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ORIGINAL ARTICLE

PET/CT and MIBG scans in diagnosis and management of Neuroblastoma

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Abstract

Introduction and aim: Several studies report conflicting results about ^{18}F-FDG/PET and MIBG scans and their diagnostic as well as prognostic significance in children with neuroblastoma. The current study was meant to evaluate both modalities and to compare them in relation to standardized modes of evaluation.

Patients and Methods: Paired evaluation (^{18}F-PET/CT and MIBG) was carried out prospectively (within a time interval of 1 month) at diagnosis and at different points of therapy, between June 2012 and April 2013. Thirty patients (14 males and 16 females), aged (0-18 years), diagnosed with Neuroblastoma at Children's Cancer Hospital-Egypt. They were treated according to COG A3973 for high risk patients and COG A3961 for intermediate risk patients.

Results: FDG/PET showed good results in detecting NB at all sites. FDG/PET also showed a higher sensitivity and specificity, and a better PPV/NPV than MIBG which was not statistically significant. Concordance between paired scans (MIBG, and PET) was found in 55.7% of cases (Kappa=0.001) for primary tumor site, and in 7% for bone and 19.4% for bone marrow. The significance of concordance between both modalities was only demonstrated for metastatic boney lesions. There were 13 patients having stage III neuroblastoma (43.3%) while 17 patients (56.7%) were having stage IV disease. 23 Patients were categorized as high risk (76.7%) while 7 patients (23.3%) were intermediate risk. Both, PET/CT scan and MIBG were more sensitive in detecting disease at stage IV than stage III.

Conclusion: ^{18}F-FDG/PET scan can be used effectively in both diagnosis and management decisions for children with neuroblastoma, it is a good complementary tool especially in detecting bone metastasis, although further clinical trials must agree on definite analytical aspects between both modalities.

Key words

Pediatric oncology, Neuroblastoma, ^{18}F-FDG/PET scan, MIBG scan

1 Introduction

With a sensitivity of about 90% and specificity of nearly 100% ^{123}I-metadiodbenzylguandine (^{123}I-MIBG), scan is the main imaging modality in neuroblastoma diagnosis [1]. Distribution of ^{123}I-MIBG occurs mainly into organs that excrete

catecholamines, like the urinary bladder, and gastrointestinal system. It is also normally taken up by the liver; and to a lesser extent the spleen, lungs, salivary glands, thyroid, skeletal muscles and myocardium. In evaluating MIBG scan results it is important to identify the normal distribution to avoid false positive scans [2].

Fluorine-18-fluorodeoxy-glucose (^{18}F-FDG) positron emission tomography (PET) (^{18}F-FDG PET) has experienced tremendous involvement in cancer imaging. Neuroblastomas (NB) can concentrate ^{18}F-FDG which is a positron-emitting glucose analog concentrated within cells using the glucose transporter. In evaluating neuroblastoma, there are several conflicting results about ^{18}F-FDG, because of its lower tumor-to-non tumor uptake ratio especially after therapy. The uptake of ^{18}F-FDG in non-tumor sites (such as bone marrow, thymus, and bowel) can cause false positive or false-negative results [3].

The superiority of ^{123}I-MIBG in evaluating bone or marrow metastases of stage 4 neuroblastoma, was not found in stages 1 and 2, in which the disease extent can be better delineatedby ^{18}F-FDG uptake in different body locations as chest, abdomen, and pelvis. It was also found that ^{18}F-FDG uptake provides important information for patients with tumors that accumulate ^{123}I-MIBG [4]. While MIBG scan is significantly more sensitive for individual lesion detection in relapsed neuroblastoma than FDG-PET, FDG-PET can sometimes play a complementary role, particularly in soft tissue lesions [4]. Some investigators reported that ^{18}F-FDG PET/CT had significant implications on prognosis in high-risk neuroblastoma patients [5].

The purpose of this prospective study was to evaluate the diagnosis of neuroblastoma with ^{18}F-FDG PET/CT and to compare it with ^{131}I-metaiodobenzylguanidine scintigraphy at different phases of disease.

