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ORIGINAL ARTICLE

# Diagnostic value of [$^{18}$F]-FDG PET/CT in children with fever of unknown origin or unexplained signs of inflammation

**Niklas Jasper · Jan Däbritz · Michael Frosch · Markus Loeffler · Matthias Weckesser · Dirk Foell**

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**Abstract**
*Purpose* Fever of unknown origin (FUO) and unexplained signs of inflammation are challenging medical problems especially in children and predominantly caused by infections, malignancies or noninfectious inflammatory diseases. The aim of this study was to assess the diagnostic value of $^{18}$F-FDG PET and PET/CT in the diagnostic work-up in paediatric patients.
*Methods* In this retrospective study, 47 FDG PET and 30 PET/CT scans from 69 children (median age 8.1 years, range 0.2–18.1 years, 36 male, 33 female) were analysed. The diagnostic value of PET investigations in paediatric patients presenting with FUO (44 scans) or unexplained signs of inflammation without fever (33 scans) was analysed.
*Results* A diagnosis in paediatric patients with FUO or unexplained signs of inflammation could be established in 32 patients (54%). Of all scans, 63 (82%) were abnormal, and of the total number of 77 PET and PET/CT scans 35 (45%) were clinically helpful. In patients with a final diagnosis, scans were found to have contributed to the diagnosis in 73%. Laboratory, demographic or clinical parameters of the children did not predict the usefulness of FDG PET scans.
*Conclusion* This is the first larger study demonstrating that FDG PET and PET/CT may be valuable diagnostic tools for the evaluation of children with FUO and unexplained signs of inflammation. Depicting inflammation in the whole body, while not being traumatic, it is attractive for use especially in children. The combination of PET with CT seems to be superior, since the site of inflammation can be localized more accurately.

**Keywords** Inflammation · Fever of unknown origin · Children · $^{18}$F-Fluorodeoxyglucose · PET · PET/CT

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-This article contains original unpublished work and has not been and will not be submitted for publication elsewhere.
The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

N. Jasper · J. Däbritz · M. Frosch · D. Foell (✉)
Department of Pediatrics, University of Muenster,
Albert-Schweitzer-Str. 33,
48149 Muenster, Germany
e-mail: dfoell@uni-muenster.de

M. Loeffler · M. Weckesser
Department of Nuclear Medicine, University of Muenster,
Albert-Schweitzer-Str. 33,
48149 Muenster, Germany

M. Loeffler
Department of Radiology, Clemenshospital,
Düesbergweg 124,
48153 Muenster, Germany

## Introduction

Fever of unknown origin (FUO) and unexplained signs of inflammation are challenging medical problems which are predominantly caused by infections, malignancies, autoimmune diseases and other noninfectious inflammatory diseases [1]. Currently, there are more than 200 known reasons for FUO [2, 3]. FUO is defined as a temperature higher than 38.3°C on several occasions and lasting longer than 3 weeks, with a diagnosis that remains uncertain after at least 1 week of investigation in a hospital [3–6].

The diagnostic approach in children with FUO is extensive, ranging from physical examination, standardized laboratory tests to radiological scanning procedures and invasive techniques including biopsies and bone marrow examinations. If this strategy fails, there is frequently a need for exploratory

treatment with antibiotic or steroid therapy. The diagnostic work-up, although retrospectively sometimes unhelpful in children, may be traumatic. In addition, these investigations prolong the diagnostic process, and the consequent delay in treatment may cause prolonged illness resulting in retardation of growth and development. Despite extensive investigations, 12% to 67% of FUO cases in children remain undiagnosed [7–11]. Therefore, reliable tools for the detection of sites of inflammation are needed.

There is no gold standard for the diagnostic work-up of FUO, but the limited data of prospective studies in adults indicate that $^{18}$F-FDG PET and its combination with CT have the potential to serve as a second-line procedure in the management of patients with FUO if standard diagnostic approaches reveal ambiguous results [12–16].

