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ORIGINAL ARTICLE

Diagnostic value of FDG-PET/(CT) in children with fever of unknown origin and unexplained fever during immune suppression

Gijsbert J. Blokhuis · Chantal P. Bleeker-Rovers · Marije G. Diender · Wim J. G. Oyen · Jos M. Th. Draaisma · Lioe-Fee de Geus-Oei

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Abstract
Purpose Fever of unknown origin (FUO) and unexplained fever during immune suppression in children are challenging medical problems. The aim of this study is to investigate the diagnostic value of fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) and FDG-PET combined with computed tomography (FDG-PET/CT) in children with FUO and in children with unexplained fever during immune suppression.
Methods All FDG-PET/(CT) scans performed in the Radboud university medical center for the evaluation of FUO or unexplained fever during immune suppression in the last 10 years were reviewed. Results were compared with the final clinical diagnosis.
Results FDG-PET/(CT) scans were performed in 31 children with FUO. A final diagnosis was established in 16 cases (52 %). Of the total number of scans, 32 % were clinically helpful. The sensitivity and specificity of FDG-PET/CT in these patients was 80 % and 78 %, respectively. FDG-PET/(CT) scans were performed in 12 children with unexplained fever during immune suppression. A final diagnosis was established in nine patients (75 %). Of the total number of these scans, 58 % were clinically helpful. The sensitivity and specificity of FDG-PET/CT in children with unexplained fever during immune suppression was 78 % and 67 %, respectively.
Conclusions FDG-PET/CT appears a valuable imaging technique in the evaluation of children with FUO and in the diagnostic process of children with unexplained fever during immune suppression. Prospective studies of FDG-PET/CT as part of a structured diagnostic protocol are warranted to assess the additional diagnostic value.

Keywords FUO · FDG-PET · FDG-PET/CT · Children

Introduction

FUO is well defined in adults [1–5]. There is, however, no clear definition of FUO in children. In 1965, Brewis defined FUO in children as a temperature of 38.3 °C (101 °F) or higher persisting for at least 5 to 7 days in a patient with no localizing signs on physical examination, but he did not include any preliminary investigations in his definition [6]. Three years later, Dechovitz and Moffet included children with a fever persisting for more than 2 weeks [7]. In 2011, Chow and Robinson performed a systematic review, and concluded that most recent paediatric FUO case series required persistence of fever for only 1 or 2 weeks with negative preliminary investigations, but the investigations required varied widely per study [8]. Because of this lack of consensus in the definition of FUO in children, we adopted the widely accepted criteria of FUO for adults, as described by Bleeker-Rovers et al. [9].

In diagnosing FUO it is important to identify potential diagnostic clues (PDC) from the history, physical examination

G. J. Blokhuis · M. G. Diender · W. J. G. Oyen · L.-F. de Geus-Oei (✉)
Department of Nuclear Medicine, Radboud University Medical Center, Nijmegen, The Netherlands
e-mail: lioe-fee.degeus-oei@radboudumc.nl

C. P. Bleeker-Rovers
Division of Infectious Diseases, Department of Internal Medicine, Radboud University Medical Center, Nijmegen, The Netherlands

J. M. T. Draaisma
Department of Paediatrics, Radboud University Medical Center, P.O. Box 9101, Nijmegen 6500 HB, The Netherlands

L.-F. de Geus-Oei
MIRA Institute for Biomedical Technology and Technical Medicine, Biomedical Photonic Imaging Group, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands

and laboratory tests. In FUO, extensive laboratory testing, imaging techniques (such as ultrasound and computed tomography [CT]) and invasive investigations (such as biopsies and bone marrow examinations) are often requested. When not contributory, these diagnostic tests prolong the time to diagnosis and treatment that may lead to increased morbidity and higher mortality rates. Therefore, a short and adequate diagnostic protocol is important in finding the cause of FUO in children. Conventional imaging techniques, such as CT and magnetic resonance imaging (MRI), are very accurate in imaging morphological changes, but they lack the ability to visualize the pathological processes that often precede these changes [10, 11]. Furthermore, these techniques are used for imaging of a specific part of the body.

