Clinical Value of $^{18}$F-fluoro-Deoxyglucose Positron Emission Tomography for Patients with Fever of Unknown Origin

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We describe the diagnostic contribution of $^{18}$F-fluoro-deoxyglucose (FDG) positron emission tomography (PET) scan in 58 consecutive cases of fever of unknown origin (FUO) and compare this new approach with gallium scintigraphy. This investigation was performed from March 1996 through October 1998 at Gasthuisberg University Hospital in Leuven, Belgium. A final diagnosis was established for 38 patients (64%). Forty-six FDG-PET scans (79%) were abnormal; 24 of these abnormal scans (41% of the total number of scans) were considered helpful in diagnosis, and 22 (38% of the total number) were considered noncontributory to the diagnosis. In a subgroup of 40 patients (69%), both FDG-PET and gallium scintigraphy were performed. FDG-PET scan and gallium scintigraphy were normal in 23% and 33% of these cases, respectively; helpful in diagnosis in 35% and 25%, respectively; and noncontributory in 42% each. All foci of abnormal gallium accumulation were also detected by use of an FDG-PET scan. We conclude that FDG-PET is a valuable second-step technique in patients with FUO because it yielded diagnostic information in 41% of the patients in whom the probability of a definite diagnosis was only 64%. FDG-PET scan compares favorably with gallium scintigraphy for this indication. Because of the quick results (within hours instead of days), FDG-PET scan may replace gallium scintigraphy as a radiopharmaceutical for the evaluation of patients with FUO.

Several studies have established the value of $^{18}$F-fluoro-deoxyglucose (FDG) positron emission tomography (PET) in the diagnosis of malignant diseases [1–3], but very few studies have evaluated its usefulness in the diagnosis of inflammatory or infectious disorders [4–7] or in the workup of classic fever of unknown origin (FUO) [8]. FUO can be caused by >200 diseases; major causes are infections, tumors, and noninfectious inflammatory conditions, which are sometimes grouped as rheumatologic disorders [9].

In a previous study, we reported our experience with gallium-67 scintigraphy in the diagnostic approach of patients with FUO [10]. Gallium scintigraphy yielded diagnostic information in 29% of the patients, and we decided to use this examination as a second-step procedure (not as a last-resort procedure) for patients with FUO. Some researchers agree with these conclusions; others doubt the usefulness of this and other scintigraphic techniques in patients with FUO [9, 11–13].

The exact role and place of nuclear medicine in the investigation of FUO has not yet been delineated [13]. FDG is a glucose analogue that is transported across the capillary and sarcolemmal membranes in proportion to the rate of glucose uptake. Increased FDG uptake can be observed in cells with high metabolic requirements, such as inflammatory and tumor cells. FDG cannot leave the cell once it is taken up, and hence it can be expected to be a useful radiopharmaceutical in the evaluation of patients with FUO. The lack of...
specificity to discriminate between infectious and noninfectious inflammation is an advantage rather than a drawback in this clinical setting [13]. We evaluated the role of FDG-PET scintigraphy as a second-step examination in 58 consecutive patients with FUO and compared it with gallium scintigraphy.

PATIENTS AND METHODS

Patients. Patients who met the revised definition criteria of FUO (febrile illness of >3 weeks' duration, temperature >38.3°C, and no diagnosis after 3 days of in-hospital investigation) [14] were prospectively entered in a study protocol to evaluate the role of FDG-PET scan as a second-step investigation technique. We did not use a rigid investigation protocol for the diagnostic workup of patients with FUO, but written guidelines were available on the wards. These guidelines consisted of a checklist of diagnostic procedures, divided into first-, second-, and third-level tests. FDG-PET scan and gallium scintigraphy were ordered for patients in whom first-step examinations (history, clinical examination, routine laboratory tests, cultures, serology, chest radiographs, and abdominal echography) yielded no potentially diagnostic clues.

Subsequent diagnostic studies consisted of either tests (CT or MRI scans, endoscopy, or biopsy) directed by the findings of PET and gallium scintigraphy, or—in case of normal or misleading scintigraphic results—of a series of investigations based on the relative frequencies of possible underlying disease. When fever or signs of inflammation subsided during the observation, no further examinations were performed, and the patients were followed closely as outpatients.