$^{18}$F-FDG is a structural analogue of 2-deoxyglucose and is therefore preferably enriched in tissues with high glucose consumption [1]. FDG accumulates in tumour cells, as well as in proliferating inflammatory cells such as granulocytes, monocytes and lymphocytes, enabling imaging of acute and chronic inflammatory processes [17]. Since FDG PET indicates functional activity of inflammation in the whole body, this technique might be superior to other radiological techniques such as MRI, which are useful to diagnose (advanced) inflammatory processes with morphological alterations [18]. Moreover, FDG can detect inflammatory and infectious processes undetected by routine anatomical imaging [19].

To the best of our knowledge, the diagnostic value of FDG PET in FUO has been investigated in only one small study in a selected population of children prior to liver transplantation [20], while two studies have been performed in children with inflammatory bowel disease [18, 21]. The aim of this retrospective study was to assess the diagnostic value of FDG PET and its combination with CT in the diagnostic work-up in paediatric patients with FUO or unexplained signs of inflammation.

## Patients and methods

### Patients

Between 1998 and 2008, a total of 610 PET scans and 793 PET/CT scans were performed in children (aged 0–18 years) at the University Hospital of Muenster, Germany. The vast majority of these investigations were performed during staging or follow-up of children with malignancies. All parents gave informed consent. In total, 145 scans were performed during the diagnostic check-up for inflammatory conditions, and in 77 of them the primary site was unclear (Fig. 1). In this retrospective study, 47 PET and 30 PET/CT scans in 69 patients (median age 8.1 years, range 0.2–18.0 years, 36 male, 33 female) were analysed (Table 1). All the patients had unexplained inflammatory signs including fever, increased leucocyte count, C-reactive

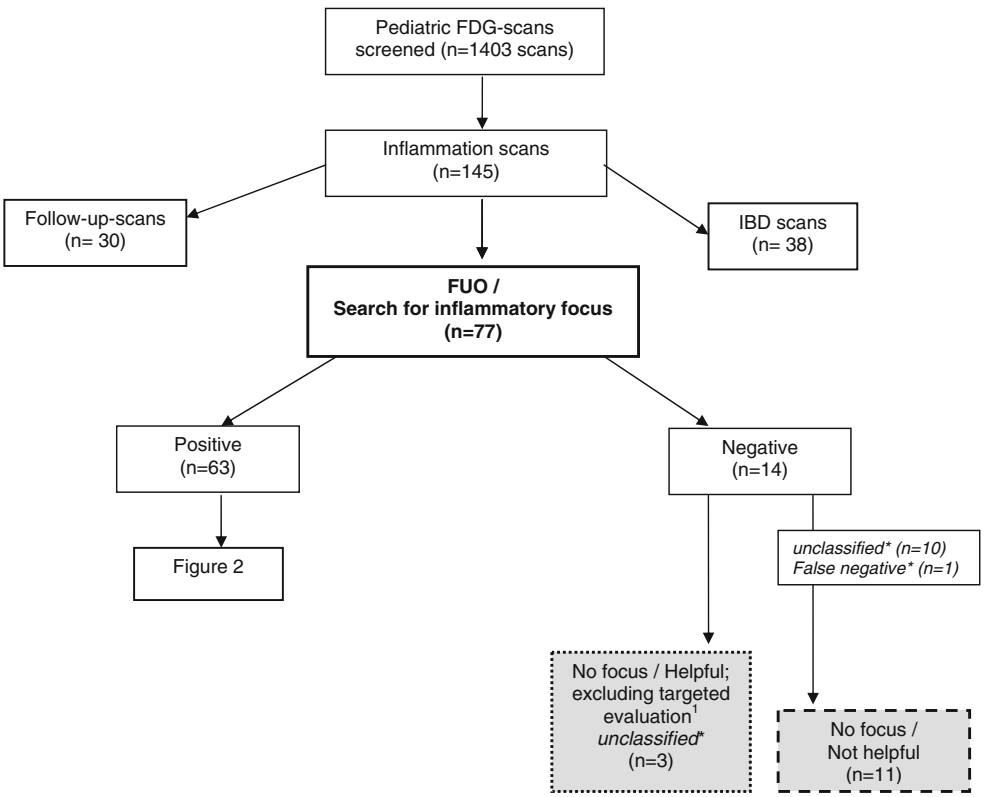


**Fig. 1** Evaluation of all scans performed (asterisks no evident reason for the symptoms could be found despite extensive diagnostic approaches and a clinical follow-up of 6 months; [1]excluding abscesses and focal infection in patients with FUO, thus driving the differential diagnosis towards autoinflammation)