In a systematic review, Dong et al. showed that 32.2 % of all FDG-PET scans for the age groups 17 to 82 years old are useful in finding the cause of FUO. For FDG-PET/CT this turned out to be considerably higher: 62.1 %. They concluded that FDG-PET/CT should be considered among the first diagnostic tools for patients with FUO in whom conventional diagnostic tools have been unsuccessful [12].

Data on this subject in children are scarce. Only one case series, published by Jasper et al. in 2010, described the use of FDG-PET and FDG-PET/CT in 44 children with FUO and 33 children with fever that did not fulfil the criteria for FUO. They concluded that FDG-PET might be a valuable diagnostic tool for the evaluation of children with FUO and children with unexplained signs of inflammation, with FDG-PET/CT being superior to FDG-PET alone. However, they used the quantitative requirement of one week hospitalization instead of the new qualitative diagnostic requirement and also did not define true negative results [13].

The aim of this study was to investigate the diagnostic value of FDG-PET/(CT) in children with FUO. Additionally, we investigated a second group consisting of children with unexplained fever during immune suppression.

Material and methods

Patients All children (age 0–17 years) that underwent FDG-PET or FDG-PET/CT because of FUO or unexplained fever during immune suppression between September 2003 and June 2013 were identified using the database of the Nuclear Medicine Department of the Radboud University Medical Center.

FUO was defined as a febrile illness of more than 3 weeks' duration, with a temperature ≥38.3 °C (101 °F) on several occasions, without a diagnosis after a set of specific diagnostic procedures as proposed by Bleeker-Rovers et al. [9].

The second group with unexplained fever during immune suppression consisted of all children with a suppressed immune system, either because of underlying diseases or because of the effect of treatment. For this group we did not incorporate the criterion for a minimal duration of fever for >3 weeks since these patients have a high risk of quick deterioration and, therefore, need a rapid diagnostic workup.

FDG-PET/(CT) FDG-PET scans were performed on a dedicated, full-ring PET scanner (ECAT-EXACT, Siemens/CTI, Knoxville, TN, USA) and FDG-PET/CT scans on an integrated PET/CT scanner (Siemens Biograph until 2012 and after 2012 Siemens Biograph mCT, Knoxville, TN). Prior to FDG injection, patients were fasted for 4–6 h [14, 15]. Children younger than 6 months fasted for a maximum of 3 h. There were no preterm neonates included in this study, to whom even stricter fasting regulations apply. 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: $\frac{6.4 \cdot body\ weight\ (kg)}{minutes\ per\ bed\ position} MBq$ with a minimum of 20 MBq. The necessity and dose of furosemide injection was individually determined by the attending clinician. One hour after intravenous injection of FDG and furosemide, emission images of the whole body were acquired. Images were corrected for attenuation using ^{68}Ge transmission images for FDG-PET and using a low-dose CT scan for FDG-PET/CT. The low-dose CT images, obtained sections were also used for anatomic correlation. Images were reconstructed using the ordered subsets-expectation maximisation algorithm.

Interpretation The original PET scans were reported by five nuclear physicians with 4–11 years of experience in PET-reading. The original, unmodified reports of all scans in this study were analysed retrospectively in a multidisciplinary session in the presence of a paediatrician, infectious diseases specialist, and nuclear medicine physician. The clinical utility of each FDG-PET and FDG-PET/CT scan was determined by consensus. All available clinical data of each patient were taken into account. A scan was defined as abnormal if focal accumulation of the radioactive tracer was seen outside the areas of physiological or nonspecific uptake. Variable nonspecific and physiological uptake can be observed in several locations such as epiphyseal plates, salivary glands, muscles, and brown fat [14–16]. Physiological colonic activity is extremely variable in children and can affect all or part of the colon [16]. Of particular importance in this study is the non-specifically enhanced FDG uptake in bone marrow during febrile episodes, which is interpreted as non-pathologic in children with fever [17].