2 Patients and methods

2.1 Patients

A prospective study with paired evaluation (PET/CT and MIBG) was carried out on children (0-18 years) mean age was 3.77 years, and a median of 2.5 years. Thirty patients (14 males and 16 females) with a male: female ratio of 0.875:1 are all diagnosed and treated at the Children's Cancer Hospital-Egypt (CCHE/57357) according to COG A3973 for high risk patients and COG A3961 for intermediate risk patients. All patients were staged according to International Neuroblastoma Staging System (INSS) criteria, and extent of disease was evaluated by computed tomography of the chest and abdomen, 99Tc bone scan, bilateral bone marrow aspirates and biopsies, and MIBG scan. All our patients did ^{131}I-MIBG and ^{18}F-FDG PET scans (within a time interval of 1 month) either at diagnosis or at different points during their management, with each patient doing both modalities at least once during his course of therapy. Scans were acquired between June 2012 and the end of April 2013. The treatment decisions for patients (according to their risk stratification; local control surgery; or referral for high dose chemotherapy and stem cell rescue) were based on results of all combined modalities. Informed consent was obtained according to the IRB standards of our hospital.

2.2 Technique

FDG-PET and ^{131}MIBG scans were reviewed by one nuclear medicine physician, and one radiologist. The anatomic location and type of lesion (soft tissue or osteomedullary) were recorded. FDG-PET and MIBG positive lesions were mapped onto body images. The scans FDG-PET/CT and MIBG images were viewed simultaneously.

Initial radiology reports (CT scans or MRI), bone scan results, and bone marrow biopsy results were also reviewed.

2.3 Image analysis

The effectiveness of ^{131}I-MIBG and ^{18}F-FDG PET in detecting NB was assessed by recording the uptake pattern for each radiopharmaceutical material at: primary tumor site, distant bone, and bone marrow metastases. Both paired ^{131}MIBG and

^{18}F-FDG PET scans for each patient were reviewed by radiologists and nuclear medicine physician for optimum comparison between those studies to determine the differences in the number and distribution of disease sites in these locations.

For ^{18}F-FDG PET/CT interpretation, any focal, uptake in ^{18}F-FDG at the primary mass, or skeleton was interpreted as positive or abnormal. Patchy ^{18}F-FDG uptake of the bone marrow, was interpreted as positive for bone marrow infiltration.

The maximum standardized uptake values (SUV max) were recorded for the most intense primary soft-tissue mass, bone, and bone marrow lesions perpatient. ^{131}I-MIBG and ^{18}F-FDG PET/CT scans were assigned scores for bone, and bone marrow lesions according to a previously applied semi-quantitative method [6, 7].

Comparison with CT scans/MRI for primary site, bilateral bone marrow biopsies result for bone marrow affection and bone scan for bone metastasis, developed a method to assess sensitivity and specificity of both modalities.

2.4 Statistical methods

Sensitivity: The proportion of true positives that are correctly identified by the test.

Specificity: The proportion of true negatives that are correctly identified by the test.

Positive predictive value: Proportion of patients with positive test results who are correctly diagnosed.

Negative predictive value: Proportion of patients with negative test results who are correctly diagnosed.

The lesions found on FDG-PET/CT and MIBG scans were compared. The concordance rate reflects the number of lesions seen by both modalities divided by the number of lesions seen by at least one of the imaging methods. McNemar's test, based on the non-concordant lesions (*i.e.*, lesions seen in one modality but not seen in the other) was used to compare the two modalities. All reported *P* values are based on McNemar's test.

Some studies mentioned that quantitization of both MIBG and PET has not been yet standardized. Semi-quantitative scoring systems have been tested for MIBG, which are correlated with response and, in some cases, event-free survival [7, 12]. To document change on PET scans, a standardized uptake value (SUV), is measured for each lesion that can be observed over time to determine response to treatment.

We report here the comparative disease evaluation or response by ^{131}I-MIBG and FDG-PET in patients treated in a single institute (CCHE). We also compared lesions identified on concomitant MIBG and FDG/PET scans using the previous semi-quantitative scoring for overall concordance, in bone, bone marrow and soft tissue.