**Table 1** Characteristics of the 69 patients

| Characteristic | Value |
|---|---|
| Sex (*n*) | |
| Male | 36 |
| Female | 33 |
| Age (years) | |
| Range | 0.2–18.1 |
| Median | 8.1 |
| Hospitalization (days) | |
| Range | 0–118 |
| Median | 15 |
| CRP (mg/dl) | |
| Range | 0–26.4 |
| Median | 5.0 |
| ESR (mm/h) | |
| Range (1 h) | 4–120 |
| Range (2 h) | 8–128 |
| Median | 49/98 |
| Leucocytes ($\times 10^3$/μl) | |
| Range | 2.0–31.2 |
| Median | 8.7 |
| Haemoglobin (mg/dl) | |
| Range | 7.0–13.9 |
| Median | 9.9 |
| Final diagnosis (*n*) | |
| Infection | 10 (14%) |
| Multisystem diseases | 13 (19%) |
| Vasculitis | 3 (4%) |
| Neoplasm | 4 (6%) |
| Genetic disorder | 2 (3%) |
| Miscellaneous | 5 (7%) |
| No diagnosis | 32 (46%) |

protein (CRP) and erythrocyte sedimentation rate (ESR), and a thorough initial work-up which had failed to provide a clear diagnosis before the PET scan. Of the 77 scans, 44 were performed in patients presenting with FUO, and the remaining 33 were performed in patients presenting with unexplained signs and symptoms of inflammation which did not fulfil the criteria for FUO as outlined above. The seven children who received multiple scans (time between scans 2–53 months, median 22 months) either had recurrent FUO or a known autoimmune disease and conditions which made it difficult to differentiate between organ manifestations attributable to the underlying disease and infections during immunosuppressive therapy.

In all patients PET alone or PET/CT was performed to reveal the focus responsible for the unexplained signs or symptoms.

## Scan specifications and procedure

We used a dedicated full-ring PET scanner (ECAT EXACT 921/47; Siemens, Knoxville, TN) for FDG PET data acquisition, and a dual modality PET/CT scanner (Biograph Sensation 16; Siemens Forchheim, Germany, and Hoffmann Estates, IL) providing images that could be viewed separately or in fused mode combining morphological and functional image data. The injected activity of the radioactive tracer was adjusted to the body weight, taking into account the recommendations of the European Association of Nuclear Medicine (EANM) [22, 23]. After a fast of at least 6 h, a body mass-adapted $^{18}$F-FDG activity of 4 MBq/kg was injected intravenously. Images were acquired 1 h later. Injected $^{18}$F-FDG activities and X-ray radiation doses of the CT scanner were reduced to the necessary minimum. The radiation exposure from a low-dose CT scan was thus reduced to 1–20% of a standard-dose CT scan [24–26]. Detailed information concerning PET/CT in paediatric patients has been published recently [27, 28]. The results were interpreted by physicians board certified in nuclear medicine and for the PET/CT scans also by board-certified radiologists.

## Analysis of diagnostic accuracy

In this retrospective analysis, the PET scan results were considered either "helpful" or "not helpful" regarding the final diagnosis, taking into account the results of other diagnostic approaches performed. Scans were considered "helpful" if they revealed a focus which could be subsequently evaluated by further investigations including biopsy or endoscopy, leading to a final diagnosis. On the other hand, PET scans could be helpful by driving the differential diagnosis towards autoimmune diseases, if no inflammatory focus was detected in the whole body. In this scenario unnecessary additional investigations could be avoided. The results were documented according to the STARD guidelines [29].

