Controversy persists as to the need for both MIBG and bone scanning in routine evaluation of neuroblastoma.

**Aim:** To compare the efficacy of I-131- metaiodobenzylguanidine (MIBG) scan against that of conventional Tc99m- methylene diphosphonate (MDP) bone scan for the detection of skeletal deposition of neuroblastoma.

**Methods and Material:** The study included 57 patients (36 boys, 21 girls: age range 1-14 years) of neuroblastoma who underwent both bone scan with Tc99m-MDP and I-131-MIBG scan within 15 days of each other at presentation and during follow-up.

**Results:** At presentation 11(19.2%) patients had evidence of skeletal metastases on MDP scan against 7 patients who showed bony secondaries on MIBG scan. Of the 7 patients, with positive MIBG and MDP scans, MDP scan detected 11 sites whereas MIBG scan detected 7 sites. On follow-up study, 3 patients with initial abnormal MDP scan but normal MIBG scan, developed skeletal metastases detectable on MIBG scan, whereas 3 of the 46 patients who had normal MDP and MIBG scan at presentation; developed skeletal metastases detectable on MDP scan. MIBG scan was concordant in 2 of them but was normal in the third patient.

**Conclusion:** I-131-MIBG underestimates skeletal disease burden in neuroblastoma. Therefore, Tc99m-MDP bone scan should remain a part of routine assessment of patients with neuroblastoma.

**KEY WORDS:** Neuroblastoma, Tc99m-MDP bone scan, I-131-MIBG, Metastases.

Neuroblastoma is the second most common solid tumour in childhood and frequently metastasises to the bone marrow and bone matrix and many times patients present with distant metastases.<sup>1</sup> Skeletal scintigraphy has long been used as the procedure of choice to assess bony involvement in diseases of diverse aetiology including neuroblastomas.<sup>2,3</sup> The detection of neuroblastoma deposits has been facilitated by the development and application of the radiopharmaceutical metaiodobenzylguanidine (MIBG) labelled with <sup>131</sup>I or <sup>123</sup>I, which localizes in both primary and secondary deposits of neuroblastoma.<sup>4</sup> Controversy persists as to the need for both MIBG and bone scanning in routine evaluation of neuroblastoma.<sup>5-7</sup> The purpose of our study was to compare the utility of the I-131-MIBG scan with conventional Tc99m-MDP (Methyl Diphosphonate) bone scan for detection of skeletal deposition of neuroblastoma.

## Methods and Materials

**Patients:** This prospective study included fifty-seven patients (36 boys, 21 girls: age range 1-14 years) of neuroblastoma who underwent both bone- and MIBG- scan within fifteen days of each other at presentation and during follow-up between 1999 to April 2004. Patients were classified into various stages using the International Neuroblastoma Staging System (INSS). These patients were enrolled in the study only after obtaining informed consent from legal guardians of the

subjects.

**Scintigraphy:** Bone scan was performed 3 hours after intravenous administration of 185–1000MBq (5-27 mCi) of Tc99m-Methylene diphosphonate (Tc99m-MDP) using a dual head gamma camera fitted with low energy high resolution collimator (Varicam and MillenniumVG, General Electric, Milwaukee, USA). The dose was calculated on the basis of the patient's body surface area [adult dose of 1,000MBq/1.73m<sup>2</sup>]. Whole body acquisition was done using step and shoot method with 180 seconds per view. For any spinal lesion single photon emission computed tomography (SPECT) of the involved vertebra was performed.

MIBG scintigraphy was performed 48 and 72 hours after intravenous administration of 7.4-18.5 (0.2- 0.5 mCi) of I-131-Metaiodobenzyl Guanidine. Overlapping views from skull to feet were obtained for 20 minutes or 100,000 counts / view; whichever came first using a single head gamma camera equipped with a high-energy parallel-hole collimator (Orbitar, Siemens, Germany).

**Quality Assurance of MIBG And Tc99m-MDP:** Quality control studies for I-131-MIBG were performed by the manufacturer (Radio Pharmacy division, Board of Radioisotope and Technology, Government of India) by high-pressure liquid chromatography (HPLC) method and were certified to have more than 90% radiochemical purity at room temperature after thawing, when stored in a dry ice container. Any preparation that did not conform to this specification was not used.