Clinical assessment of test results and diagnosis The results of all FDG-PET/(CT) scans were compared to the final diagnosis. The final diagnosis was based on positive blood or tissue culture, biopsy, surgery, or autopsy. When this was not possible, a probable diagnosis was made based on clinical follow-up, serology or conventional radiological studies. The final diagnosis was never based on FDG-PET or FDG-PET/CT results alone. Abnormal scan results were considered to be true positive when abnormal FDG uptake was either directly diagnostic or pointed to the organ or tissue where the cause of fever was eventually found. Abnormal results were categorised as false positive when the abnormality was not related to the illness or when no final diagnosis could be made. A normal scan was considered true negative when no cause of the symptoms was identified despite an extensive diagnostic workup and clinical follow-up. A normal scan was considered false negative when a focal infection, inflammation or malignancy was diagnosed, except for infection or inflammation in the brain (in which FDG-PET and FDG-PET/CT have a known low sensitivity due to high physiological cerebral FDG-uptake). Subsequently, scans were evaluated for their diagnostic contribution. All true positive results were regarded as helpful in diagnosis, because they pointed to the organ or tissue where the cause of the symptoms was eventually found by additional conventional diagnostic techniques. False positive, true negative and false negative results were regarded as non-contributory to diagnosis.

CRP For all patients C-reactive protein (CRP) on the scanning date (±3 days) was determined. Patients were divided into a group with normal CRP (<10 mg/l) or increased CRP (≥10 mg/l).

Statistical analysis For statistical analysis we used SPSS software package version 20.0.0 (SPSS, Chicago, IL, USA). Sensitivity, specificity, positive, and negative predictive value of FDG-PET/CT were calculated for both FUO and unexplained fever during immune suppression. Furthermore, it was determined if CRP was a significant predictor of a clinical useful scan outcome using the one-sided Fisher's exact test.

Results

From September 2003 to June 2013, a total of three FDG-PET scans and 28 FDG-PET/CT scans were performed for the evaluation of FUO. The second group of scans for the evaluation of children with unexplained fever during immune suppression consisted of one FDG-PET scan and 11 FDG-PET/CT scans.

Fever of unknown origin Of 31 children with FUO, 15 were male and 16 were female, with a median age of 8.1 years (range 0–16 years). Only one of these patients had a malignancy in his medical history: an astrocytoma 6 years prior to the PET scan. Thirty-one scans were performed in 31 paediatric patients. Infectious causes for the fever were found in two patients (6 %), malignancy in two patients (6 %), non-infectious inflammatory diseases in 11 patients (35 %), and

Table 1 Final diagnoses in children with FUO and classification of the results of FDG-PET/(CT) scanning for each category

Category	No. of scans	Abnormal scans		Normal scans (non-contributory)
		Contributory	Non-contributory	
Infection	2 (6 %)	1	1	–
Pneumonia	1	1	–	–
Klebsiella sepsis	1	–	1	–
Neoplasm	2 (6 %)	1	1	–
Sex cord-stromal ovary tumour	1	–	1	–
Hepatosplenic T-cell lymphoma	1	1	–	–
Non-infectious inflammatory disease	11 (35 %)	7	–	4
Systemic juvenile idiopathic arthritis (FDG-PET n=1)	7	5	–	2
Systemic lupus erythematosus (FDG-PET)	1	1	–	–
Polyarteritis nodosa	1	–	–	1
SAPHO syndrome	1	1	–	–
Weber-Christian	1	–	–	1
Miscellaneous	1 (3 %)	1	–	–
Pressure ulcer (FDG-PET)	1	1	–	–
No diagnosis	15 (48 %)	–	2	13
Total	31	10 (32 %)	4 (13 %)	17 (55 %)