FDG-PET scan. Whole-body images were obtained with a CTI-Siemens 931/08/12 scanner, with an axial field of view of 10.1 cm. A total of 6.5 MBq/kg were injected iv 1 h before the scan. Whole-body imaging was performed with a 5 min per bed position for head, thorax, and abdomen and with a 4 min per bed position for the lower extremities. Total time of the scan was ~90 min. Patients fasted for ≥6 h before the examination.

Gallium-67 scan. Total body imaging was performed 72 h after iv injection of 75 MBq gallium-67 citrate. All patients received a bowel preparation the evening before the scanning in order to reduce the normal accumulation of gallium-67 in the colon. Abdominal imaging was repeated 12–24 h after a second cleansing enema if there was increased abdominal tracer accumulation. The images were acquired by a large field of view camera (Siemens) equipped with a medium energy collimator. The projections (anterior and posterior) of the head, chest, and abdomen were acquired during 6 min.

FDG-PET and gallium scintigraphy were ordered simultaneously, but because of the limited availability of gallium citrate, FDG-PET was always performed as the first procedure. When diagnosis was established or when the fever subsided in the interval between the FDG-PET scan and the scheduled gallium scintigraphy, the latter procedure was canceled.

Interpretation. FDG-PET and gallium scintigraphy were read independently. The scans were always interpreted by 2 of 3 staff members of the department of nuclear medicine and rated as normal or abnormal. Results were judged to be abnormal if focal accumulation of the tracer was detected outside of the areas of physiological uptake. If there were differing interpretations of the scan result, the 3 staff members involved in the study had to reach a consensus.

Clinical assessment of abnormal test results. Abnormal FDG-PET and gallium scans were retrospectively evaluated by the clinicians (D.B. and J.D.C.) for their diagnostic contribution. This assessment was based on the final diagnosis, established at the time of discharge or during follow-up. Abnormal scintigraphic studies were categorized as “helpful in diagnosis” or “noncontributory to diagnosis.” They were regarded as helpful in diagnosis when the abnormal uptake pointed to the organ or tissue where the cause of the fever was eventually found by additional techniques, such as CT scan, MRI, endoscopy, or biopsy. They were regarded as diagnostically noncontributory when the detected abnormality was considered to be unrelated to the illness causing the FUO. Abnormal scans of patients in whom no or limited further investigation was performed because their fever subsided were also labeled as diagnostically noncontributory.

Statistical analysis. The χ² test was used for comparison of categorical data.

RESULTS

Patients. Fifty-eight patients with FUO underwent FDG-PET scanning from March 1996 through October 1998. In 10 patients (18%), an infectious underlying disease was found: tuberculous meningitis, tuberculous spondylodiscitis, miliary tuberculosis, bacterial spondylodiscitis, infected bronchiectasis, atypical pneumonia, osteomyelitis, urinary tract infection (n = 2), and cytomegalovirus infection. A malignant disorder was the cause of FUO in 6 patients (10%): acute aleukemic myeloid leukemia (n = 2), chronic myelomonocytic leukemia, lymphoma, colon cancer, and transitional cell carcinoma of the bladder. A multisystem inflammatory disease or vasculitis was found in 17 patients (29%): adult-onset Still’s disease (n = 4), sarcoidosis (n = 3), reactive arthritis of the knee, systemic lupus erythematosus, giant cell arteritis or polymyalgia rheumatica (GCA-PMR; n = 3), Henoch-Schönlein purpura, periarthritis, microscopic polyangiitis, cutaneous polyarteritis nodosa, and relapsing polychondritis. Two patients had recurrent hyperthermia, and in 3 patients, an inflammatory pseudotumor was the cause of FUO.
Table 1. Diagnostic contribution of [18F]fluoro-deoxyglucose positron emission tomography scan to the different diagnostic categories of fever of unknown origin.

