Role of Iodine-131 MIBG Scanning in the Management of Paediatric Patients with Neuroblastoma

G.M. Shah Syeda, H. Naseerb, G.N. Usmanib, M.A. Cheemab

aDepartment of Nuclear Medicine, Faculty of Medicine Kuwait University, Kuwait, and
bShaukat Khanum Memorial Cancer Hospital & Research Centre, Lahore, Pakistan

Abstract

Objective: To evaluate the role of iodine-131 metiodo-benzylguanidine (iodine-131 MIBG) scanning in the management of paediatric patients with neuroblastoma.

Subjects and Methods: Forty-three iodine-131 MIBG scans were performed on 26 children, 18 male and 8 female, ranging in age from 8 months to 11 years. Bone scan, computed tomography (CT) images and findings of bone marrow biopsy were compared with the iodine-131 MIBG scan findings.

Results: Of the 26 patients, 18 (69%) showed abnormal iodine-131 MIBG avidity and were proven to have a neural crest tumour on histology. The remaining 8 (31%) patients had normal iodine-131 MIBG scans, and histology showed a malignancy other than a neural crest tumour. Iodine-131 MIBG scans showed the primary site in 16 of 17 patients while CT showed 14 primary sites. In follow-up studies, the results were as follows: iodine-131 MIBG showed no evidence of disease in 4 compared with 3 on CT, persistent disease in 2 on iodine-131 MIBG and 4 on CT; recurrence in 1 on iodine-131 MIBG and 0 on CT; MIBG scans detected double the number of bony lesions compared with bone scans. The findings on iodine-131 MIBG scans and bone marrow biopsy were in agreement in 16/18 cases. Patients in whom iodine-131 MIBG scans showed disease resolution had better clinical outcomes.

Conclusion: The findings indicate that iodine-131 MIBG scanning is useful for the diagnosis, staging, evaluation of response to therapy and detection of recurrences in patients with neuroblastoma. It exhibited a clear advantage over CT in detecting the primary site and soft issue metastases and was also superior to bone scanning in detecting skeletal metastases. It also reliably demonstrated bone marrow involvement.

Introduction

Neuroblastoma is one of the most common solid tumours in children. Approximately 80% of patients with neuroblastoma are under the age of 5 years [1]. Arising from neural crest cells, neuroblastoma is found in a variety of locations such as the adrenal medulla, the sympathetic chain, the posterior mediastinum, pelvis, cervical region and rarely in the posterior cranial fossa. The diagnosis and staging of neuroblastoma require measuring urinary catecholamine levels, a plain radiography, an intravenous pyelogram, an ultrasonogram, a CT or an MRI scan of the region and a bone scan. Biopsy provides the
final histological diagnosis. Light microscopy supplemented by electron microscopy and immuno-histochemical techniques helps to differentiate neuroblastoma from other round blue-cell tumours. The bone marrow biopsy helps to detect bone marrow involvement. Many studies have shown the usefulness of radiolabelled iodine-131 MIBG imaging in patients with neuroblastoma in establishing diagnosis, tumour staging, prognosis and assessing the response to treatment [2–6]. Sensitivity and specificity of the test are above 85 and 94%, respectively [7, 8]. This study was done to evaluate the role of iodine-131 MIBG in the diagnosis, staging and response to treatment in pediatric populations with neural crest tumours and compare the findings to those of bone scan and bone marrow biopsy.

**Subjects and Methods**

Twenty-six (18 male and 8 female) consecutive patients, during a four year period (1996–1999), under the age of 17 years with a histopathologically confirmed diagnosis or clinical suspicion of neuroblastoma were included in the study. Median age and standard deviation at the time of diagnosis was 5 ± 3 years and ranged from 8 months to 17 years. For each patient, the history was recorded and a physical examination and clinical diagnosis were performed. CT, urinary catecholamine levels and bone marrow biopsy were performed in all 26 patients while bone scans were done only in 12 patients with positive iodine-131 MIBG studies.