3 Results

Of the 30 patients' scans examined, ^{18}F-FDG/PET resulted positive in 18 cases (60%) for primary site when compared with CT scan (see Table 1), 7 scans were positive for bone (23.3%) when compared with bone scan (see Table 2), and 4 scans were positive for bone marrow infiltration (13.3%) when compared with bone marrow biopsy result (see Table 3), whereas MIBG scan was positive for primary site in 11 cases (36.7%) compared to CT scan (see Table 4), 3 scans were positive for bone (10%) compared to bone scan (see Table 5), and another 3 positive for bone marrow affection (10%) compared to bone marrow biopsy result (see Table 6).

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Table 1. Positivity of PET/CT at primary site in relation to diagnostic CT/MRI scan

Result of PET/CT	Number of patients	Percentage of Patients
Negative	12	40%
Positive	18	60%
Total	30	100%

Table 2. Result of PET/CT in Assessing Bone using Bone Scan as a reference

Result of PET/CT	Number of patients	Percentage of Patients
Negative	23	76.7%
Positive	7	23.3%
Total	30	100%

Table 3. Results of PET/CT on Bone Marrow using BMA/BMB as a referenc

Result of PET/CT	Number of Patients	Percentage of Patients
Negative	26	86.7%
Positive	4	13.3%
Total	30	100%

Table 4. MIBG scan of primary site using CT/MRI as a reference

Results of MIBG on Primary Site	Number of Patients	Percentage of patients
Negative	19	63.3%
Positive	11	36.7%
Total	30	100%

Table 5. MIBG scan of Bone using Bone Scan as a reference

Results of MIBG scan	Number of Patients	Percentage of Patients
Negative	27	90%
Positive	3	10%
Total	30	100%

Table 6. MIBG scan of Bone Marrow using BMA/BMB as a reference

Results of MIBG scan	Number of Patients	Percentage of Patients
Negative	27	90%
Positive	3	10%
Total	100	100%

Our scan analysis was based on comparison with CT scan for the primary site, bone scan for boney metastases, and bone marrow aspirate plus bilateral bone marrow biopsies results for bone marrow involvement, both imaging modalities showed sensitivity, specificity, NPV, PPV, and accuracy as shown in Table 7 for PET/CT, along with the principal patients' characteristics, scan findings and final outcome with respect to reference standard are also reported, as well as for MIBG in Table 8.

Table 7. Sensitivity, specificity, PPV, and NPV of PET/CT

	Primary Site	Bone	BM
Sensitivity	0.818 (0.589-0.940)	0.600 (0.273-0.863)	0.285 (0.095-0.579)
Specificity	1 (0.597-1.000)	0.950 (0.730-0.997)	1 (0.759-1.000)
Positive Predictive Value	1 (0.781-1.000)	0.850 (0.4200-0.992)	1 (0.395-1.000)
Negative Predictive Value	0.666 (0.354-0.887)	0.826 (0.604-0.942)	0.615 (0.407-0.790)
Overall Accuracy	86.6%	83.3%	66.6%

Table 8. Sensitivity, Specificity, NPV, PPV for MIBG

	Primary	Bone	BM
Sensitivity	0.500 (0.288-0.711)	0.300 (0.080-0.646)	0.214 (0.057-0.511)
Specificity	1 (0.597-1.000)	1 (0.799-1.000)	1 (0.759-1.000)
Positive Predictive Value	1 (0.678-1.000)	1 (0.309-1.000)	1 (0.309-1.000)
Negative Predictive Value	0.421 (0.211-0.660)	0.740 (0.534-0.881)	0.592 (0.390-0.769)
Overall Accuracy	86.6%	76.6%	66.3%

Concordance between paired scans (MIBG, and PET) was found in 55.7% of cases (p=.001) for primary tumor site, and although concordance was 7% for bone and 19.4% for bone marrow, both results were statistically non-significant. No false-negative scans were observed for 18F-FDG/ PET. Maximum time elapsed between the 2 imaging modalities was (33 days) (mean=13.17 days) (SD=2.066).

