**18-F FDG-PET/CT in detecting metastatic infection in children**

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**Abstract**

**Purpose of the Report**: Metastatic infection is a severe complication of bacteraemia with high morbidity and mortality. The aim of this study is to investigate the diagnostic value of 18F-fluorodeoxyglucose-positron emission tomography combined with computed tomography (FDG-PET/CT) in children suspected of metastatic infection.

**Materials and Methods:** The results of FDG-PET/CT scans performed in children because of suspected metastatic infection from September 2003 to June 2013 were analyzed retrospectively. The results were compared to the final clinical diagnosis.

**Results:** FDG-PET/CT was performed in 13 children with suspected metastatic infection. Of the total number of FDG-PET/CT scans, 38% were clinically helpful. Positive predictive value of FDG-PET/CT was 71% and negative predictive value was 100%.

**Conclusions:** FDG-PET/CT appears to be a valuable diagnostic technique in children with suspected metastatic infection. Prospective studies of FDG-PET/CT as part of a structured diagnostic protocol are needed to assess the exact additional diagnostic value.

**Keywords:**

FDG-PET/CT; metastatic infection; bacteraemia; children

**Introduction**

One of the main complications of bacteraemia is secondary metastatic infection caused by spreading of the microorganisms to distant sites, especially in case of *Staphylococcus aureus* and *Streptococcus* spp. bacteraemia and candidemia (*1*). Reported incidence of these metastatic foci varies between 16% and 36% (*2-8*). Early detection and treatment of metastatic foci is important as morbidity and mortality are higher in patients with metastatic infectious disease, probably due to incomplete eradication during initial treatment (*6*).

To date, conventional radiologic techniques such as CT, MRI, and ultrasonography are often used to detect focal infectious disease. These techniques require the presence of guiding symptoms because usually only a fixed part of the body is visualized. However, metastatic foci are often asymptomatic. Vos et al. reported in 2012 that only 41% of the cases had symptoms guiding the attending physician in the diagnostic workup (*2*). 18F-fluorodeoxyglucose-positron emission tomography combined with CT (FDG-PET/CT) is increasingly utilized in infectious diseases and has proven its effectiveness in diagnosing infectious foci and has shown great results in fever of unknown origin (*9*). Also, FDG-PET/CT proved to be a valuable imaging technique in adult patients at high risk of metastatic infectious disease, even when the results of other diagnostic procedures are normal. In a retrospective study of 40 adult patients with bacteraemia and a high risk of complications, FDG-PET was used to diagnose a clinically relevant new focus in 45% of cases, while, on average, four conventional diagnostic tests had already been performed previously (*1*). A prospective study on the value of FDG-PET/CT in 115 adult patients with Gram-positive bacteraemia and at least one risk factor for metastatic infectious disease showed that routine FDG-PET/CT is a cost-effective tool to reduce morbidity and mortality (*10*).

Since no comparable studies have been performed in children, the aim of this study was to assess the diagnostic value of FDG-PET(/CT) to detect metastatic infectious foci in children with bacteraemia.

**Material and methods**

*Patients*

All children (age 0-17 years) who underwent FDG-PET/CT because of suspected metastatic infection after bacteraemia between September 2003 and June 2013 were identified using the database of the Nuclear Medicine Department of the Radboud university medical center. Metastatic infection was suspected when there were signs of infection more than 48h before initiation of appropriate treatment, or fever more than 72h after initiation of appropriate treatment, or positive blood cultures more than 48h after initiation of appropriate treatment. According to the Dutch law, this study was exempt from approval by an ethics committee, because of the retrospective character of this study and the anonymous storage of data.

*FDG-PET/CT*

FDG-PET/CT scans were performed on an integrated PET/CT scanner (Siemens Biograph until 2012 and after 2012 Siemens Biograph mCT, Knoxville, TN). Prior to FDG injection, patients fasted for at least 6 hours. Intake of sugar-free liquids was permitted. In all patients, glucose levels were checked and were below 10 mmol/l. Immediately prior to the procedure, patients were hydrated with an amount of water adapted to age up to 500 ml. If drinking was not possible, the patient was well hydrated with intravenous normal saline solution. The dose of FDG (Mallinckrodt Medical, Petten, The Netherlands or IBA, Amsterdam, The Netherlands) was calculated using the following formula: $\frac{6.4∙body weight \left(kg\right)}{minutes per bed position}MBq$ with a minimum of 20 MBq. The attending physician individually determined the necessity and dose of furosemide injection. One hour after intravenous injection of FDG and furosemide, emission images of the whole body were acquired. Images were corrected for attenuation using using a low-dose CT scan for FDG-PET/CT. The low-dose CT images were also used for anatomic correlation. Images were reconstructed using the ordered subsets-expectation maximisation algorithm.