miscellaneous disease in one patient (3 %). In 15 patients (48 %), the cause of the fever was not found (Table 1). The follow-up in patients with no final diagnosis ranged from 8 to 474 days, with an average of 156 days and a median of 126 days. Fourteen scans (45 %) were considered abnormal. Of these abnormal scans, 10 (71 %) pointed to the correct source of the fever (Figs. 1 and 2). The remaining 17 scans (55 %) were normal and, therefore, non-contributory to diagnosis. Four scans were considered false positive, since the FDG-PET/(CT) results pointed to locations not associated with the fever. One of these false positive scans showed abnormal FDG uptake para-aortal in a girl with a non-malignant sex cord-stromal tumour as final diagnosis. Another false positive scan showed extensive increased FDG uptake in lymph nodes throughout the whole body, but further investigations (echography, MRI, and biopsies) did not yield any clues for the cause of fever and no final diagnosis was established. In a 1.5-month old infant two FDG hotspots were seen, one para-vertebral and one near the clavicle. However, his symptoms resolved spontaneously during the following days and, therefore, no further investigations were done. In a 4-year-old girl increased FDG-uptake was seen in the thyroid gland and left ovary, but routine blood tests and conventional imaging techniques could not confirm these findings and no diagnosis was established. Her symptoms resolved spontaneously. The false negative results consisted of two patients with a final diagnosis of juvenile idiopathic arthritis and one with polyarteritis nodosa. All three scans showed no abnormalities. PET results were considered true negative in 13 patients without a revealed cause of fever during follow-up (Table 1).

Thus, two FDG-PET scans and eight FDG-PET/CT scans of all 31 scans made for the evaluation of FUO were clinically helpful (32 %). A final diagnosis was established in 16 patients (52 %). In this group of patients with a final diagnosis, 63 % of all scans were considered contributory.

Calculation of sensitivity, specificity, and positive and negative predictive value were not performed for FDG-PET without CT because there were only three scans, of which two

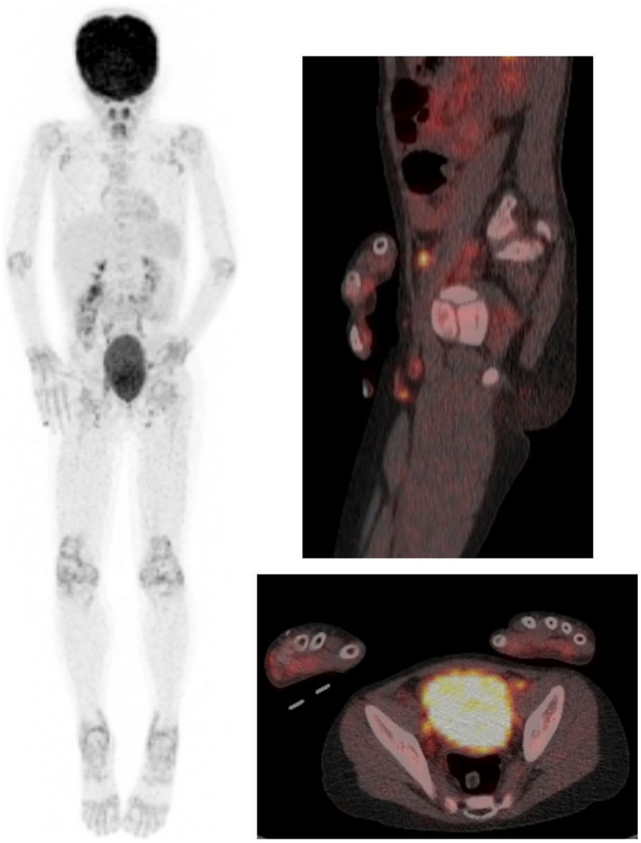

Fig. 1 This 6-year-old girl presented with fever and diffuse body pains. Physical examination showed hydrops in ankles and knees. The erythrocyte sedimentation rate was 116 mm/h (normal 2–12 mm/h), leucocytes 13.7×10^9/l (normal 4-11×10^9/l), thrombocytes 791×10^9/l (normal 210-430×10^9/l), haemoglobin 5.0 mmol/l (normal 7.1-9.0×10^9 mmol/l), alkaline phosphatase 269 U/l (normal <100 U/l). ASAT and ALAT were normal. Because of high clinical suspicion of auto-immune disease, anakinra had already been started, but did not have any effect on her symptoms. PET revealed pathological FDG uptake in almost all joints and in axillary, inguinal and popliteal lymph nodes. Final diagnosis was systemic juvenile idiopathic arthritis. Her symptoms resolved upon treatment with prednisone and methotrexate

