Optimized Diagnostic Strategy for Neuroblastoma in Opsoclonus-Myoclonus

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Infantile myoclonic encephalopathy (opsoclonus-myoclonus or IME) is a rare clinical syndrome associated with occult neuroblastoma in 20%–50% of all cases. IME is the initial presentation of neuroblastoma in 1%–3% of children. Imaging approaches including chest radiography and abdominal computed tomography (CT) have been proposed to detect neuroblastoma in IME. Metaiodobenzylguanidine (MIBG) is highly effective in the detection of neuroblastoma. These scans can identify both soft-tissue and skeletal lesions anywhere in the body. Our purpose was to attempt to determine the best screening method for detection of occult neuroblastoma in patients with IME. Records of all neuroblastoma patients from 1983 to May 1991 were reviewed. Four cases of IME with neuroblastoma were identified in which imaging studies included an MIBG scan. All four patients had positive MIBG scans (100%) while only two had masses on initial CT (50%). In the three patients initially evaluated by traditional methods, the mean time to diagnosis and the mean number of advanced radiologic studies were 7.5 mo and 7.3 studies respectively. The patient screened with MIBG had only cranial and abdominal CT prior to surgery. Although based on a limited number of patients, results suggest that MIBG may prove to be a useful screening procedure in patients with IME. Traditional imaging modalities can then be directed to evaluate sites of disease identified by MIBG scans.

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Infantile myoclonic encephalopathy (opsoclonus-myoclonus or IME) is a rare clinical syndrome characterized by random, irregular eye movements (opsoclonus) and uncontrolled limb movements (myoclonus) usually accompanied by cerebellar ataxia. Originally this constellation of findings was attributed to either an idiopathic or a postviral etiology (*1*). In 1968 Solomon and Chutorian (*2*) suggested a causal relationship between opsoclonus-myoclonus and neuroblastoma. Since then, many reports of IME associated with neuroblastoma have been published (*3–12*). In fact, it is currently accepted that IME is associated with occult neuroblastoma in 20%–50% of all cases and is the initial presentation of neuroblastoma in 1%–3% of all cases.

Various imaging strategies for the diagnosis of occult neuroblastoma in patients with IME have been proposed. Farrely et al. (*8*) found computed tomography (CT) to be more sensitive than chest and abdominal radiography, intravenous pyelogram or technetium bone scans in tumor detection in these patients. The use of CT also shortened the interval between presentation and final diagnosis, thus avoiding unnecessary investigations. Other authors (*9–11*) concurred and suggested a diagnostic protocol utilizing chest radiography, abdominal CT and 24-hr urine collection for vanillymandelic acid (VMA) and metanephrine. All of the foregoing authors recommended thorough and repeated diagnostic evaluations of these patients, including total body CT if necessary, to find an occult tumor.

Despite the reportedly favorable prognosis for survival in patients with coincident IME and neuroblastoma (*9,12*), overall prognosis in neuroblastoma is most strongly dependent upon patient age and stage at presentation (*13,14*). A single screening study which is sensitive, specific and able to identify both soft tissue and osseous metastatic disease would provide more rapid diagnosis, simultaneous staging and possibly improve outcome.

Metaiodobenzylguanidine (MIBG) is a norepinephrine analog which has been demonstrated to be highly sensitive (90%–95%) and specific (100%) in the detection and post-therapeutic follow-up of patients with neuroblastoma (*15,16*). When radiolabeled with either ^{123}I or ^{131}I, MIBG normally localizes in the heart, liver, salivary glands, bladder and occasionally in the lacrimal glands, colon and normal adrenal glands (*17,18*), osseous uptake is not expected; thus MIBG scanning can easily identify sites of osseous metastases in addition to detecting the primary mass. Moreover, although previously contested in the literature, several recent studies have clearly shown MIBG to be superior to technetium (^{99m}Tc-MDP) bone scintigraphy—the current gold standard—for detection of osseous metastatic disease in neuroblastoma (*19–21*). These factors suggest that MIBG rather than CT and chest radiography may be the most appropriate and effective initial imaging study in patients with IME. Following MIBG localization of the

