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Consolidating the role of *I-MIBG-scintigraphy in childhood neuroblastoma: five years of clinical experience

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Abstract. In recent years, *I-MIBG (*I-metaiodobenzylguanidine), which is transported and stored in the chromaffin cells, has been shown to allow good visualization of neuroblastomas in children. This paper deals with 30 *I-MIBG-scans performed in 20 children: 16 with neuroblastoma, 3 with retinoblastoma, and 1 with a malignant paraganglioma. A high detection rate was found for both primary and secondary sites of neuroblastoma. *I-MIBG was generally superior to ^{99m}Tc-MDP bone scintigraphy in the detection of bone metastases. Our experience illustrates the unique place of *I-MIBG-scintigraphy compared with other imaging techniques: it makes it possible to define the nature of the tumour, particularly in cases with normal catecholamine levels; to establish how extensive the lesions are at the time of diagnosis; and to confirm complete remission. No abnormal *I-MIBG uptake was noted in the 3 cases of retinoblastoma.

During the past few years interest in the use of *I-MIBG (*I-metaiodobenzylguanidine) scintigraphy for the diagnosis of tumours originating from the neural crest has increased rapidly. While this technique had already proved successful in the diagnosis of pheochromocytoma, since the first description of a huge ^{131}I-MIBG uptake by an abdominal neuroblastoma [1] several papers have reported the usefulness of this technique in the diagnosis and follow-up of patients with neuroblastoma. The sensitivity appears to be over 90% and the specificity around 100% [2–4]; MIBG has clearly proved more sensitive than catecholamine urinalysis in the detection of adrenergic activity [4]. ^{131}I-MIBG was used by some authors [2, 4] for detection of the lesions, whereas others [3, 5] gave preference to ^{123}I-labeling.

The aim of this paper is to present our clinical experience in this field and to evaluate the accuracy of *I-MIBG scintigraphy in the detection of primary and metastatic neuroblastomas.

Materials and methods

Patients

In our department, 16 patients with neuroblastoma, 3 patients with retinoblastoma and 1 patient with a malignant paraganglioma have been studied.

In the neuroblastoma cases, *I-MIBG scintigraphy was performed before any therapy in 12 patients and after therapy in 4 children; in 2 cases *I-MIBG scintigraphy was performed both before and after therapy. Three children were in remission after treatment at the time of their first *I-MIBG scan. According to the Evans classification of neuroblastoma, 2 children were in stage I, 2 in stage II, 4 in stage III, 5 in stage IV, and 3 in stage IVS. Urinary catecholamine metabolites were elevated in the majority (15 out of 16 patients).

In all, 30 *I-MIBG scans were performed: 17 with ^{123}I as radionuclide and 13 with ^{131}I.

Preparation of ^{123}I- and ^{131}I-MIBG

MIBG is synthesized using a modified method developed by Wieland et al. [6] with meta-iodobenzylamine and cyanamide. After HPLC purification MIBG is obtained in its sulphate form. Radioiodination of MIBG in a kit-form preparation is based on a nucleophilic isotopic exchange in the presence of Cu (I) and an excess of reducing agents. A radiochemical yield of more than 99% is reached at 100 °C within 25 min reaction time [7]. After synthesis, the reaction mixture is made isotonic and subsequently sterilized through a 0.22-μm filter so that *I-MIBG is ready for injection.

In the majority of studies the amount of radioactivity injected was approximately 2 mCi for ^{123}I (specific activity 2 mCi/mg) and 0.5 mCi for ^{131}I (specific activity 0.5 mCi/mg). Gamma camera images were obtained 24 h after MIBG injection when ^{123}I was used; in doubtful cases a 48-h control was performed. With ^{131}I-MIBG, 48-h images were generally sufficient. Potassium perchlorate or lugol solution was administered before and after tracer injection, in order to avoid *I uptake by the thyroid gland. In some cases, other tracers (especially ^{99m}Tc-DTPA for kidney visualization and ^{99m}Tc-colloid for liver and spleen visualization) were used to obtain a more precise idea of the localization of abnormal *I-MIBG uptake sites.