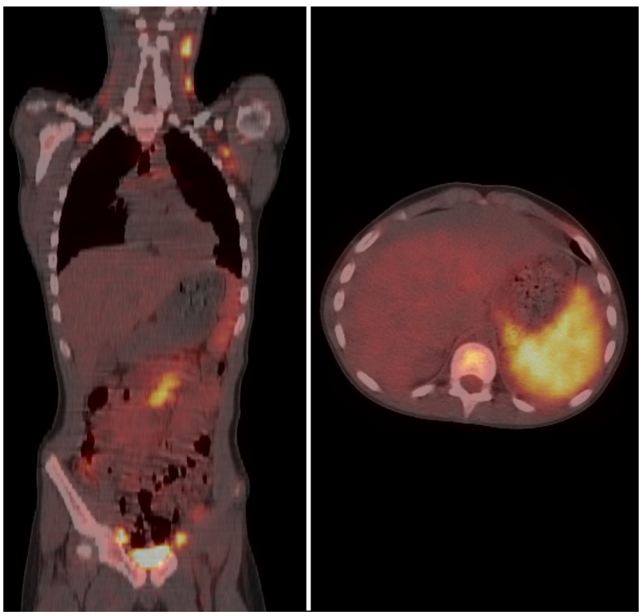

Fig. 2 This 12-year-old boy presented with fever, vomiting, diarrhoea, and arthralgia in knees and fingers. He lost 5 kg in 3 weeks. Physical examination showed mild generalized erythema and urticarial skin lesions on the lower legs. C-reactive protein was 58 mg/l (normal <10 mg/l). Haemoglobin, leucocytes, and angiotensin converting enzyme were normal. ANCA was negative, but anti-tissue transglutaminase (a coeliac disease marker) was positive and duodenal biopsies confirmed the diagnosis of coeliac disease. Gluten-free diet was started, but this gave only a brief relief of symptoms followed by a relapse. Chest X-ray and abdominal ultrasound were negative. FDG-PET/CT revealed generalized lymphadenopathy and an enlarged spleen. Biopsies of the spleen showed that this child had a rare hepatosplenic T-cell lymphoma with cerebral involvement. The patient died because of cerebral complications before treatment could be started

contributed to diagnosis and one showed a false negative test result. Sensitivity of FDG-PET/CT was 80 %, specificity 78 %, positive predictive value 67 %, and negative predictive value 88 %.

An increased CRP did not increase the a priori chance for a useful FDG-PET/(CT) scan outcome (p=0.082). However, none of the five scans in children with a normal CRP were contributory.

Unexplained fever during immune suppression Of 12 children with unexplained fever during immune suppression, five were male and seven were female, with a median age of 9.4 years (range 1–17 years). Five of these children had an underlying oncological disease: two with acute lymphoblastic leukaemia, one with B-cell chronic lymphocytic leukaemia, one with myelogenous leukaemia, and one with myeloid leukaemia. Infectious causes for the fever were found in four patients (33 %), non-infectious inflammatory diseases in four (33 %), miscellaneous diseases in one patient (8 %), and no malignancies were found as cause of fever. In three scans (25 %) no origin for the fever was found (Table 2). The follow-up in patients with no final diagnosis ranged from 19 to 206 days, with an average of 99 days and a median of 73 days. Eight scans (67 %) were considered abnormal. Of these abnormal scans, seven (88 %) pointed to the correct source of the fever (Fig. 3). The remaining four scans (33 %) were normal and, therefore, non-contributory to diagnosis. One scan was false positive, showing high FDG uptake in cervical lymph nodes, but subsequent biopsies showed no abnormalities. In another patient, biopsies showed yeast infection of the liver, which had not led to abnormalities on the PET scan (false negative result). *Clostridium difficile* was diagnosed in one patient, but the scan did not show significant abnormalities (Table 2).

