Accuracy of FDG-PET/CT and paraneoplastic antibodies in diagnosing cancer in paraneoplastic neurological syndromes

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Objective: There is still no consensus about whether to perform PET/CT to detect carcinoma in paraneoplastic neurological syndromes (PNS) in patients with or without antibodies. The aim of this study is to determine the diagnostic accuracy of PET/CT and antibodies in patients with PNS.

Material and Methods: A retrospective study was conducted on patients with clinically suspected PNS between 2008 and 2013. The association between histopathological findings, paraneoplastic antibodies, and PET/CT findings were evaluated. Sensitivity and specificity for the detection of underlying malignancy were calculated for PET/CT and paraneoplastic antibodies.

Results: A total of 42 patients were analyzed. Of these 42 patients, 32 (75%) had a classical PNS, 6 (14%) had positive PET/CT findings, and 34 were tested for the presence of antibodies (anti-Hu Ab, anti-Yo Ab, and anti-Ri Ab). Twenty one of 34 patients had positive antibodies. Of the 6 patients with positive PET/CT findings, 6 had positive histopathological results. Among 21 patients with positive biomarkers, carcinoma was confirmed in only 5 patients. One patient with negative antibodies, but positive PET/CT findings, was diagnosed with a tumor. Gastric carcinoma was detected in 1 patient with negative PET/CT findings and antibodies during follow-up. Based on the results, PET/CT was found to have 85.71% sensitivity, 100% specificity, 100% positive and 97.22% negative predictive values in the detection of tumors.

Conclusion: PET/CT has a certain diagnostic accuracy for detecting underlying malignancy in patients with PNS, regardless of the presence of paraneoplastic antibodies.

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Utilidad de la PET/TC con FDG y los anticuerpos paraneoplásicos para el diagnóstico de neoplasia en el síndrome neurológico paraneoplásico

Objetivo: No hay un criterio unánime para realizar PET/TC en la detección de carcinoma en pacientes de síndrome neurológico paraneoplásico (PNS), con o sin anticuerpos. Nuestro objetivo es buscar la utilidad diagnóstica de la PET/TC y los anticuerpos en pacientes con PNS.

Material y métodos: Se examinaron retrospectivamente los pacientes con sospecha clínica de PNS estudiados entre 2008 y 2013. Se evaluó la asociación entre los resultados histopatológicos, los anticuerpos y los resultados de la PET/TC. Se calcularon la sensibilidad y la especificidad de la PET/TC y de los anticuerpos paraneoplásicos para la detección de malignidad.

Resultados: Se analizaron un total de 42 pacientes. De ellos 32 pacientes (el 75%) tenían un PNS clásico. A todos se les había realizado PET/TC y 6 (el 14%) tuvieron resultados positivos. Se determinó la presencia de anticuerpos en 34 pacientes (anticuerpos anti-Hu, anticuerpos anti-Yo y anticuerpos anti-Ri). Veintiuno de los cuales dieron positivo. Los 6 pacientes con resultados PET/TC positivos tuvieron resultados histopatológicos positivos. Entre los 21 pacientes con biomarcadores positivos, el carcinoma se confirmó solo en 5 pacientes. A un paciente con resultado negativo para anticuerpos, pero positivo en la PET/TC, se le diagnosticó un tumor. Se detectó carcinoma gástrico en un paciente con resultados negativos en la PET/TC y anticuerpos en el periodo de seguimiento. Según los resultados, se comprobó que la PET/TC tiene un 85.71% de sensibilidad, un 100% de especificidad, con valor predictivo positivo de 100% y valor predictivo negativo de 97.22% en la detección de tumores.

Conclusión: La PET/TC tiene un cierto grado de exactitud diagnóstica para detectar malignidad subyacente en pacientes con PNS, sin importar la presencia de anticuerpos paraneoplásicos.

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Introduction

Paraneoplastic neurological syndromes are rare diseases, which are not directly related to the primary tumor and metastasis. PNS may be immune-mediated and occur several months or years before the diagnosis of cancer. The signs and findings of PNS may regress by treatment of the related malignancies. The wide clinical spectrum of PNS may manifest as an underlying cancer or a first sign and symptom of a new cancer. Although the incidence of PNS is less than 1%, it is important to consider these diseases as their clinical presentation could manifest with a first and prominent sign of a new or deep-seated cancer. Therefore, early diagnosis of the underlying malignancies can play a crucial role to start the accurate treatment. The clinically diagnostic criteria of PNS were reported in 2004. To contribute to the diagnosis, serum antibodies (Ab) are screened in patients suspected of having PNS. However, the abnormal Ab are not always associated with occurrence of PNS. Moreover, these antibodies can increase without clinical manifestations of PNS. Conventional imaging modalities contribute to the screening of malignant lesions in patients with PNS. However, these imaging modalities do not have a high specificity or sensitivity for the detection of the cancer. These situations make the diagnosis of underlying cancer difficult. Several studies have shown the utility of FDG PET/CT in the diagnosis of cancer in patients with PNS. However, there is no consensus whether FDG PET/CT should be performed for the detection of cancer in the clinically suspected PNS patients with or without detectable antibody.