Table 1. Overall results in each patient

Patient no.	Sex	Age	Primary tumour site	Metastases	Grade (Evans)	UCM	Results with imaging			
							Primary tumour		Metastases	
							MIBG	Other techniques[a]	MIBG	Other techniques[a]
1	M	1y2m	Left hemithorax	o	II	⇑	+	+	–	–
2	M	1w	Left posterior hemithorax	o	II	⇑	+	+	–	–
3	M	1w	Left adrenal	Liver	IV S	⇑	+	+	?	+
4	M	3m	Right adrenal	o	I	N	+	+	–	–
5	M	1w	Suprapubic	o	III	⇑⇑	+	+	–	–
							–ϑ	–ϑ	–ϑ	–ϑ
6	F	4.5m	Left mediastinum	Liver	IV S	⇑	+	+	+	+
							–ϑ	–ϑ	–ϑ	–ϑ
7	M	3y2m	Left adrenal	o	I	⇑⇑	+	+	–	–
8	M	1y9m	Retroperitoneum	o	III	⇑	/	+	/	–
							–ϑ	–ϑ	–ϑ	–ϑ
9	M	2m	Left adrenal	Liver	IV S	⇑	–	+	+	+
10	M	3y	Left adrenal	Bone	IV	⇑	+	+	+	MDP-scan partly +
11	M	6.5m	Chest	o	III	⇑	+	+	–	–
12	F	6y	Right adrenal	o	III	⇑	/	+	/	–
							–ϑ	–ϑ	–ϑ	–ϑ
13	F	2y8m	Left adrenal	Bone Bone marrow Liver	IV	⇑	+	+	+ + +	MDP-scan partly +
14	M	4.5y	Retroperitoneum	Bone Bone marrow Liver Lymph nodes	IV	⇑⇑	/	+	/	+ + + +
							–ϑ	↓ϑ	New bone lesionsϑ	MDP-scan partly +ϑ
15	M	3y	Left adrenal	Bone Bone marrow Cerebellum	IV	⇑	/	+	/	+ + +
							–ϑ	–ϑ	–ϑ	+ϑ
16	M	3.5y	Right adrenal	Bone Bone marrow	IV	⇑⇑	+	+	+ +	MDP scan –
17	M	12y	Malignant paraganglioma right paravesical region	Liver hilus	III	⇑	?	+	+	–

w, week; m, month; y, year; UCM, urinary catecholamine metabolites; o, no metastases; N, normal level; ⇑, elevated level; ⇑⇑, strongly elevated level; +, positive result; –, negative result; ?, doubtful result; ϑ, after treatment; /, not performed; ↓, regression of lesion(s)

[a] X-ray; sonography; CT scan (^{99m}TC-MDP bone scan)

Results

The results are summarized in Table 1

Before any therapy. In 11 out of 12 patients (nos. 1–7, 10, 11, 13, 16) the primary tumour was detected by *I-MIBG scan; the false-negative result (patient 9) concerned a grade IVS-neuroblastoma with massive liver invasion: the *I-MIBG image showed a very intense tracer uptake in the liver, whereas the primary left adrenal lesion was not visualized; sonography and/or CT scan were positive in all 12 cases. Liver metastases were seen with certainty on *I-MIBG images in 3 out of 4 cases (nos. 6, 9, 13); the remaining patient (no. 3) was a 7-day-old neonate with heterogeneous liver activity, and it was difficult in this case to decide whether or not the image of the liver corresponded to metastases. In all cases, liver lesions were detected by sonography and or CT scan. In 4 patients (nos. 10, 13, 14, 16) bone metastases were observed by means of the MIBG scan, whereas the classic ^{99m}Tc-MDP bone scan was positive in 3 patients. Moreover, in these 3 cases several bone lesions were overlooked on bone scan.