Scans were considered "positive" when they revealed a clear focus with increased $^{18}$F-FDG uptake, or showed nonspecific inflammatory signs such as raised activity in lymphoid tissues, spleen or bone marrow. When physiological $^{18}$F-FDG uptake was detected, scans were considered "negative". Results were categorized as "true positive" if pathological FDG uptake pointed to an area that turned out to be the cause of the symptoms. Results were categorized as "false positive" if further exploration revealed abnormal FDG uptake to be misleading and the finding turned out not to be related to the patients' signs and symptoms. Results were categorized as "false negative" if a focal infection, inflammation or neoplasm was diagnosed after the scan showed normal FDG uptake.

It is very difficult to define "true-negative" investigations in the evaluation of FUO. The variety of causes of FUO, the relatively high number of patients in whom no diagnosis can be established and the lack of a gold standard investigation as a reference makes a definition difficult. Hence, true-negative results were not defined in this study. Instead, physiological FDG uptake, where no evident reason for the symptoms could be found despite extensive diagnostic approaches and a clinical follow-up of 6 months, was categorized as "unclassified".

### Statistical analysis

To estimate the diagnostic value of PET and PET/CT, patients were divided into two groups: "positive scan" and "negative scan". The results were retrospectively reevaluated by the responsible paediatricians and then separated into three groups: "helpful, excluding further investigations" (group 1), "helpful, allowing targeted evaluation" (group 2), and "not helpful" (group 3). The retrospective work-up, segmentation of the cohort and classification of the results are outlined in the flow charts presented in Figs. 1 and 2. Statistical analysis was performed with SPSS software package version 11.5 (SPSS, Chicago, IL). All continuous variables were compared using the Mann-Whitney *U*-test (two-tailed). Differences were considered to be statistically significant at $p<0.05$.

## Results

### FUO and unexplained signs of inflammation

The PET findings contributed to the final diagnosis in 35 patients (45%) by either excluding or allowing further targeted investigations (Table 2). Within the group of helpful scans a final diagnosis was established in 77% ($n$=27) of the patients. On the other hand, 55% ($n$=42) of all scans were not helpful in the diagnostic work-up, but rather confusing or misleading, causing unnecessary or traumatic investigations, e.g. biopsy or endoscopy. When FUO was the reason for the investigation, 43% of scans were helpful, while 48% of scans for signs of inflammation were considered meaningful (Table 3). A diagnosis was established in 54% of all scans in children presenting with FUO or unexplained signs of inflammation (Tables 1 and 4). In children with a final diagnosis ($n$=37), PET was considered diagnostically helpful in 73% ($n$=27). Table 4 lists the diagnoses which were established.

Neither demographic nor laboratory parameters showed significant differences between helpful or non-helpful investigations.

### Positive scans versus negative scans (approach to sensitivity)

A total of 63 scans (82%) were interpreted as positive and 14 (18%) as normal (Fig. 1). PET and PET/CT pointed to a focus in 41 scans and in 80% ($n$=33) the focus was confirmed. Of all abnormal scans, 51% were clinically helpful. Negative scans were considered diagnostically helpful in three patients, since they allowed an inflammatory focus to be excluded. On the other hand 11 physiological scans were not helpful in the search for the inflammatory focus, and 10 of these were considered as "unclassified" after at least 6 months of follow-up of the patients.

CRP ($p$=0.016), neutrophil granulocytes ($p$=0.029) and thrombocytes ($p$=0.040) correlated significantly with positive scans.