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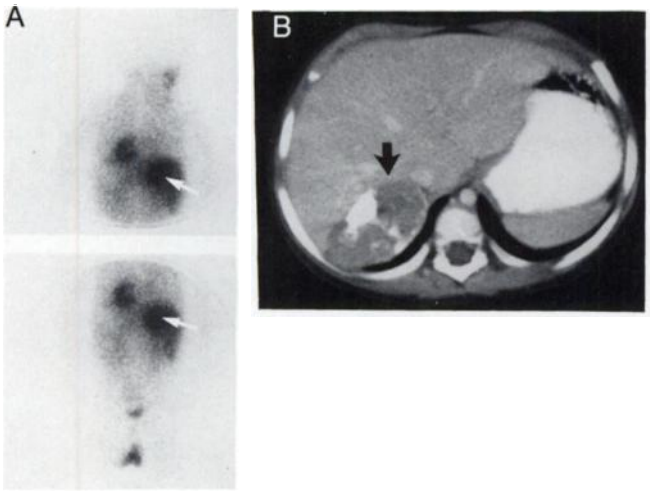

FIGURE 1. (A) Posterior images 24 hr following the administration of 1.5 mCi of ^{123}I-MIBG (Patient 1) reveal abnormal radionuclide uptake consistent with neuroblastoma in the region of the right adrenal gland (arrow). (B) Single transaxial image from a directed abdominal CT confirms the presence of a calcified right adrenal mass surgically shown to be neuroblastoma (arrow).

primary tumor, a directed CT or MRI can be obtained for precise anatomic delineation of the mass prior to surgery.

METHODS

To test this hypothesis, records of all patients with neuroblastoma seen at our institution from 1983 to May 1991 were reviewed. Four cases of IME associated with neuroblastoma were identified. All four patients had been evaluated with both traditional imaging modalities and MIBG. Their case histories and imaging studies were examined to determine the optimal imaging screening procedure for tumor detection in IME.

For diagnostic scanning, the patients were injected intravenously with 30–100 μCi (1.11–3.7 MBq)/kg of ^{123}I MIBG (average dose: 2 mCi [74 MBq] per scan) and scanned 24 hr later. Using a 40-cm field of view gamma camera (1 cm thick detector), a series of 10-min scintiphotos anteriorly and posteriorly spanning the body were obtained. A single 20% symmetric window was centered on the principal photopeak of the isotope and a 200 keV optimized collimator was used. The total data sets were approximately 6×10^6 events for ^{123}I.

Case Reports

Case 1. A 19-mo-old girl was referred to the neurology service 6 days after the acute onset of ataxia. Previous evaluation included a lumbar puncture and brain CT, both failing to show an abnormality. With the exception of ataxia, the past medical history and physical exam were unremarkable. Acute cerebellar ataxia was diagnosed and the child was followed closely with two additional neurological examinations over a 4-wk interval. The patient's ataxia worsened and was purportedly accompanied by myoclonic activity. Although opsoclonus was not present, the lack of clinical improvement and a borderline elevated spot urine test for VMA led to referral for an MIBG scan 6 wk after the onset of symptoms. The MIBG scan (Fig. 1A) was positive for a right retroperitoneal mass, probably adrenal in origin. No osseous metastases were present. A directed abdominal CT scan (Fig. 1B) confirmed the presence of a calcified retroperitoneal mass and at surgery, a right adrenal neuroblastoma with metastases to ipsilateral lymph nodes was removed. Following resection, IME symptoms improved and the patient is currently disease free.

Case 2. A 17-mo-old girl presented to an outlying hospital with 1 mo of ataxia and 3 days of fever, vomiting and cough. On physical exam, opsoclonus, myoclonus, ataxia and decreased right sided muscle tone were present along with right otitis media. In the initial evaluation, the following studies were obtained and were normal or negative: blood culture; spinal fluid analysis including cell count, protein, glucose, gram stain, acid fast bacilli (AFB) stain, cryptococcal antigens and culture; electrolytes; serum alpha-feto-protein; urine for toxicology; amino acids; culture; 24-hr urine collection for metanephrine and VMA; and brain CT.