*Interpretation of FDG-PET/CT*

FDG-PET/CT results were defined as abnormal if focal accumulation of the tracer was seen outside the areas of physiological or nonspecific uptake. Variable nonspecific and physiological uptake can be seen in bowel, epiphyseal plates, salivary glands, activated muscles, thymus, activated brown fat, brain, urogenital tract, and myocardial tissue. Non-specifically, symmetrically, homogeneously enhanced FDG uptake during febrile episodes can be observed in bone marrow and spleen, which is interpreted as non-pathologic in children with fever (*11*).

*Clinical assessment of test results and diagnosis*

The results of all FDG-PET/CT scans were compared to the final or probable clinical diagnosis to determine the diagnostic value of the FDG-PET/CT scans. The final diagnosis was not based on FDG-PET/CT results alone. All patients were evaluated with other imaging modalities and laboratory tests as were considered clinically appropriate. An abnormal scan was considered to be true-positive when abnormal FDG uptake pointed to the organ or tissue where the cause of the symptoms was eventually found. FDG uptake in the source of the infection, as well as in metastatic infectious foci, was considered as a true-positive result. True-positive results were further categorized as a “clinically relevant new finding” when the abnormality caused a change of treatment (longer duration of antibiotic therapy, switching to another antibiotic or combination of antibiotics, drainage of abscesses, or surgical intervention), as a “clinically irrelevant new finding” when the abnormality did not change treatment, or as “already known” when FDG-PET/CT showed only metastatic foci already diagnosed by other diagnostic techniques. Abnormal results were categorized as false-positive when the abnormality was not in accordance with the final or probable clinical diagnosis. A normal scan was considered to be true-negative when no metastatic complication or relapse of infection was diagnosed during clinical follow-up of at least 3 months. A normal FDG-PET/CT was considered false-negative when a focal infection or metastatic infectious disease was diagnosed by other means. High physiological uptake of FDG within the brain, urogenital tract and heart (without low-carb diet) makes FDG-PET/CT less suitable for the detection of infectious foci in these organs. Therefore, these organs were not evaluated for metastatic foci. Subsequently, scans were evaluated for their diagnostic distribution. True positive results were regarded as contributory when considered clinically relevant. False positive, true negative and false negative results were regarded as non-contributory to diagnosis.

*Statistical analysis*

For statistical analysis we used SPSS software package version 20.0.0 (SPSS, Chicago, IL).

**Results**

From September 2003 to June 2013 13 FDG-PET/CT scans were performed because of suspected metastatic infection in children. Patient characteristics and FDG-PET/CT results are shown in Table 1. None of the patients had neutropenia or malignancy in the medical history. All patients had at least one risk factor for developing metastatic infection. Thirty-eight percent of infections were community-acquired. In patients with metastatic infection, 80% of infections were community-acquired. Blood culture results are also shown in Table 1. *Staphylococcus aureus* and enterobacteriaceae were the most common cause of bacteraemia (8 episodes; 62%). Both patients with *Streptococcus milleri* bacteraemia were diagnosed with metastatic complications; one patient had abscesses in lung and liver (Figure1) and one patient had spondylodiscitis, lung abscesses and a subcutaneous focus. Other metastatic infections were localised in lung, liver, intestines, and pacemaker infection. The portal of entry was known in 6 episodes (46%; Table 2). One patient was suffering from a community-acquired sinusitis, one patient had nosocomial pneumonia, one patient had a nosocomial wound infection, and three patients had bacteraemia due to a central venous catheter.
Results of FDG-PET/CT were negative in 6 patients. None of these patients were diagnosed with metastatic complications or relapse after a follow-up period of three months. Therefore, these results were considered as true-negative. FDG-PET/CT results were true-positive in 5 cases (38%). In two patients, FDG-PET/CT was false-positive. In one patient with *E. cloacae* bacteraemia, FDG-PET/CT showed FDG uptake in the transverse colon, which turned out to be physiological. The second patient was diagnosed with a *Salmonella* sepsis and FDG-PET/CT showed rectal FDG uptake, but no abnormalities were seen at further investigations. FDG-PET/CT was clinically helpful in 5 patients (38%) by detecting metastatic infection (Figure 2). In the 13 FDG-PET/CT cases studied, the positive predictive value of FDG-PET/CT was 71% (n = 7) and the negative predictive value was 100% (n = 6).