Prior to administration of iodine-131 MIBG, it was ensured that no patient was taking any medication that could interfere with the uptake of iodine-131 MIBG. Ten drops of Lugol’s solution were given to each patient 1 day before the injection and patients were advised to keep on taking it for 7 days thereafter in order to block the uptake of iodine-131, a metabolic product of iodine-131 MIBG, by the thyroid gland. Each patient was injected slowly with iodine-131 MIBG intravenously (M/S, Amersham, UK). The administered dose was 0.5–1 MBq (0.01–0.03 mCi)/kg body weight, not exceeding 18.5 MBq (0.5 mCi). In each case, scans were acquired on a digital camera (Diacam from M/S Siemens) at 24, 48 and 72 h after dose administration. For acquisition, matrix size was set at 128 × 128 × 128, with a 15% energy window centred at 140 keV. A zoom factor of 1.23 was used for small children. Overlapping static images of the skull, pelvis, chest and spine were acquired in anterior and posterior projections using a low-energy general purpose collimator. The posterior spine image was acquired for 750 K counts while all other views were acquired for this same time period. Anterior views of the lower limbs were also acquired for 5 min. The acquired images were then copied onto radiographic films.

**Results**

Of the 26 patients, 18 (69%) had positive iodine-131 MIBG scans and were proven histologically to have neuroblastoma. One of these patients had the primary site surgically removed prior to iodine-131 MIBG scanning, but was positive due to metastasis to the soft tissues. The remaining 8 patients had normal iodine-131 MIBG scans but histologically were shown to have non-neuroblastoma tumours (table 1).

Table 1. Histological diagnosis and abnormal 131I MIBG avidity

<table>
<thead>
<tr>
<th>Histological diagnosis</th>
<th>MIBG scan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>positive</td>
</tr>
<tr>
<td>1 Neuroblastoma or related tumour (n = 18)</td>
<td>18</td>
</tr>
<tr>
<td>2 Ewing sarcoma (n = 2)</td>
<td>0</td>
</tr>
<tr>
<td>3 Primitive neuroectodermal tumour (n = 2)</td>
<td>0</td>
</tr>
<tr>
<td>4 Retinoblastoma (n = 2)</td>
<td>0</td>
</tr>
<tr>
<td>5 Rhabdomyosarcoma (n = 1)</td>
<td>0</td>
</tr>
<tr>
<td>6 Ganglioneuroma (n = 1)</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2 shows the comparison between iodine-131 MIBG and the CT scans. Iodine-131 MIBG scans showed the primary site in 17 of the 18 patients with histologically proven neural crest tumour while CT detected primary lesions in 14 patients.

In 7 patients, 12 follow-up iodine-131 MIBG scans were compared with CT scans. Iodine-131 MIBG scans showed disease resolution in 4 patients (6 studies), persistent disease in 2 patients (5 studies) and recurrence was noted in 1 patient. CT scan showed disease resolution in 3 patients (4 studies) and persistent disease in 4 patients (8 studies).
Fig. 1. a Iodine-131 MIBG-avid lesions in lower abdomen and pelvis (arrows) which are not seen on corresponding CT slices (b).

Table 2. Comparison of MIBG and CT scanning in patients with neuroblastoma

<table>
<thead>
<tr>
<th></th>
<th>MIBG</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>positive</td>
<td>negative</td>
</tr>
<tr>
<td><strong>Baseline study</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary disease only</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Primary lesion and metastatic disease</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Metastatic disease only</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Follow-up studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease-free</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Partial/persistent disease</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Recurrent disease</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

In the head, neck and chest regions, findings on 14 iodine-131 MIBG studies and corresponding CT scans were in complete agreement. In the abdominal region, however, 18 iodine-131 MIBG studies showed abnormal avidity while the CT examination detected lesions in only 16. Four pelvic CT scans were available for comparison with iodine-131 MIBG pelvis views. In 1 case the results were similar; however, in 3 patients, the CT scan missed some of the lesions. Figure 1a shows an iodine-131 MIBG scan acquired 48 h after injection. Abnormal tracer accumulation in abdomen and pelvis is noted. Corresponding CT slices (fig. 1b) failed to show any abnormality.
Iodine-131 MIBG Scanning in Neuroblastoma

Twelve bone scans were available for comparison with iodine-131 MIBG studies. Seven bone scans were positive for metastases and a total of 13 lesions were seen. Iodine-131 MIBG scans were positive for metastases in 6/7 of these cases and a total of 24 lesions were seen. Hence 12 additional sites of bony metastasis were seen on iodine-131 MIBG scans. In 1 case, the iodine-131 MIBG scan did not show a lesion noted on the bone scan.