The association of opsoclonus-myoclonus with occult neuroblastoma led to the child's transfer for further evaluation. Additional studies obtained included negative urine metanephrine and VMA levels, negative chest and abdominal CT scans with and without contrast enhancement and a negative brain MRI. A MIBG scan (Fig. 2) suggested an abnormal focus of uptake in the left infrarenal region and a second, possibly abnormal focus in the region of the right adrenal gland. No osseous metastatic disease was noted. An extensive left perirenal and retroperitoneal surgical exploration and dissection followed. No tumor was present on the left but a psoas muscle biopsy was not performed. In the site of abnormal uptake near the right adrenal gland, a 2 × 2.5 cm lesion histologically representing metastatic ganglioneuroblastoma was found. The primary tumor was not identified. With resection, IME resolved and at present, this child has no evidence of disease.

Case 3. A 12-mo-old girl presented with acute onset of myoclonus, occasional opsoclonus and ataxia. Initial evaluation included cranial CT; spinal fluid for cell count, gram, AFB and

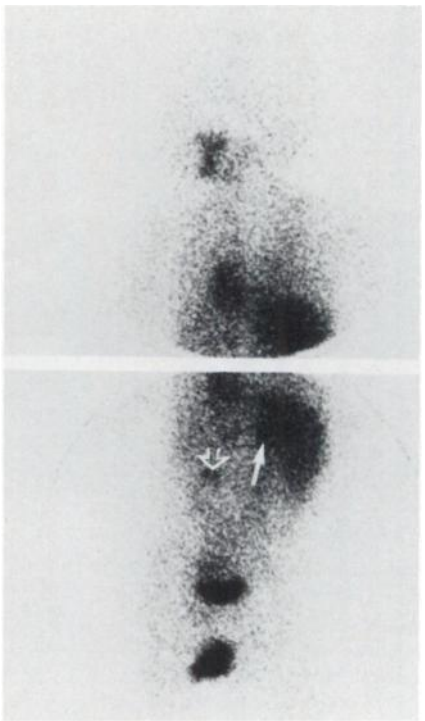

FIGURE 2. Posterior images from an ^{123}I-MIBG scan (1.6 mCi) 24 hr postinjection (Patient 2) show abnormal foci of uptake in the left infrarenal fossa (open arrow) and in the right adrenal gland (thin arrow). CT scans were negative. Surgical pathology confirmed metastatic ganglioneuroblastoma in the right adrenal gland.

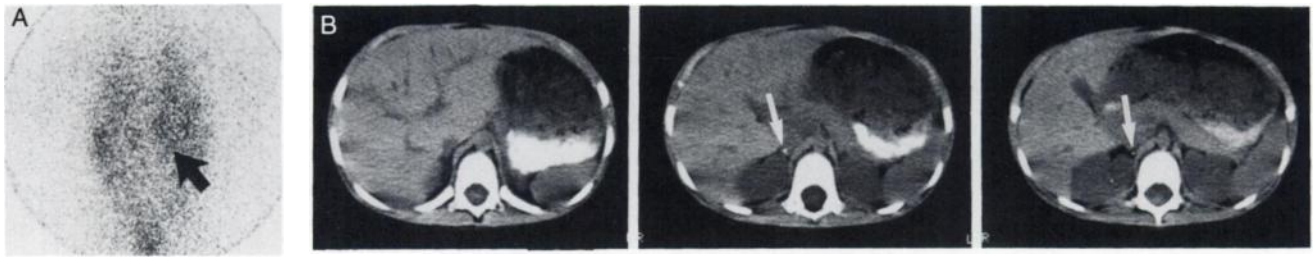

FIGURE 3. (A) Posterior images at 24 hr following injection of 3 mCi of ^{123}I MIBG (Patient 3) reveal a subtle focus of abnormal uptake in the region of the right adrenal gland (arrow). (B) Subsequent contiguous 1-mm transaxial CT images through the region of the right adrenal gland demonstrate abnormal adrenal calcification (arrow) surgically proven to be neuroblastoma. The MIBG scan led to this directed study using a much smaller slice thickness, allowing depiction of the lesion missed on three prior CT or MRI studies.

cryptococcal stains, glucose, protein and culture; and a 24-hr urine collection for VMA and metanephrines. All these studies were normal or negative. The patient was followed with repeatedly negative urine VMA and metanephrine levels, negative cranial MRI, and negative CT and MRI of the abdomen.