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>n</th>
<th>Normal</th>
<th>Helpful in diagnosis</th>
<th>Noncontributory to diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>10</td>
<td>2</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Tumor</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Multisystem disease</td>
<td>9</td>
<td>2</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>8</td>
<td>0</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Persistent hyperthermia</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>No diagnosis</td>
<td>20</td>
<td>4</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>12 (21)</td>
<td>24 (41)</td>
<td>22 (38)</td>
</tr>
</tbody>
</table>

In 20 patients (36%), the cause of FUO was not found. In 14 of these patients, fever and inflammation subsided spontaneously. All patients were followed as outpatients, and they remained well. Four patients had had intermittent fever for several years, and no diagnosis could be established. For one patient, treatment with nonsteroidal anti-inflammatory agents was started, which resulted in normalization of the patient’s temperature and signs of inflammation. For another patient with unexplained pulmonary infiltrates, treatment with corticosteroids was started, with good results.

**FDG-PET scan results.** Forty-six (79%) of 58 PET scans were interpreted as abnormal and 12 (21%) as normal. Twenty-four of 46 abnormal scans correctly pointed to the source of fever, whereas 22 abnormal scans were clinically judged to be noncontributory to the diagnosis. Thus only 52% of the abnormal scans were clinically helpful.

Table 1 shows the result of FDG-PET scan in the different major diagnostic categories of patients with FUO. Fifty-six percent of FDG-PET scans were helpful in the diagnosis of infection or malignancy. For the patients with tuberculous meningitis, spondylodiscitis, osteomyelitis, infected bronchiectasis, and pneumonia, FDG-PET scan directly pointed to the source of fever. The same was true for patients with a solid-tissue tumor or lymphoma. In the patients with aleukemic leukemia, FDG-PET scan was not helpful in diagnosis.

For the 9 patients with multisystem inflammatory diseases without underlying vasculitis, FDG-PET scan was judged helpful in diagnosis in 5 patients. For 2 patients with Still’s disease, it was judged helpful in diagnosis because of FDG uptake in the knees and in the lymph nodes, spleen, and bone marrow. For 2 of 3 patients with sarcoidosis, hilar FDG uptake suggested the diagnosis, but the increased FDG uptake in the lungs, dorsal spine, and abdomen of the third patient was judged diagnostically noncontributory.

The 8 patients with vasculitis all displayed increased FDG uptake either in the vessels of the legs (GCA-PMR, Henoch-Schönlein purpura, microscopic polyangiitis, cutaneous polyarteritis nodosa, and relapsing polyarthritis) or in the thoracic arteries (GCA-PMR [n = 2] and thoracic periaortitis). The increased vascular FDG uptake was considered helpful in diagnosis for 7 of these patients; we considered the vascular uptake noncontributory to diagnosis of relapsing polyarthritis because there was no increased FDG uptake in the inflamed cartilage.

As could be expected, FDG-PET scan was normal for the 2 patients who had habitual hyperthermia but abnormal for the 3 patients who had inflammatory pseudotumor. The clinical value of the abnormal uptake in the undiagnosed patients could not be determined because a definite diagnosis was lacking for these patients.

Table 2. Diagnostic contribution of [18F]fluoro-deoxyglucose positron emission tomography (FDG-PET) scan and gallium scintigraphy for 40 patients with fever of unknown origin who underwent both isotopic examinations.

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>n</th>
<th>FDG-PET scan</th>
<th>Gallium scan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Infection</td>
<td>6</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Tumor</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Multisystem disease</td>
<td>8</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Persistent hyperthermia</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No diagnosis</td>
<td>16</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>9 (23)</td>
<td>14 (35)</td>
</tr>
</tbody>
</table>

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An 18F-fluoro-deoxyglucose (FDG) positron emission tomography (PET) scan, visualized on a lateral view, showing increased FDG uptake in the cervical and thoracic spinal canal (arrows) of a 51-year-old man who was admitted to our hospital with a 3-month history of temperature $>39^\circ C$. The patient had no signs or symptoms other than fever. A thorough exploration in another hospital had not revealed a focus of the fever, and empirical therapy with broad-spectrum antibiotics had been unsuccessful. CSF from a lumbar puncture had a high protein content (4.23 g/dL), a low glucose content (24 mg/dL), and an elevated WBC count (532 cells/µL: 82% lymphocytes, 10% monocytes, and 8% neutrophils). Results of cultures for bacteria, fungi, and Mycobacterium tuberculosis remained negative. Around that time, the patient developed difficulties with walking and cognition. Brain biopsy showed noncaseating granulomas with acid-fast bacilli. Triple tuberculostatic treatment was successful.