Quality control of MDP preparations was performed at our laboratory by instant thin layer chromatography (ITLC) after every preparation of Tc99m-MDP to check the percentage of MDP molecule labelled by Tc99m. Any preparation with less than 98% labelling was discarded.

Data Analysis: Two experienced nuclear medicine physicians evaluated both sets of scans independently and both of them were blinded to findings of other investigations but were aware of primary disease and its location. All lesions were marked on standardized body maps for subsequent comparison.

Statistical analysis: Chi-square test was performed to assess any significant association between Tc99m-MDP bone scan and I-131-MIBG scan findings. A p value of <0.05 was considered statistically significant.

### Result

Of the fifty-seven patients, eleven (19.2%) patients had evidence of skeletal metastases at presentation on MDP bone scan. Out of these eleven patients with bone scan evidence of skeletal metastases; four had a normal MIBG scan for skeletal metastases. Of the seven patients, where both MIBG and MDP scan suggested skeletal metastases, MDP scan detected eleven sites whereas MIBG scan detected seven sites. Number of lesions was identical in both MDP and MIBG scan in three patients (Figure 1a, b).

On follow-up study (mean of 8.5 months after initial study) 3 patients with abnormal MDP scan but normal original MIBG scan, developed skeletal lesion that was detected by MIBG scan at the sites of abnormal MDP accumulation.

Three of the 46 patients who demonstrated no skeletal

metastases initially on MDP and MIBG scans, developed skeletal lesions which were detected on MDP scan on follow up. Follow-up studies were carried out at a mean of 8.5 months after the initial study MIBG scan was concordant in 2 of them but was normal in the third patient.

There was no statistically significant difference between MDP bone scan and MIBG scan for detection of skeletal metastases at presentation and even during follow-up studies (Table 1). However the number of patients with skeletal metastases is very small (n=14) for any meaningful statistical analysis.

### Discussion

Radionuclide scintigraphy using various agents such as F-18, Tc99m-pyrophosphate, Tc99m-methylene diphosphonate and Gallium-67 has played a critical role in the evaluation of skeletal involvement in patients with neuroblastoma.<sup>8-10</sup> MIBG that is taken up specifically by the tissues of sympathetic nervous system and related tumours, has been shown to localize in both primary tumour and secondary deposits of neuroblastoma.<sup>11</sup> It has been suggested that MIBG scan may obviate the need for routine skeletal scintigraphy in cases of neuroblastoma since it can detect both soft tissue and skeletal lesions. However, this view has not been accepted universally. Although Shulkin

Table 1: showing the comparison of Tc99m-MDP bone scan and I-131-MIBG scan for detection of skeletal metastases at presentation and during follow-up.

	MDP bone scan	MIBG scan	P value
Positive scan at presentation	11	7	0.34
Positive scan at follow-up	14	9	0.24



Figure 1a: Showing increased Tc99m-MDP uptake over right frontal bone (arrow 1), left parietal (arrow 2), and left supra orbital margin (arrow 3) in a 11 Year old boy

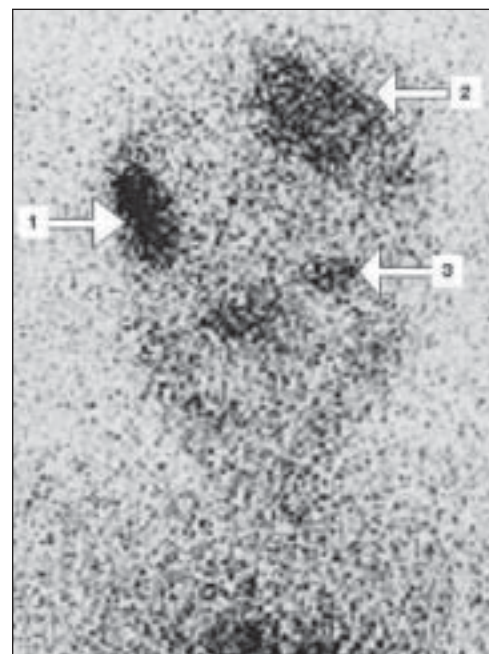


Figure 1b: Showing increased I-131-MIBG uptake over right frontal bone (arrow 1), left parietal (arrow 2), and left supra orbital margin (arrow 3) in the same patient