The aim of this study is to investigate the role of FDG PET/CT and well characterized serum Ab in diagnosis of cancer in patients with clinically suspected PNS. In addition, this study sets out to determine whether or not the method of PET/CT is suitable for accurate detection of underlying cancer in patients with clinically suspected PNS.

Material and methods

Between January 2008 and September 2013, patients with clinically suspected PNS who were transferred to PET/CT unit for FDG PET/CT imaging were examined retrospectively and included in the study. PNS was diagnosed by the referring physicians on the basis of recommended criteria. Patients with PNS were divided into two groups as classical and non classical. The association between clinical follow-up, histopathological findings, paraneoplastic Ab and PET/CT findings were evaluated. Patients with low possibility of PNS, who had not met the PNS criteria and not performed the anatomical imaging methods were excluded. Paraneoplastic Ab including anti-Hu Ab, anti-Yo Ab and anti-Ri Ab in blood and cerebrospinal fluid were evaluated. These Ab detected by immunohistochemistry/immunofluorescence methods. The FDG PET/CT results were compared with the histopathological diagnosis to validate the specificity and sensitivity of the method.

PET/CT protocol

PET/CT studies were performed by using 6-slice CT integrated high resolution PET scanner (Siemens Biograph LS O Hi-REZ PET/CT Illinois, USA). FDG injection (370–555 MBq (10–15 mCi)) was applied intravenously to the patients with a minimum 4 h fasting blood glucose level of under 150 mg/dl. 1–1.5 h after the injection, iv unenhanced lower dose CT and then the PET images of the area including the vertex-lower extremity were taken. The images were generally taken at ~8 bed position and in 3 min bed mode.

In the evaluation of PET/CT images; the attenuation corrected PET images were examined as a standard. When necessary; noncorrected PET images were also examined. Also non-enhanced CT images were shortly reviewed. A higher FDG uptake than physiological background activity (maximum standardized uptake value more than 2.5 g/ml) was accepted as PET positivity. The images were interpreted by two experienced nuclear medicine specialist.

Statistical analysis

The normality of the distribution of data was assessed using Shapiro–Wilk and single-sampling Kolmogorov–Smirnov tests. Parametric distributed data are presented as mean ± standard deviation, and non-parametric distributed data as medians and minimum–maximum values. Nominal and categorical variables are presented as frequencies and percentages. The parametric distribution was compared with the student t-test in independent groups and the others with the Mann–Whitney U-test. Categorical variables were evaluated with chi-square and Fisher’s exact contingency tests. The tests were two-sided. P values of <0.05 were considered to indicate statistical significance. Statistical analysis was performed with SPSS statistical software, version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

In this retrospective study, we examined the data of 241 patients with suspected paraneoplastic syndrome who had been referred for FDG PET/CT. Forty-two of 241 patients classified as classical or non classical PNS according to the recommended criteria were included to study. Most of these patients had classical syndromes, including lymbyc encephalitis in 14 (33%), cerebellar degeneration in 12 (28%), Lambert–Eaton in 3 (7%) and encephalomyelitis in 3 (7%). Patients with classical and non classical PNS are presented in Table 1. Table 2 shows demographic and baseline clinical characteristics of patients.

Table 1

<table>
<thead>
<tr>
<th>Presentation of patients with classical and non classical paraneoplastic neurological syndromes.</th>
<th>Classical PNS n (%)</th>
<th>Non classical PNS n (%)</th>
</tr>
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<tbody>
<tr>
<td>Limyic encephalitis 14, (33)</td>
<td>Motor neuron deficiency 4, (9)</td>
<td></td>
</tr>
<tr>
<td>Cerebellar degeneration 12, (28)</td>
<td>Myasthenia gravis 3, (7)</td>
<td></td>
</tr>
<tr>
<td>Lambert Eaton 3, (7)</td>
<td>Optic neuritis 2, (6)</td>
<td></td>
</tr>
<tr>
<td>Encephalomyelitis 3, (7)</td>
<td>Sensory neuropathy 1, (3)</td>
<td></td>
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</table>