At 2.5 yr of age, 18 mo after the onset of symptoms, an MIBG scan (Fig. 3A) demonstrated a subtle focus of abnormal uptake in the region of the right adrenal gland. A subsequent directed thin section (1 mm thick transaxial slice) CT (Fig. 3B) confirmed two tiny calcifications in the expected location of the right adrenal gland with no mass identified. Exploratory surgery confirmed a 2.5 × 1 cm flat mass adherent to the right adrenal gland and calcifications in an adjacent caudal lymph node. Histology showed a mixture of neuroblastoma, ganglioneuroma and mature ganglion cells classified as Stage 2 disease. Neither MIBG nor subsequent bone scan or bone marrow aspirate showed skeletal metastases. Following tumor resection, IME symptoms resolved and currently the child is tumor free.

Case 4. A 14-mo-old boy with new and progressive clumsiness and regression of motor development milestones presented to an outlying hospital. Spinal fluid analysis and CT scan of the brain were normal and he was treated for viral encephalitis. Continued symptoms resulted in referral for evaluation 2 mo later.

Opsoclonus, myoclonus and ataxia were present and occult neuroblastoma was sought with laboratory studies including CBC, serum electrolytes and ferritin, urinalysis, and urine for VMA and metanephrines. CT and MRI of the chest, abdomen and pelvis showed a large calcified right paravertebral mass in the region of the adrenal gland which crossed midline (Fig. 4A). Intraspinal extension could not be excluded and a lumbar spine MRI was obtained (Fig. 4B). On chest CT, a focal area of consolidation in the right upper lobe and possible right hilar adenopathy was noted. A MIBG scan (Fig. 4C) confirmed a right adrenal neuroblastoma and excluded focal pulmonary involvement. No bone or distant soft-tissue metastases were identified. At surgery, a large tumor mass originating in the right adrenal was removed. Follow-up studies postresection and chemotherapy revealed no evidence of disease and improved IME symptoms.

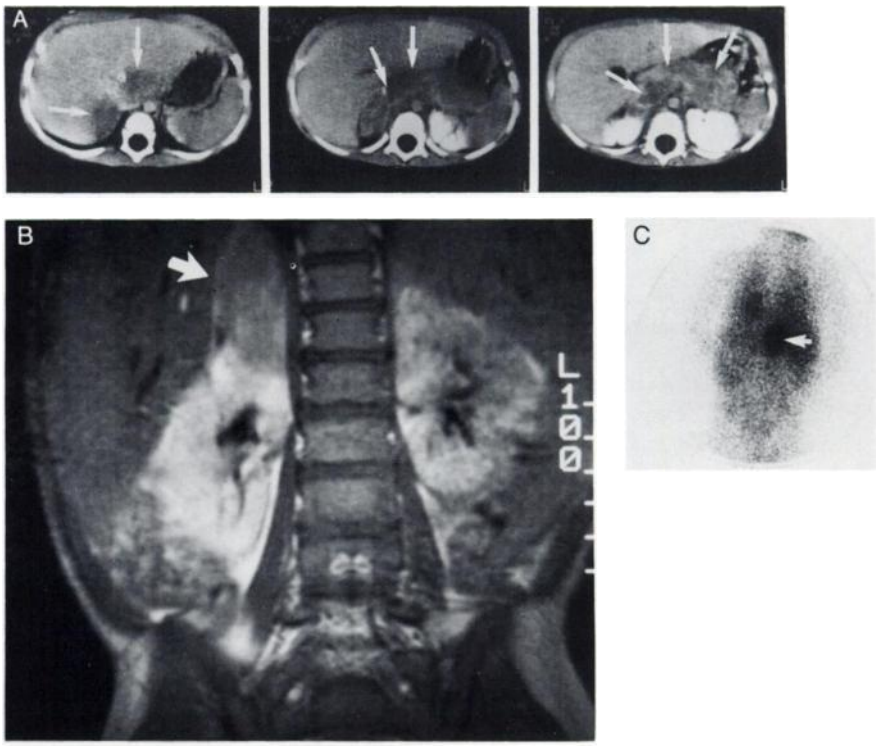

FIGURE 4. (A) Contiguous transaxial CT images through the region of the right adrenal gland (Patient 4) show a large, calcified right adrenal/paravertebral mass extending across the midline (arrows). (B) Coronal images from a lumbar MRI again demonstrate the mass (arrow) and exclude intraspinal extension. (C) Posterior images 24 hr following ^{123}I-MIBG injection confirming the neuroectodermal origin of the tumor (arrow) and excluding osseous and focal pulmonary metastases. Diffuse pulmonary MIBG uptake can occur normally.