There were 13 patients having stage III neuroblastoma (43.3%) while 17 patients (56.7%) had stage IV disease. 23 Patients were categorized as high risk (76.7%) while 7 patients (23.3%) were intermediate risk.

Although sensitivity of PET and MIBG differed between stage III and stage IV of disease, PET was more sensitive in detecting primary disease in stage IV (91.6% for stage IV versus 70% for stage III), also MIBG was more sensitive in detecting primary tumor in stage IV (58.8% for stage IV versus 40% for stage III). The decisions for staging, local control with surgery and stem cell transplantation were all based on combining the results of all modalities.

4 Discussion

NB is a malignancy arising from the sympathetic nervous system. Diagnosis is a result of combined clinical, laboratory, and radiological data.

CT is not considered the sole diagnostic modality for a new case of NB because of its limited value in bone marrow involvement, and the reduced ability to differentiate primary tumor from adjacent metastasis, as well as in cases of diffused liver metastasis easily misread on CT [10].

MIBG scintigraphy is used routinely and is mandatory in most investigational clinical trials both for the initial staging of the disease, the evaluation of the response to treatment, as well as for the detection of recurrence during follow-up [2]. A study stated that meticulous correlation with radiological examinations and recognition of the normal distribution pattern of MIBG in children is vital to obtain optimal results [14].

With its technical superiorities, positron emission tomography/computed tomography (PET/CT) can be successfully introduced into the diagnostic workup of NB [14].

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In our study, combined modality scans for 30 children with a pathological diagnosis of neuroblastoma, were done at different points of treatment protocol. The ^{131}I-MIBG and18F-FDG PET/CT scans for all patients were performed concomitantly. We also sought to study neuroblastoma patients with different stages (stages III, and IV), and different risk categories (Intermediate, and high), at different points of management. Although since all our patients performed both scans at different periods of their treatment which implies no uniformity in timing of performing both modalities but our aim was to report discrepancy between the 2 modalities at different management stages and different disease status.

When considering separately the different sites of disease, we found different sensitivities between ^{18}FDG PET/CT (0.818) and MIBG (0.5), in detection of primary location which was statistically significant (p=.008). Although PET/CT showed better sensitivity (0.6) than MIBG (0.3) for detecting bone, and bone marrow affection in neuroblastoma (0.285 for PET; 0.214 for MIBG), yet this was all not statistically significant. It was found that post-therapy I-^{131} MIBG imaging reveals more metastatic neuroblastoma lesions compared with pre therapy I-^{131} MIBG imaging and thus post-therapy I-^{131} MIBG scans are thought to delineate the true extent of disease more accurately.

By analyzing our results, we found a concordance rate of 55.7% between MIBG and PET scan in detection of primary site but inter-rater test (Kappa) was of poor strength, while it conveyed high strength (0.666) in detecting bone metastasis, this finding coincides with the Korean study [12].

Comparing both modalities in detecting various tumor sites we found that both modalities were very close in their diagnostic ability (86.6% for both modalities in detecting primary tumor site, 83.3 for PET/CT and 76.6% for MIBG in accurately detecting boney lesions, 66.6% for PET/CT and 66.3% for MIBG in detecting Bone marrow infiltration), this shows that PET/CT is an efficient modality in detection of neuroblastoma cells at various body regions.

The surprisingly limited value of MIBG in detecting primary tumor involvement (sensitivity 0.58, PPV 0.56-1, NPV 0.5) can be mostly explained by its dependence on degree of uptake of radioactive iodine, the more active role of MIBG scan in detecting response to therapy and recurrence [2].

It should be stated that ^{18}F-FDG/ PET-CT good results is due to tumor-to-background contrast and high tracer uptake by NB lesions, and also coupling PET scan with CT imaging made the result more representative and well delineated. In another study ^{123}I-MIBG scintigraphy and $^{(18)}$ F-FDG PET showed noticeable differences in their uptake patterns. ^{18}F-FDG PET was more sensitive and specific for the detection of neuroblastoma lesions [13].