Thus, one FDG-PET scan and six FDG-PET/CT scans of all 12 scans made for the evaluation of unexplained fever during immune suppression were clinically helpful (58 %). A final diagnosis was established in nine patients (75 %). In this group of patients with a final diagnosis, 78 % of all scans was considered contributory.

Calculation of sensitivity, specificity, and positive and negative predictive value were not performed for FDG-PET without CT because there was only one scan, which contributed to diagnosis by pointing to the correct location of a mediastinal infection by *Mycobacterium kansasii* (Fig. 3). Sensitivity of FDG-PET combined with CT was 78 %, specificity 67 %, positive predictive value 88 % and negative predictive value 50 %.

Table 2 Final diagnoses and underlying immune diseases in children with unexplained fever during immune suppression and classification of the results of FDG-PET/(CT) scanning for each category

Final diagnosis	Underlying immune disease	No. of scans	Abnormal scans		Normal scans (non-contributory)
			Contributory	Non-contributory	
Infection	–	4 (33 %)	2	–	2
Disseminated candidiasis	Acute lymphoblastic leukaemia	1	1	–	–
Hepatic candidiasis	Acute lymphoblastic leukaemia	1	–	–	1
Mycobacterium kansasii	Unexplained leukopenia	1	1	–	–
Clostridium difficile	B-cell chronic lymphocytic leukaemia	1	–	–	1
Neoplasm	–	–	–	–	–
Non-infectious inflammatory disease		4 (33 %)	4	–	–
Systemic juvenile idiopathic arthritis	1) Suspected auto-immune disease and anakinra treatment 2) Unexplained leukopenia	2	2	–	–
Auto-immune disease of unknown origin	Suspected auto-immune disease and anakinra treatment	1	1	–	–
Pancolitis	Ulcerative colitis	1	1	–	–
Miscellaneous		1 (8 %)	1	–	–
Post-transplant lymphoproliferative disorder	Aplastic anaemia	1	1	–	–
No diagnosis	1) Immunosuppressive therapy after kidney transplantation 2) Stem cell transplantation after chronic myelogenous leukaemia treatment 3) Treatment for acute myeloid leukaemia	3 (25 %)	–	1	2
Total		12	7 (58 %)	1 (8 %)	4 (33 %)

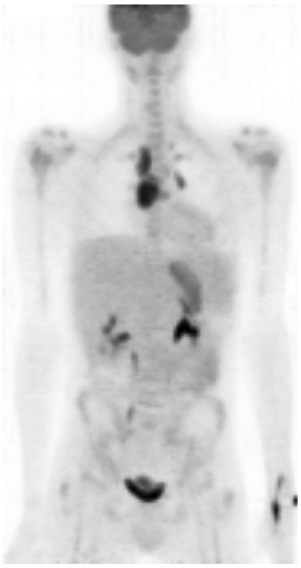

Fig. 3 This 15-year-old boy presented with fever and a non-productive cough. Medical history showed an unexplained neutropenia some years ago. Physical examination showed erythema on arms and legs. Leucocytes were 0.3×10^9/l (normal 4-11×10^9/l), thrombocytes 140×10^9/l (normal 210-430×10^9/l), haemoglobin 4.6 mmol/l (normal 7.1-9.0×10^9 mmol/l), C-reactive protein 322 mg/l (normal <10 mg/l). The tuberculin skin test was negative. Chest X-ray and chest CT showed no clear abnormalities. FDG-PET revealed a large area with abnormal mediastinal FDG-uptake. Bone marrow and mediastinal lymph node biopsies showed a *Mycobacterium kansasii* infection, which was treated with levofloxacin, rifampicin and ethambutol. Further bone marrow investigations also showed acute myeloid leukaemia. The child died from respiratory insufficiency caused by pneumonia not responding to treatment

An increased CRP was significantly correlated to a useful scan outcome ($p=0.045$). None of all three scans with a normal CRP were contributory to diagnosis.