During or after therapy. In 5 cases (no. 5, 6, 8, 12, 15), the primary tumour site was no longer visualized, on either

*I-MIBG scintigraphy or on sonography and/or CT scan. The liver metastases seen at diagnosis in patient 6 were no longer visible on either MIBG scan or CT scan. In patient 14 both MIBG and MDP scintigraphy permitted the detection of new bone lesions during treatment, but more sites were detected by MIBG; in patient 15, MIBG scan revealed no metastases, whereas bone and marrow biopsies remained positive. In one patient (no. 14), an obvious occipital metastasis confirmed by X-ray examinations was detected during follow-up by *I-MIBG scan. Progressive regression of this lesion was observed with further chemotherapy, and a few months later only small, but still significant, activity was seen at that level, whereas a skull X-ray was normal. The biopsy performed at that site did not reveal any tumour cells, and no further therapy was administered. The next *I-MIBG scintigraphy was normal, and the question arises as to whether the MIBG scan performed at the moment of the biopsy gave a false-positive result. In the paraganglioma case (patient 17) the primary tumour mass located in the right paravesical region could not be identified with certainty by MIBG because of normal urinary bladder activity. On the other hand, in this child *I-MIBG-scintigraphy showed a small lesion with very intense uptake near the liver hilus, which was not seen on sonography of CT scan. In the 3 cases of retinoblastoma the *I-MIBG scan was normal.

Discussion and conclusions

The molecular structure of MIBG can be considered as the fusion of the benzyl part of bretylium with the guanidine group of guanethidine, both of which are potent selective blockers of adrenergic nerve terminals. Although the exact uptake mechanism has not yet been fully explained, it has been demonstrated that MIBG is transported and stored in the distal storage granules of chromaffin cells in the same way as noradrenaline. Because *I-MIBG is theoretically captured in all organs with a rich sympathetic innervation, a normal image contains visualization of myocardium, liver, thyroid gland, salivary glands, kidneys, colon, urinary bladder and inferior parts of the lungs. Visualization of normal adrenal medualla remains a controversial point. Radiation absorbed dose calculations for ^{131}I-MIBG (based on the MIRD method) performed by Ertl et al. [8] show very low values for all organs (0.108–0.176 mGy MBq^{-1}), whereas larger, but still acceptable, doses are obtained for thyroid gland (5.69 mGy MBq^{-1}) and normal adrenal medulla (18.67 mGy MBq^{-1}). The results presented here show a high detection rate for primary and secondary sites of neuroblastoma using *I-MIBG scintigraphy. Moreover, we found that several bone metastases were only detected by MIBG and not by ^{99m}Tc-MDP bone scan. During follow-up, MIBG scan also seems to be of great value in detecting tumour relapse and (new) metastases. In our experience, except in one doubtful case, an abnormal accumulation of *I-MIBG was never observed in the absence of active neuroblastoma or an allied disorder. We did not find any difference in the detection of lesions using either ^{123}I or ^{131}I.

Despite a spatial resolution that is definitely lower than that of other imaging techniques, such as ultrasound and CT scan, *I-MIBG scintigraphy is helpful in defining the nature of the lesions and thus establishing the diagnosis of neuroblastoma thanks to its high specificity, even in patients with normal catecholamine levels.

As suggested by the findings in patient 17, paraganglioma detection and follow-up also seems to be a good indication for MIBG scintigraphy.

As previously mentioned, we also performed MIBG scans in children with retinoblastoma, because of the close histological similarity of this tumour with neuroblastoma; in none of these 3 cases, however, was MIBG uptake in the tumour site observed.

In summary, we can make the following statements concerning the use of MIBG scintigraphy in neuroblastoma. It allows:

- Definition of the nature of the tumour, particularly in the (rare) cases with normal catecholamine levels;
- Determination of the extension of the lesions at the time of diagnosis and during follow-up;
- Confirmation of complete remission, whereas X-ray, ultrasound, CT scan and MDP bone scan are unable to differentiate residual lesions from still active lesions.

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