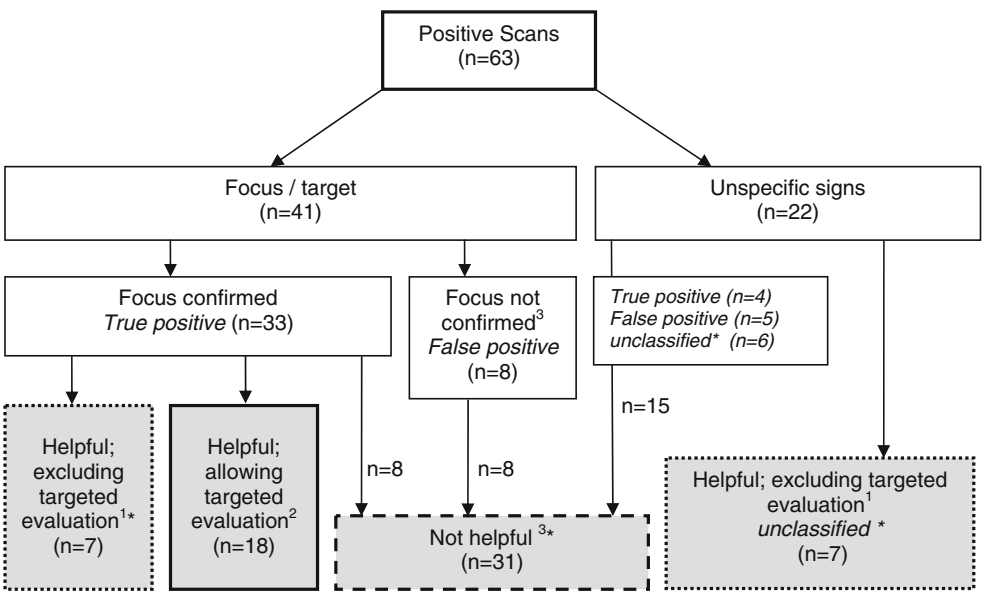


**Fig. 2** Evaluation of all positive scans (*asterisks* no evident reason for the symptoms could be found despite extensive diagnostic approaches and a clinical follow-up of 6 months; [1]excluding abscesses and focal infection in patients with FUO, [2]allowing biopsy or further targeted imaging or diagnostic tests for an inflammatory focus, [3]driving the differential diagnosis towards a false focus, e.g. prompting unnecessary interventions)

**Table 2** Diagnostic value of PET and PET/CT. Values are number of scans with percentages in parentheses

| | Scans results | | |
|---|---|---|---|
| | Helpful, excluding further investigations (group 1) | Helpful, allowing targeted evaluation (group 2) | Not helpful (group 3) |
| All scans (*n*=77) | 17 (22%) | 18 (23%) | 42 (55%) |
| PET | | | |
| FUO (*n*=27) | 7 (26%) | 5 (19%) | 15 (56%) |
| Inflammatory focus (*n*=20) | 4 (20%) | 3 (15%) | 13 (65%) |
| Total (*n*=47) | 11 (23%) | 8 (17%) | 28 (60%) |
| PET/CT | | | |
| FUO (*n*=17) | 3 (18%) | 4 (24%) | 10 (59%) |
| Inflammatory focus (*n*=13) | 3 (23%) | 6 (46%) | 4 (31%) |
| Total (*n*=30) | 6 (20%) | 10 (33%) | 14 (47%) |

Scans revealing a focus versus nonspecific scans (approach to specificity)

Scans with positive results were subdivided into two categories: scans revealing a focus of increased glucose uptake and nonspecific positive scans, where there was no evident correlation with inflamed areas (Fig. 2). A high proportion (68%, *n*=15) of all nonspecific scans turned out to be diagnostically unhelpful. Thus, the rate of unhelpful scans, in contrast to explicitly positive scans, was significantly higher ($p$=0.029). Furthermore, lymphocytes as part of the adaptive immune system were increased in patients with an inflammatory focus ($p$=0.008), whereas granulocytes as part of the innate immune system were increased in patients in whom the PET scan revealed nonspecific signs of increased glucose metabolism ($p$=0.013).

FDG PET versus PET/CT

Of the combined PET/CT scans, 53% were considered helpful, whereas FDG PET without CT was helpful in only 40% (Table 2). Despite difficulties on reading, PET/CT was superior to FDG PET with a higher sensitivity (100%) and positive predictive value (82.4%).