Eighteen iodine-131 MIBG scans were compared with the results of bone marrow biopsy performed at the same time. The results of 16 iodine-131 MIBG scans and corresponding bone marrow biopsies were in complete agreement (5 positive and 11 negative). In 2 patients the bone marrow biopsies were positive but the iodine-131 MIBG scan did not show bone marrow involvement. Figure 2 shows a positive iodine-131 MIBG scan acquired 48 h after injection with symmetrical skeletal uptake suggestive of extensive bone marrow involvement. A 3-year follow-up was available in 8/18 patients. Three patients showed complete resolution of the disease on follow-up iodine-131 MIBG scans and were still clinically stable. One scan showed resolving disease and the patient was alive (follow-up period of 21 months). In another patient where the iodine-131 MIBG scan showed resolution of lesions, death occurred during treatment due to complications from chemotherapy. The remaining 3 patients had persistent iodine-131 MIBG avid lesions and died from the disease within 12 months of follow-up.

Discussion

Accurate tumour staging is necessary for therapeutic decision making and assessment of prognosis in patients with neuroblastoma. Iodine-131/123 MIBG, the radiolabelled analogue of norepinephrine, is taken up by the functioning neuroblastoma. Fibrotic or necrotic tumours do not accumulate this radiopharmaceutical. Post-treatment uptake of the radioiodine-labelled MIBG helps in monitoring the response of the lesions to therapy. Thus iodine-131/123 MIBG scintigraphy is a simple non-invasive test that helps in diagnosing, staging and monitoring response to therapy with high sensitivity and specificity [9, 10]. Although iodine-123 MIBG produces a better image quality and localization of lesion than iodine-131 MIBG [11, 12], the latter was used in this study due to difficulty in procuring iodine-123 MIBG because iodine-123 has a short half-life of 13 h.

In our study, all patients who had abnormal accumulation of iodine-131 MIBG were proven to have neuroblastoma or a related tumour while those who had a negative iodine-131 MIBG scan had a tumour other than neuroblastoma. Hence, in this study population there was no false-positive or false-negative case, thereby giving a sensitivity and specificity of 100%, each consistent with previously published reports [13–16].

In comparing iodine-131 MIBG findings with those of CT, iodine-131 MIBG scanning had a clear advantage over CT as it detected not only the primary site in all patients (CT missed two), but also more lesions than CT. Iodine-131 MIBG also provided accurate information on the functional status of the disease in 6 cases where CT failed to detect or underestimated the disease. Similar findings regarding the lower sensitivity and specificity of CT have been reported by Lastoria et al. [17]. In addition, CT may detect residual masses while the iodine-131 MIBG scan is normal because only iodine-131 MIBG scanning can confirm the viability of a tumour [17]. In this study there were 2 such cases plus a third in which iodine-131 MIBG detected a recurrence on follow-up scans, while the CT scan failed to do so. Overall, iodine-131 MIBG was more helpful than CT in localising the pri-
mary site, accurately staging the disease by detecting metastatic sites, in differentiating between active disease and fibrosis and in detecting recurrences, as has been previously reported [18].

In comparison to bone imaging, the extent of bony involvement was higher on iodine-131 MIBG scan than on bone scans; in fact iodine-131 MIBG detected twice the number of lesions compared with bone scans. Only one patient had a positive bone scan when the iodine-131 MIBG scan findings were negative. In this patient the iodine-131 MIBG scan failed to detect a skull lesion. This could be a false-negative finding; but it is possible that the lesion in the skull on the bone scan was a benign process. Localised radiographs could not be done to establish the nature of the lesion. However, bone scanning offers better site localisation than iodine-131 MIBG scanning. Similar findings have been reported previously [8].

Previous studies have described a pattern on iodine-131 MIBG scans that is highly suggestive of bone marrow involvement. This pattern has been shown as symmetrical uptake in vertebrae, pelvis and other bones [19]. Whenever iodine-131 MIBG is positive, the likelihood of bone marrow involvement is high, as shown in this study where all 5 positive iodine-131 MIBG were also positive on bone marrow biopsy. However, there remains a possibility of missing bone marrow involvement based on iodine-131 MIBG scanning as in this study, where 2 of 7 patients were negative.

**Conclusion**

The findings indicate that iodine-131 MIBG scanning is useful for the diagnosis, staging, assessment of response to therapy and in detecting recurrences in patients with neuroblastoma. It has a clear advantage over CT in detecting the primary site and soft tissue metastases. It is also superior to bone scanning in detecting skeletal metastases. It also reliably demonstrates bone marrow involvement.

**References**