et al reported that I-131-MIBG scan detects twice the number of skeletal lesions when compared with MDP bone scan.<sup>7</sup> Gordon et al showed that I-123-MIBG scan tends to underestimate the prevalence of bone involvement when compared to MDP bone scan.<sup>6</sup> The current study, using I-131-MIBG, reveals that at the time of diagnosis, MDP bone scan is more sensitive than I-131-MIBG scan in determining the presence or absence of bone involvement. When bone involvement was present, bone scan detected more lesions than MIBG scan. Moreover, MDP scan could detect skeletal metastases earlier in their stage of development than MIBG scan.

Precise documentation of individual foci of tumour deposit is less important for staging purpose than whether or not skeletal deposition is present.<sup>12</sup> High quality Tc99m-MDP bone scan images are required if the skeletal metastases of neuroblastoma, which generally develop in the metaphyses of long bones, are to be detected. Skeletal involvement in neuroblastoma can be focal or diffuse and sometimes bilaterally symmetrical. These abnormalities can be identified with experience on MDP bone scan only with meticulous attention to technical details. Disadvantages of bone scan include the physiological uptake in the growth plate of children, difficulty in detecting bilaterally symmetrical bone involvement and the lack of specificity for neuroblastoma. With good imaging techniques and experience, skeletal involvement of neuroblastoma can be detected with confidence on MDP bone scan. In the present study, it was observed that in patients with abnormal bone scan but normal MIBG scan, MIBG scan became abnormal during follow up period. This suggests that bone scan can detect skeletal metastases from neuroblastoma earlier than MIBG scan.

It has been suggested that MIBG may be a more sensitive tracer since it is specifically taken up by adrenal medulla and by tumours arising from adrenal medulla but not by normal bone. Therefore, bone involvement should be more readily detectable by MIBG scan. Despite the specificity of the underlying mechanism for tumour localization, there are disadvantages in the use of I-131-MIBG for the detection of skeletal involvement by neuroblastoma. These include longer imaging time (typically more than 20 minutes/view) due to low photon flux and low detection efficiency of sodium-iodide (TI) crystal for the 364 KeV gamma photon, leading to a poor image quality and the necessity of imaging the patient up to 72-96 hours post-injection. The higher radiation burden per unit activity injected limits the permissible dose to 0.5-1.0 mCi/1.73 square meter body surface area. Pre-scan and post scan thyroid blockade with potassium iodide for up to seven days is required to prevent free I-131 from entering the thyroid gland. Despite this protection, up to 64% of patients develop thyroid dysfunction.<sup>13</sup> Moreover, many drugs like beta-blockers, calcium channel blockers, tricyclic anti-depressants, reserpine, amphetamine and related compound interfere in the uptake and storage of MIBG.<sup>14-15</sup> However, in our study drug interference was unlikely to be a significant contributing factor for the false negative MIBG studies as the referring paediatric oncologists were advised to discontinue any drugs known to interfere with MIBG uptake or storage, 72-94 hours prior to administration of MIBG

till the completion of imaging and substitute them with alternative non-interfering drugs.