**Discussion**

In this study, the value of FDG-PET/CT in children with suspected metastatic infection was evaluated. FDG-PET/CT was clinically relevant in 38% of all patients. In these cases, FDG-PET/CT detected metastatic foci that were not found by other diagnostic techniques. To our knowledge, this is the first study investigating the value of FDG-PET/CT in metastatic infection in children. In adults, previous studies showed positive results for FDG-PET/CT in diagnosing metastatic infection. Bleeker-Rovers et al. retrospectively evaluated 40 FDG-PET scans in patients with suspected metastatic infection (*1*). Metastatic infection was diagnosed in 75% of all cases. The positive predictive value of FDG-PET was 91% and the negative predictive value of FDG-PET was 100%. Vos et al. investigated the value of FDG-PET/CT in 115 prospectively included adult patients with suspected metastatic infection (*10*). Results were compared with a matched historical control group of 230 patients in whom no FDG-PET/CT was performed. Significantly more patients were diagnosed with metastatic infections in the study group (67.8% vs. 35.7% in the control group). Sensitivity, specificity, negative predictive value, and positive predictive value of FDG-PET/CT were 100%, 87%, 100%, and 89%, respectively. Metastatic infectious foci were detected in 73% of all 115 patients. Another study in 47 adults suspected of metastatic infection showed that for FDG-PET/CT sensitivity, specificity, negative predictive value, and positive predictive value were 100%, 80%, 100%, and 90%, respectively (*12*). A cost-effectiveness analysis in this study of Vos et al. was performed and showed a cost-effectiveness ratio of $72,487 per prevented death that is well within the range that is considered to be efficient according to Dutch guidelines (*13*). This cost increase is due to in-hospital treatment of metastatic infectious foci and not due to extra diagnostic tests.

In adult studies, the percentage of metastatic foci found by FDG-PET/CT was higher than in the present study. In our study we did not include endocarditis as metastatic focus, because FDG-PET/CT was performed without prior low-carb diet for adequately suppressing the cardiac FDG uptake. Also, FDG-PET/CT was not systematically evaluated for the diagnosis of endocarditis and not all children underwent echocardiography while in the adult studies endocarditis was systematically evaluated in most patients. In the present study, three children were diagnosed with infective endocarditis according to the revised Duke criteria. Cardiac foci were not evaluated by FDG-PET/CT in this study. In the future, for diagnosing metastatic endocarditis it is necessary to perform FDG-PET/CT in combination with a prior low-carb diet if feasible even in children.

Furthermore, it is known that community acquisition is a major risk factor for metastatic foci in bacteraemia (*4,7*). In the adult studies, 70-75% of bacteraemia were community-acquired. In the present study, only 38% of patients had community-acquired bacteraemia. In patients with metastatic infection 80% of infections were community-acquired. Because the lack of appropriate treatment in the first days of infection was a selection criterion in this study, this could also be a reason for community acquisition being a risk factor for metastatic foci in bacteraemia. When comparing the present study with the adult studies, more patients with Gram-positive bacteraemia were included in adult studies. Gram-positive bacteraemia is a known risk factor for metastatic infection (*3*).

A limitation of this study is its retrospective nature. Selecting only patients with an FDG-PET/CT scan in their diagnostic workup leads to selection-bias. Calculation of sensitivity and specificity of FDG-PET/CT in patients with suspected metastatic infection is difficult. First, the interpretation of FDG-PET/CT is hampered because of a lack of a gold standard, especially in the case of a negative FDG-PET/CT. Second, physiologic FDG uptake in the brain, heart, kidney, bladder and variable uptake in the bowel can lead to false-positive interpretation. In two children in the present study, FDG-PET/CT showed false-positive FDG uptake in the bowel that turned out to be physiological. These children were suffering from bacteraemia with *Enterobacteriaceae* and therefore the clinical context may have influenced the interpretation of the FDG-PET/CT. In retrospect, the uptake in the bowel of these two children was physiological FDG uptake. To assess the additional diagnostic value of FDG-PET/CT in metastatic infection in children, prospective studies as part of a structured protocol are necessary.

In conclusion, FDG-PET/CT may be a valuable diagnostic technique in children with suspected metastatic infection as reported in adults previously.

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**Figure legends**

**Figure 1.** Images are shown for FDG-PET/CT of a 14-year-old boy with *Streptococcus milleri* bacteraemia and persisting fever without clear focus. FDG-PET/CT detected abscesses in liver and lung. The patient received prolonged antibiotic treatment.

**Figure 2.** Images are shown for FDG-PET/CT of a 4-year-old girl with *Staphylococcus aureus* bacteraemia and a sternal abscess originated after cardiac surgery because of a hypoplastic left heart syndrome. FDG-PET/CT detected a large abscess behind the sternum; no other metastatic foci were seen. The patient received prolonged antibiotic treatment.