Overall, ^{18}F-FDG/ PET demonstrated a good imaging quality, with high sensitivity and specificity. Comparing both modalities (MIBG and PET scan) between stages III and IV disease, it showed better delineation of lesions at all sites in stage IV than stage III which might be attributed to more tumor burden in stage IV.

A lot of studies are in concordance with our results, as Shulkin et al. (1996) who reported tumoral ^{18}F-FDG avidity in 16 out of 17 patients, yet in most cases MIBG was superior for tumor delineation [3]. The marginal superiority of PET/CT over MIBG in our study might be explained by coupling PET with CT imaging, while it was found that difference in sensitivity between both modalities is significant (P = .00815).

In a retrospective study of 85 paired scans in 40 patients (with stage IV NB), ^{131}I-MIBG was superior to ^{18}F-FDG PET [4, 5]. Similarly, ^{131}I-MIBG was more sensitive overall and for bone lesions than ^{18}F-FDG PET in the study patients, assessed before ^{131}I-MIBG therapy [8].

In our study after comparing with CT scan, bone scans and bone marrow biopsy results, taking into consideration PPV, and NPV of both scans, the overall accuracy for PET/CT was 86.6% in primary tumor detection, 83.3% in bone metastases detection, and 66.6% for bone marrow detection while for MIBG scan it was 86.6% for primary site, 76.6% for bone and 66.3% for bone marrow detection. This finding of both modalities, although statistically not significant after comparing

their diagnostic value in neuroblastoma, yet considers PET/CT a very useful complementary tool in diagnosis and management of neuroblastoma patients.

Another study comprising 51 high-risk patients with neuroblastoma showed that ^{18}F-FDG PET is better than MIBG in detecting both extracranial osteomedullary and soft-tissue lesions, but it was inferior in detecting skull lesions, unless these demonstrated a considerable soft-tissue component, mainly because of the adjacent high physiologic ^{18}F-FDG [9].

The main advantage of ^{131}I-MIBG over ^{18}F-FDG was its superiority in showing clearly the bone–bone marrow component of the disease. This finding was confirmed in our study showing that strength of agreement between both modalities was only seen in detecting boney lesions (Kappa=0.666) while to a lesser extent the strength of agreement was fair (Kappa=0.28) in detecting B.M infiltration and it was very poor in detecting primary lesions (Kappa=0.001). So we conclude that PET/CT scan can aid as a complementary study in detecting boney lesions.

We also found that ^{18}F-FDG may exhibit physiologic accumulation in the bone marrow regardless of whether it is infiltrated or not, as 6 of our patients showed PET/CT uptake in bone marrow while their BM biopsies were negative for malignancies.

It has been stated that ^{18}F-FDG could be better in detecting liver lesions [10, 11] because of physiologic ^{131}I-MIBG distribution in the liver, this hypothesis was not confirmed by our results in 3 patients having hepatic lesions.

The decisions for diagnostic staging, local control with surgery and stem cell transplantation or even giving radiation therapy to positive sites prior to stem cell transplantation, may be based on combining the results of all modalities.

We believe a more sound therapeutic decision may be taken for each patient incorporating PET/CT results with other diagnostic modalities in decision making.

We are aware that our study has its drawbacks as it is carried out on a limited number of patients, and that the real diagnostic impact of ^{18}F-FDG PET/CT in the management of NB should be further investigated, as well as the standardization of comparing both techniques is not till now optimum. However, the new potential applications of this tracer in pediatric cancer population should be further investigated. The exact role of ^{18}F-FDG PET/CT in neuroblastoma is yet to be determined.

In conclusion, PET/CT is a good diagnostic tool for children with neuroblastoma. It conveys a high sensitivity and specificity in diagnosing neuroblastoma in children. It is complementary with other tools in detecting lesions at various sites especially bone lesions, and its impact in managing neuroblastoma should be furtherly investigated. We believe that both modalities are efficient in detecting neuroblastoma and should be complementary used in diagnosis and management decisions of neuroblastoma.

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