Discussion

In the present study, 32 % of all FDG-PET/(CT) scans were useful in diagnosing the cause of FUO while the probability of a diagnosis was only 52 %. Keeping in mind that FUO is a challenging diagnostic problem, with no diagnosis in almost half of our study population, our results indicate that PET scanning may be a valuable tool in diagnosing the cause of the fever in children comparable to the findings in adults. The percentage of PET scans helpful in the diagnostic workup in children with FUO is only reported in one other case series with 44 scans by Jasper et al. They found a proportion of 43 % scans being helpful with an established diagnosis in 54 % of all children [13]. However, they used a different definition of FUO and considered some of the negative scan results useful, whereas in our study, negative scan results were never considered contributory because they do not help in diagnosing the underlying cause of the fever. In adults, the percentage of helpful scans in the diagnostic process of patients with FUO varies from 16 %–69 % for FDG-PET [18–26] and from 42 %–67 % for FDG-PET/CT [27–36]. The percentage of adult cases in which a final diagnosis is established varies from 50 %–90 % for FDG-PET [18–26] and 58 %–92 % for FDG-PET/CT [27–36].

A special remark should be made for the children in whom a final diagnosis of juvenile idiopathic arthritis (JIA) was established. Of nine scans in children with a final diagnosis of JIA, seven were contributory (78 %), suggesting that FDG-PET/(CT) is a potent diagnostic tool for this specific disease. This is supported by the findings of Jasper et al., who found that all six scans in children with a final diagnosis of JIA were contributory to diagnosis [13].

One child underwent an unnecessary colonoscopy because of abnormal FDG uptake in the ascending colon that proved to be normal. Whether physiological bowel activity or pathological processes are responsible for FDG uptake is often a matter of debate. Results must always be related to the patient's symptoms and other diagnostic findings to justify further invasive investigations [37]. The child with a final diagnosis of polyarteritis nodosa had a normal PET scan. Polyarteritis nodosa typically affects medium-sized muscular arteries and is detected by FDG-PET/(CT) scanning only if large vessels are also involved or if there is associated damage of adjacent tissues [38].

For children with unexplained fever during immune suppression, we found a useful result in 58 % of all scans, while the probability of a diagnosis in this group was 75 %. There are no paediatric studies investigating this specific group, but in adult populations it seems that imaging of infectious processes is possible in patients with severe neutropenia. FDG uptake in inflammatory foci is not hampered by the lack of circulating neutrophils [39–43].

As the patient group with unexplained fever during immune suppression is of limited size, it is difficult to draw definite conclusions, but there seems a role for FDG-PET/(CT) in this specific population.

In scans made for the evaluation of unexplained fever during immune suppression, an increased CRP was a significant predictor of a useful scan result. This was not observed for FUO, probably related to the small number of cases. However, in both groups, none of the scans of children with a normal CRP showed contributory findings. Similar results were reported in adults by Bleeker-Rovers et al., where FDG-PET/(CT) was never helpful in patients with fever and normal erythrocyte sedimentation rate and CRP [24]. Therefore, FDG-PET/(CT) scan should not be recommended in children with a normal CRP.

Study limitations The present study was retrospective, selecting only those paediatric FUO cases with an FDG-

PET/(CT) scan in their diagnostic workup, leading to selection bias. Therefore, to assess the additional diagnostic value of FDG-PET/(CT), prospective studies as part of a structured diagnostic protocol are necessary.

In conclusion, FDG-PET/CT may be a valuable tool in the diagnosis of FUO in children and children with unexplained fever during immune suppression, providing similar results as in the adult population.

Conflicts of interest None.

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