**Comparison between FDG-PET scan and gallium-67 scintigraphy.** Forty patients underwent both FDG-PET and gallium-67 scintigraphy. Table 2 shows the results of both examinations in the different major diagnostic categories. FDG-PET scan was judged helpful in diagnosis for 35% of the patients and gallium scintigraphy for 25% ($P = .7$; not significant). All foci of abnormal gallium accumulation were also detected by FDG-PET scan. An example of the difference between the 2 imaging techniques was the normal gallium scintigraphy in the case of tuberculous meningitis diagnosed by CSF analysis, which was prompted by the finding of increased FDG uptake in the lumbar canal on FDG-PET scan (figure 1). Gallium scintigraphy did not yield any indication of vasculitis, but we judged it helpful in diagnosis for 2 patients with GCA-PMR because of increased uptake in the shoulders. Gallium scintigraphy was also normal, in contrast to the intense FDG uptake, in the case of massive inflammation of the thoracic aorta (periaortitis), eventually diagnosed by means of CT scan and nuclear MRI (figure 2). In the case of transitional cell carcinoma of the bladder, FDG-PET scan pointed to pelvic pathology, but gallium scintigraphy was normal (figure 3).

**DISCUSSION**

FUO can be caused by >200 infectious, neoplastic, inflammatory, immunologic, and other conditions. Because of the atypical presentation, the major problem is to localize the pathology [9, 15]. Imaging techniques such as CT scan and MRI that concentrate on one area of the body have limited value if there are no localizing signs or symptoms. Gallium-67 citrate,
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Figure 3. An [18F]fluorodeoxyglucose (FDG) positron emission tomography (PET) scan showing increased FDG uptake in the bladder (arrow) and in retroperitoneal lymph nodes (arrowheads) of a 75-year-old woman who was admitted to our hospital because of temperature >38.6°C that persisted for 3 weeks after she had undergone endoscopic resection of a bladder polyp in another hospital. The patient also complained of pain in the right iliac fossa of several months’ duration. CT scan of the lower abdomen confirmed the presence of several enlarged lymph nodes and showed thickening of the bottom of the bladder. Cystoscopy showed a large, ulcerated, malignant-looking lesion; a transabdominal biopsy of an iliac lymph node showed metastasis of a large-cell carcinoma, compatible with a spread transitional cell carcinoma. Only palliative treatment could be offered.

labeled leukocytes, or IgG are the commonly used radiopharmaceuticals in the investigation of FUO [13, 16, 17].

In this prospective study of 58 consecutive patients who fulfilled the revised criteria for FUO [14], we evaluated the role of FDG-PET scan and gallium-67 scintigraphy as a second-step examination. After patients with persistent FUO gave a thorough medical history and underwent physical examination, routine blood tests, cultures, chest radiograph, and abdominal ultrasonography, they underwent FDG-PET scan and, whenever feasible, gallium-67 scintigraphy.

FDG-PET scan was considered helpful in the diagnosis of 41% of the patients. It should be kept in mind that a final diagnosis could be established for only 64% of the patients. In a previous study of FUO, we found that gallium scintigraphy yielded diagnostically useful information for 29% of the patients (n = 145) [10]. This statistically significant difference (P < .05) should be interpreted cautiously. Both groups of FUO patients,studied at different times, are similar as far as the causes of FUO and the number of undiagnosed patients are concerned (32% vs. 36%, respectively). However, in our first study, gallium was ordered as a third-level or last-resort procedure. Comparison with other series of patients who have FUO is difficult because of differences in study design [10, 13].