TABLE 1
Clinical Features of Patients with Coincident Opsoclonus-Myoclonus and Neuroblastoma

Patient no.	Sex	Age at onset of IME	Tumor location	Stage	Path	Catechol levels	Postresection/Therapy: Disease free	Postresection/Therapy: IME resolved
1	F	19 mo	Rt adrenal/retroperitoneal	2	NB	B/↑	Y	I
2	F	17 mo	near Rt adrenal	2	GNB	N	Y	Y
3	F	12 mo	Rt adrenal	2	NB/GNB	N	Y	Y
4	M	14 mo	Rt adrenal	3	NB	N	Y	I
Mean		15.5 mo						

B = borderline; ↑ = increased; N = normal; Rt = right; NB = neuroblastoma; GNB = ganglioneuroblastoma; Catechol = catecholamine; Path = pathology; I = improved; and Y = yes.

RESULTS

The clinical data compiled on these patients are listed in Table 1. Like other reported cases of opsoclonus-myoclonus and coincident neuroblastoma, there was a female predominance (*11*), a mean age of onset of symptoms of 15.5 mo (*11*), normal catecholamine levels (*6,11,12*), and a spectrum of histology ranging from neuroblastoma to benign ganglioneuroma. Unlike prior reports with a predominance of posterior mediastinal masses (*6,11,12*), our patients had intra-abdominal and primarily adrenal tumors.

More importantly, all four patients had positive MIBG scans (100%). Only two of the four had masses identified on initial abdominal CT (50%). In the three patients initially evaluated by traditional radiographic studies, the mean time to diagnosis and the mean number of advanced radiologic studies were 7.5 mo and 7.3 studies, respectively (Table 2). The patient screened with MIBG had only cranial and abdominal CT prior to surgery.

DISCUSSION AND CONCLUSIONS

In consideration of cost efficiency, the value of a sensitive and specific screening modality for patients with suspected neuroblastoma is extremely important. As seen in Table 2, the cost of an undirected diagnostic evaluation of a patient with opsoclonus-myoclonus can be high, both in regard to direct patient costs and with respect to equipment utilization and personnel time. Using a traditional radiographic approach in these patients, the average cost of diagnosis (excluding the cost of plain films) was 2–3 times as high as that of the patient screened with a cranial CT followed by MIBG scan. Moreover, these figures do not reflect costs of laboratory studies or basic radiography. Although MIBG scanning is expensive, it is comparable in price to a contrast-enhanced CT scan of the abdomen. In all of our patients, the use of an MIBG scan shortened the interval between presentation and final diagnosis. In two of our patients, MIBG localized the site of tumor when other modalities failed to do so. Given the high sensitivity and specificity of MIBG for neuroblastoma (*16–21*), the ease of scan interpretability (*21*), and the ability to obtain simultaneous staging information, MIBG seems to be the optimal screening procedure for patients with opsoclonus-myoclonus and suspected neuroblastoma. Although based on a limited number of patients, our preliminary data support this conclusion.

Based on the results of this pilot study, in patients presenting with opsoclonus-myoclonus in whom infection and other intracranial abnormality has been excluded by LP and CT scan of the brain and whose persistence of symptomatology suggests occult neuroblastoma, MIBG appears to be the most efficacious screening modality. Traditional imaging modalities can then be directed to further evaluate and delineate sites of disease identified by MIBG scans.

TABLE 2
Comparison of Time/Cost Analysis in Patients with Opsoclonus-Myoclonus First Evaluated with MIBG as Opposed to Those Evaluated First With Traditional Modalities

Patient no.	Time to Dx	Advanced radiologic studies including MIBG (no.)	Cost of all advanced radiological studies	Cost without MIBG	Laboratory studies (no.)
1*	1.5 mo	3	$3,020	$1,836	2
2†	2 mo	7	$6,371	$5,187	10
3†	18 mo	7	$6,905	$5,721	5
4†	2 mo	9	$10,658	$9,474	6
Mean (2–4)	7.3 mo	7.6	$7,978	$6,794	7

Dx = diagnosis.
*Single patient evaluated first with MIBG.
†Three patients evaluated first by traditional radiographic methods.

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