A review of literature suggests a complementary role for MIBG and MDP for evaluation of patients with neuroblastoma. Turba et al evaluated twenty-two patients of stage-IV neuroblastoma and concluded that 99mTc-MDP scan is necessary to fully assess bone involvement at diagnosis but MIBG scan is more suitable for monitoring response to therapy.<sup>10</sup> Sautter-Bihl et al evaluated twenty-three patients with both MDP and MIBG and concluded that MIBG alone may fail to visualize all skeletal involvement of neuroblastoma and should therefore be complemented by additional Tc99m-MDP scintigraphy.<sup>3</sup> Gordon et al evaluated 44 patients with both MDP and MIBG and concluded that underassessment of skeletal involvement by neuroblastoma occurs with I-123-MIBG scans and that one should not substitute I-123-MIBG for 99mTc-MDP bone scans in the staging of neuroblastoma.<sup>6</sup> Shulkin et al evaluated seventy-seven patients with both MDP and MIBG and concluded that MIBG is the better agent for characterizing the extent of disease and MDP is a valuable adjunctive agent that provides skeletal landmarks for comparison.<sup>7</sup> Parisi et al evaluated twenty patients with both MDP and MIBG and concluded that MIBG is the more efficacious agent for the scintigraphic evaluation of neuroblastoma.<sup>16</sup> Hadj-Djilani et al evaluated twenty patients with bone scan and MIBG and concluded that MIBG demonstrates more lesions than bone scan.<sup>17</sup> Hibi et al evaluated ten patients with abdominal neuroblastoma with I-131-MIBG and 99mTc-HMDP bone scan and concluded that I-131-MIBG detected metastatic lesions not predicted by 99mTc-HMDP and reflected tumour progression more sensitively than other known tumour markers such as urinary vanillylmandelic acid (VMA), homovanillic acid (HVA), serum neuron-specific enolase (NSE) and ferritin.<sup>18</sup> Bouvier et al evaluated thirty-five patients with bone scan and MIBG and reported that MIBG and bone scans are similar in the sensitivity (87.5%) for detection of skeletal metastasis but MIBG is much more specific (100%) than bone scan (81%).<sup>19</sup> However, their study included ten false negative MIBG studies, five of which were positive on bone scan. They recommended that the optimal procedure for the diagnosis of neuroblastoma, its extent and follow up, MIBG scan must be performed first; in case it does not demonstrate anything, then bone scan will greatly contribute to the diagnosis.

Findings of our study are in accordance with other reported studies in literature. In our study four of the eleven patients (36.3%) with skeletal metastases were missed on I-131-MIBG during initial staging (Figure 2a, b). The reason for higher number of lesions being detected on bone scan could be due to the fact that nearly 20 times higher dose of tracer is injected during bone scan compared to I-131-MIBG scan. During follow up, bone scans can remain positive for more than 6 months during the healing process while MIBG scan is only positive with viable functioning deposits.

Underassessment of disease is not unique to I-131-MIBG; Gordon et al also reported underassessment of skeletal disease burden using I-123-MIBG.<sup>6</sup> Hence our study raises concern

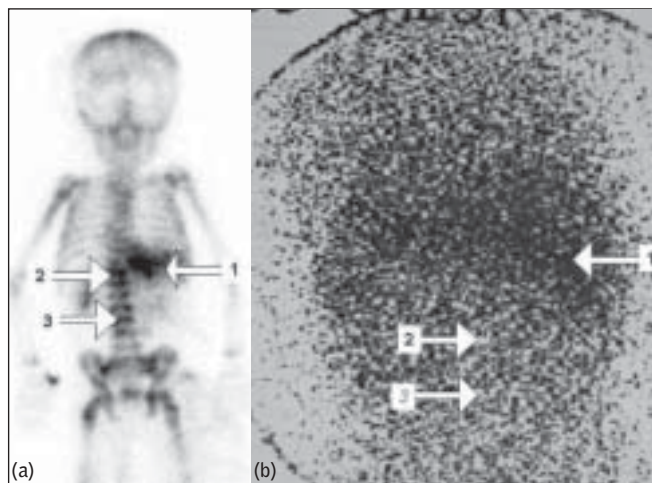


Figure 2: (a) Showing increased Tc99m-MDP uptake over, eighth thoracic to fourth lumbar vertebra (arrow 2 and 3). Primary tumour in the right adrenal gland is also showing tracer accumulation (arrow 1). (b) Corresponding slice of I-131-MIBG scan does not show any tracer accumulation over the corresponding sites (shown by arrow 2-3). Only the primary tumour in the right adrenal gland is showing increased tracer accumulation (arrow 1)

about the current trend of replacing bone scan with a MIBG scan.<sup>20-21</sup> Based on our findings, it could be recommended that Tc99m-MDP bone scan should remain a part of routine assessment of patients with neuroblastoma.