Table 2

<table>
<thead>
<tr>
<th>Demographic and baseline clinical characteristics of the patients.</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, median range)</td>
<td>58 (14–82)</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>61.9/38.1</td>
</tr>
<tr>
<td>Classical PNS/non-classical PNS (%)</td>
<td>75/25</td>
</tr>
<tr>
<td>PNS antibodies, positive (n)</td>
<td>21</td>
</tr>
<tr>
<td>Anti-Hu (n)</td>
<td>19</td>
</tr>
<tr>
<td>Anti-Yo (n)</td>
<td>18</td>
</tr>
<tr>
<td>Anti-Ri Ab (n)</td>
<td>9</td>
</tr>
<tr>
<td>PNS antibodies, negative (n)</td>
<td>13</td>
</tr>
<tr>
<td>Follow up (months)</td>
<td>35 (8–68)</td>
</tr>
</tbody>
</table>
There were 7 patients (17%) with cancer diagnosis confirmed by histopathological examination. Case 1 was confirmed by a gastric biopsy and endoscopy, case 2 confirmed based on right inferior jugular lymph node biopsy, case 3 was confirmed by anterior mediastinal mass biopsy with video-assisted thoracoscopic surgery, case 4–5–6 by cytology and bronchoscopy and case 7 was confirmed surgically. Diagnostic CT was performed in these 7 patients before referring to the PET/CT. Five of 7 patients had suspicious CT findings for malignancy whereas others had negative findings. Case 2 had a nonspecific mediastinal lymph node, case 3 had hilar lymph nodes without anterior mediastinal mass. A non specific lung nodule was detected in cases 5 and 6, case 7 had a bone lesion but primary tumor and other lesions were not detected on CT scan. All these patients were referred to PET/CT scan for a number of reasons like these. Clinical and imaging findings of the 7 patients with histopathologically diagnosed cancer were presented in Table 3.

PET/CT scan was negative only in 1 (case 1) of 7 cancer patients who had negative Ab. Out of these, 6 patients were also had a positive PET/CT results (Figs. 2 and 3). Thirty-five patients were found not to have a cancer diagnosis based on clinical follow up (83%). Based on these results, FDG-PET/CT was found to have a sensitivity of 85.71% (6 out of 7) and the specificity of 100% (35 out of 35) in the detection of tumor. Positive and negative predictive values were 100% (6 out of 6) and 97.22% (35 out of 36), respectively.

We also found that the sensitivity of Ab to detect tumor was 71.43% (5 out of 7) and the specificity was 40.74% (11 out of 27) by the evaluation of 34 patients with positive Ab. Positive and negative predictive values were 23.81% (5 out of 21) and 84.62% (11 out of 13), respectively.

Discussion

The most obvious finding to emerge from this study was that FDG PET/CT has high sensitivity and specificity in the detection of underlying malignancy in clinically suspected PNS patients. Another important subject of this study was that paraneoplastic Ab should not be an indispensable factor for performing FDG PET/CT in patients with PNS.

Several studies have reported that FDG PET/CT was a useful imaging modality for detecting underlying primary tumor in the clinically suspected PNS patients.5–10 However, there are variable results concerning FDG PET/CT utility in the detection of primary tumor in clinically suspected PNS patient having paraneoplastic Ab. Current suggestion for patients with PNS is that FDG PET/CT has a great value in detecting primary tumor with positive serum markers.11 A study indicated that FDG PET had an 83.3% sensitivity and 25% specificity and should only be performed for patients with well-characterized paraneoplastic Ab.9 On the contrary, previous studies reported high sensitivity and specificity of FDG PET/CT for detecting primary tumor in clinically suspected PNS patients without positive Ab.5,8,11 However, in these studies, paraneoplastic Ab were found positive on a small number of patients. In the present study, although we evaluated well characterized Ab, close to half of our patients had positive Ab. However, the primary tumor could be found in only 5 of them. Surprisingly, 2 tumor positive patients had negative Ab. Moreover, poor sensitivity and specificity of the Ab in the diagnoses of underlying tumor was found in the present study. These results indicated that even well characterized Ab may have a more restricted role to detect primary tumor in clinically suspected PNS. Patients with clinically suspected PNS were followed up to six years in the previous studies. They did not found an underlying malignancy even at 6-year follow up in Ab positive PNS patient.5,8,11 It is emphasized that the time between onset of PNS and the detection of a tumor in Ab positive patients might be as long as 8 years.12 It is agreed that a patient with clinically suspected PNS may have a too small tumor that may be missed by FDG PET/CT. Therefore these patients should be followed up as many years. In the present study, we also followed up patients with a negative FDG PET/CT up to 5.5 years. Only 1 patient was diagnosed as a gastric tumor by endoscopic examination. This patient had also negative Ab.