A disadvantage of FDG-PET scintigraphy is the high percentage of abnormal results (48%) that were eventually judged to be diagnostically noncontributory. This number of noncontributory scans is similar to that of gallium scintigraphy in the present study and in our previous experience [10]. Sixteen of 22 noncontributory FDG-PET scan results were found in the no-diagnosis group. Four of these patients had episodic fever, a subgroup with a known low chance of a final diagnosis being established [18]. Because we could not establish a definite diagnosis in these patients, who mostly defervesced spontaneously, we cannot consider all these abnormal results to be false positives, but we label them as clinically noncontributory or irrelevant. Indeed, if the involved body area is not completely anatomically or histopathologically investigated, the abnormal tracer accumulation cannot be considered to be a false-positive finding.

Aggressive interventions such as exploratory laparotomy are no longer recommended if the patient’s condition remains stable because 20%–30% of patients remain undiagnosed and resolve spontaneously. The main practical conclusion is that an abnormal FDG-PET scan result should be used as an indication for further intelligent testing (mainly CT, MRI, and biopsy of involved foci) but not for invasive procedures such as exploratory laparotomy. We prefer an approach guided by the results of FDG-PET instead of a standard investigation algorithm or protocol for those patients with FUO requiring further testing because their clinical condition is not stable.

The aim of our study was not only to evaluate the role of FDG-PET as a second-step procedure but also to compare it, whenever feasible, with gallium. Sixty-nine percent of the patients underwent both isotope studies. Not all patients underwent both studies because of the difference in availability of the 2 radiopharmaceuticals. Gallium can be ordered only 2 times a week at our institution, whereas FDG-PET scan is always available. Because of the costs and the risks of radiation exposure, we considered it unethical to perform gallium scintigraphy when the diagnosis was established by tests that were prompted by the FDG-PET findings or when the fever had subsided spontaneously in the interval between the 2 studies.

Because this approach might introduce a bias, in table 2 we compare the results of the 2 techniques in the subgroup of 40 patients who underwent both studies. Because of the small size of the sample, no statistically meaningful comparison can be made between FDG-PET and gallium scintigraphy, although...
FDG-PET seems to be a more useful tool (table 2). The percentage of clinically helpful abnormal results was higher, although not statistically significant (35% vs. 25%, respectively; \( P = .7 \)), whereas the percentage of noncontributory abnormal tests was the same (42%). Thus the slightly increased sensitivity of FDG-PET (i.e., higher number of abnormal test results) did not result in an increase of noncontributory tests. In other words, the increased sensitivity did not lead to loss of specificity. Moreover, all abnormalities detected by gallium scan were also detected by FDG-PET scan.

The major advantage of FDG-PET in the exploration of FUO, compared with gallium scintigraphy, lies largely in the vascular FDG uptake in patients with vasculitis, particularly in patients with GCA-PMR [19, 20]. Vascular FDG uptake pointed to vasculitis as the underlying cause for FUO in 7 patients. No side effects of FDG have been described in this application, and the radiation exposure is similar to that of gallium scintigraphy. In our country, FDG-PET is 3 times more expensive than gallium scintigraphy; however, the increased sensitivity did not result in an increase of noncontributory tests. In other words, the slightly increased sensitivity did not lead to loss of specificity. Moreover, all abnormalities detected by gallium scan were also detected by FDG-PET scan.

On the basis of our experience with 58 FUO patients and the comparison between FDG-PET and gallium scintigraphy in 40 (69%) of these patients, we conclude that FDG-PET can replace gallium scintigraphy in the workup of patients with FUO in institutions where this technique is available. The diagnostic yield of FDG-PET (i.e., higher number of abnormal test results) did not result in an increase of noncontributory tests. In other words, the increased sensitivity did not lead to loss of specificity. Moreover, all abnormalities detected by gallium scan were also detected by FDG-PET scan.

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On the basis of our experience with 58 FUO patients and the comparison between FDG-PET and gallium scintigraphy in 40 (69%) of these patients, we conclude that FDG-PET can replace gallium scintigraphy in the workup of patients with FUO in institutions where this technique is available. The diagnostic yield of FDG-PET is at least comparable to that of gallium scintigraphy, and the results are available within hours instead of days.

References