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## Expert's Comments

### Neuroblastoma: Role of bone imaging

Since the introduction of technetium-99m phosphates in 1971 by Subramanian et al, scintigraphy has become a reliable method to detect bone lesions, and has been shown to be far superior to X-ray in its simplest form, or to CT.<sup>1,2</sup> The bone is made up of minute, 50 to 400 angstrom size, hydroxyapatite crystals consisting of calcium, phosphate, and hydroxyl ions. The main difference between X-ray and scintigraphic techniques is that the former detects local bone calcium content and the latter indicates local calcium turnover rate. Irrespective of the cause, normal bone response is to repair the damage. It takes a long time to cause nearly 30% loss of local calcium before the difference between the lesion and normal bone becomes obvious on X-ray, where as the increased calcium

turnover rate at the local site of injury begins almost immediately, as early as 24 hours after injury. Because of slow calcium loss, only about 50 to 60% of bone lesions may be seen on routine bone X-ray.<sup>3</sup> A stress fracture seen with scintigraphy may never become positive on an X-ray if there is not enough demineralization around the lesion. Because of its dependence on increased calcium turnover rate, bone scan maintains a very high sensitivity for both benign and malignant lesions except in case of multiple myeloma, where calcium turnover rate remains very low, resulting in a false-negative bone scan.

Although the distribution pattern of bone lesions may help to identify the aetiology of a few of the benign and malignant

lesions, for example, Pagets disease or metastatic prostate cancer, scintigraphy, in general, lacks specificity. It cannot differentiate benign from malignant bone lesion in most cases, especially when there are only one or two bone lesions in the beginning. In patients with two or more primary malignancies, i.e. breast and lung in women or lung and prostate in men, scintigraphy fails to identify the source of bone malignancy. This is true also for X-ray, CT and MRI. Investigators have been working for more than 30 years to identify the technique that will provide specific information. Radio-labelled monoclonal antibodies were thought to provide such information, but they have so far failed to meet the expectations. There is interest in using receptor-specific small peptides that would overcome the disadvantages of the development of antihuman antibodies against monoclonal antibodies (HAMA).

In this issue of the journal, Barai et al<sup>4</sup> studied the second most common malignancy of children, neuroblastoma, using radioiodine I-131 labelled metaiodobenzylguanidine (I-131 MIBG). Neuroblastomas arise from the neural crest tissue, 50% from the adrenal medulla, 25% from abdominal sympathetic ganglia, 15% from the posterior mediastinum, and the rest from other regions of the body.<sup>6</sup> Scintigraphy is based upon the fact that norepinephrine is present in a high concentration in the neural tissue. Ganglion-blocking drug, guanethidine, structurally resembles norepinephrine.

I-131 MIBG which enters the neuroendocrine cells is stored in the catecholamine vesicles. Barai et al studied 57 children with neuroblastoma and compared detection of bone lesions with both I-131 MIBG and Tc-99m Methylene diphosphonate (Tc-99m MDP). At presentation, they found 11 positive bone scans with Tc-99m MDP and 7 positive with I-131-MIBG. On follow-up, Tc-99 MDP scan was positive in 14 as against 9 posi-

tive with I-131- MIBG. These results were very similar to a previous report by Gordon et al<sup>7</sup> using I-123-MIBG, but different from those of Shulkin et al<sup>8</sup> with I-131 MIBG. It is not clear if these results reflect the effect of dose difference, low dose with I-131 MIBG and high dose with Tc-99m MDP or the difference in the biological behaviour of the bone lesions. I suspect that the latter is the case. Since biopsy of all the positive lesions was not done, one has to assume that all Tc-99m MDP positive lesions were in fact all neuroblastoma. What if, only concordant I-131 MIBG positive and Tc-99m positive lesions were neuroblastoma, and positive Tc-99m MDP and negative I-131 MIBG were not neuroblastoma on biopsy? The primary goal of I-131 MIBG imaging should be to identify those Tc-99m MDP positive bone lesions as neuroblastoma in deciding an appropriate therapeutic strategy for the child.

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