Table 3
Clinical and imaging findings of 7 patients with histopathologically diagnosed cancer.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)/sex</th>
<th>Clinical presentation</th>
<th>Antibodies</th>
<th>PET findings</th>
<th>Histopathological diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61/male</td>
<td>Lambert–Eaton syndrome</td>
<td>Negative</td>
<td>Negative</td>
<td>Gastric carcinoma (signet ring cell type)</td>
</tr>
<tr>
<td>2</td>
<td>68/female</td>
<td>Cerebellar degeneration</td>
<td>Negative</td>
<td>Positive (multiple sites of avid FDG uptake. Supra- and infradiaphragmatic lymph nodes).</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>3</td>
<td>60/male</td>
<td>Lambert–Eaton syndrome</td>
<td>Anti-Ri</td>
<td>Positive (anterior mediastinal mass)</td>
<td>Thymic carcinoma</td>
</tr>
<tr>
<td>4</td>
<td>64/male</td>
<td>Motor neuron deficiency</td>
<td>Anti-Hu/Ri/Yo</td>
<td>Positive (left upper lobe lung nodule)</td>
<td>Small cell lung carcinoma</td>
</tr>
<tr>
<td>5</td>
<td>65/male</td>
<td>Cerebellar degeneration</td>
<td>Anti-Hu</td>
<td>Positive (left upper lobe lung nodule)</td>
<td>Small cell lung carcinoma</td>
</tr>
<tr>
<td>6</td>
<td>71/male</td>
<td>Motor neuron deficiency</td>
<td>Anti-Hu/Ri/Yo</td>
<td>Positive (increased gallbladder wall thickness, multiple lung and bone lesions)</td>
<td>Gallbladder carcinoma</td>
</tr>
<tr>
<td>7</td>
<td>54/male</td>
<td>Encephalomyelitis</td>
<td>Anti-Hu/Yo</td>
<td>Positive (left lower lobe lung nodule)</td>
<td>Thymic carcinoma</td>
</tr>
</tbody>
</table>
Fig. 2. Case 3, a 60-year-old man, presented with Lambert–Eaton syndrome. Anti-Ri antibody was positive. FDG PET/CT demonstrate right paramediastinal retrosternal hypermetabolic mass. Lesion pathology: thymic carcinoma.

A number of previously published studies have mentioned different results regarding sensitivity and specificity of FDG PET/CT for detecting primary tumor in PNS.5–10 Most of these studies have agreed on moderate to high sensitivity (85.7–100%) and specificity (82–91.3%) of FDG PET/CT in the detection of primary tumor in PNS patients.5,10 Studies which reported moderate to poor sensitivity (83.3–75%) and specificity (74.3–25%), used only PET to detect the tumor and they had also a small number of patients compared to the others.6,9 Recent studies have shown that the combination of PET and CT scanning was superior imaging modality than the using of PET or CT alone to diagnose cancer in patients with PNS.13–15 Nevertheless, it is emphasized that a negative PET/CT does not rule out primary cancer. Furthermore, we also reported one patient with negative PET/CT diagnosed with a malignancy in follow up. A recent

Fig. 3. Case 5, a 65 year-old man, presented with cerebellar degeneration. Anti-Hu antibody was positive. FDG PET/CT demonstrate paracardiac hypermetabolic lesion in the left lower lobe of the lung. Lesion pathology: small cell lung cancer.
study conducted by Vaidyanathan et al.,5 reported that the sensitivity and specificity of PET/CT to detect malignancies of PNS were 100% and 82%, respectively. They also found 100% negative predictive value of PET/CT. Similar to the aforementioned study results, we found high accuracy of FDG PET/CT to diagnose primary tumor in clinically suspected PNS patient. We also found a negative predictive value of 97.22% of PET/CT with a one false negative finding. This patient had a signet ring cell type gastric carcinoma. Most studies have agreed on FDG PET/CT has lowest sensitivity for the detection of signet ring cell type gastric carcinoma.16 Several studies reported positive predictive value ranging between 42% and 83%. In the present study we have a 100% positive predictive value with no false positive result. The relatively small number of cases and well selected patients for PET/CT imaging may explain this surprising result.

Limitations

Finally, our findings in this report were subject to several limitations. First, this study had a retrospective design. Second, the number of PNS patients seems to be small. However, it is well known that the incidence of PNS is very low. Third, although patients in the present study were followed up to 5.5 years, detection of a tumor in Ab positive PNS patients might be as long as 8 years.12 Therefore, long-term follow-up is crucial to diagnose the possible underlying tumor. Fourth, although there are many of well characterized paraneoplastic Ab, we could analyze only three well characterized paraneoplastic Ab including anti-Hu Ab, anti-Yo Ab and anti-Ri Ab.

Conclusions

According to the results obtained from this study, FDG PET/CT seems as a highly accurate diagnostic imaging modality for detecting underlying tumor in patients with clinically suspected PNS regardless of the presence of well-characterized paraneoplastic Ab.

Conflicts of interest

The authors report no conflicts of interest.

Acknowledgement

This work was supported by the Scientific Research Projects Coordination Unit of Istanbul University under project number 9555.

References