## Discussion

A few studies in adults have found that $^{18}$F-FDG PET and PET/CT might be useful to detect the inflammatory focus in FUO [1, 12, 15, 16, 30–35]. Unfortunately, there are no paediatric data available to date although any delay in adequate treatment of inflammatory processes may lead to significant morbidity, especially in children. There are

**Table 3** Comparison of FUO vs search for inflammatory focus. Data represent number, percentage or median (range)

| | Reason for scan | | *n* | *p* |
|---|---|---|---|---|
| | FUO | Search for inflammatory focus | | |
| No. of scans (*n*) | 44 | 33 | 77 | |
| Helpful, excluding focus (*n*) | 10 (23%) | 7 (21%) | 77 | 0.875 |
| Helpful, focus detected (*n*) | 9 (20%) | 9 (27%) | 77 | 0.487 |
| Not helpful scans (*n*) | 25 (57%) | 17 (52%) | 77 | 0.646 |
| Nonspecific signs detected (*n*) | 29 (66%) | 13 (39%) | 77 | 0.006* |
| Hospitalization (days) | 20 (0–96) | 8 (0–118) | 74 | 0.038* |
| CRP (mg/dl) | 7.9 (0–26.4) | 1.8 (0–10.1) | 72 | <0.001* |
| ESR (mm/h) | 66 (22–120) | 22 (4–78) | 47 | <0.001* |
| Leucocytes (×10$^3$/μl) | 9.9 (2.0–31.2) | 7.7 (2.9–17.7) | 71 | 0.045* |
| Lymphocytes (%) | 23 (4–71) | 30 (5–59) | 69 | 0.159 |
| Granulocytes (%) | 67 (8–93) | 60 (8–87) | 69 | 0.080 |
| Haemoglobin (mg/dl) | 9.5 (7.4–13.3) | 10.3 (7.0–13.9) | 70 | 0.183 |
| Thrombocytes (×10$^3$/μl) | 356 (35–834) | 331 (146–859) | 71 | 0.977 |

*$p$<0.05

**Table 4** Final diagnoses in patients with FUO or unexplained signs of inflammation

| Diagnosis[a] | Underlying disease | FUO | Scan findings | | | Scan results | | |
|---|---|---|---|---|---|---|---|---|
| | | | Positive | Nonspecific | Physiological | Helpful, excluding further investigations | Helpful, allowing targeted evaluation | Not helpful |
| Infection (*n*=10) | | | | | | | | |
| Epstein-Barr virus | None | No | Yes | No | No | No | No | Yes |
| Pulmonary aspergillosis | Chronic granulomatous disease | No | Yes | No | No | Yes | No | No |
| Pulmonary aspergillosis | Chronic granulomatous disease | No | Yes | No | No | Yes | No | No |
| Chronic osteomyelitis | None | No | Yes | No | No | No | Yes | No |
| Herpesvirus | Complete remission in ALL | Yes | Yes | Yes | No | No | No | Yes |
| Candida sepsis[b] | None | Yes/no | Yes/yes | Yes/no | No | No/no | No/yes | Yes/no |
| Psoas abscess, infectious thrombosis | Congenital kidney hypoplasia | Yes | Yes | Yes | No | No | No | Yes |
| Sinusitis | None | Yes | No | No | Yes | No | No | Yes |
| Candida pneumonia/sepsis | Microcephaly | Yes | Yes | No | No | No | Yes | No |
| Pneumonia | Langerhans cell histiocytosis | Yes | Yes | No | No | No | Yes | No |
| Multisystem diseases (*n*=13) | | | | | | | | |
| Mixed connective tissue disease | Mixed connective tissue disease | No | Yes | No | No | No | No | Yes |
| Juvenile idiopathic arthritis | Juvenile idiopathic arthritis | No | Yes | No | No | No | No | Yes |
| Systemic juvenile idiopathic arthritis | None | No | Yes | No | No | Yes | No | No |
| IPEX syndrome | None | No | No | No | Yes | Yes | No | No |
| Juvenile idiopathic arthritis[c] | Juvenile idiopathic arthritis, nonspecific colitis | No/No | Yes/Yes | No/No | No | No/No | Yes/No | No/Yes |
| Autoimmune pancreatitis | Rosai-Dorfman disease | No | Yes | No | No | No | Yes | No |
| Systemic juvenile idiopathic arthritis | Systemic juvenile idiopathic arthritis | Yes | Yes | Yes | No | Yes | No | No |
| Systemic juvenile idiopathic arthritis | None | Yes | Yes | Yes | No | Yes | No | No |
| Systemic juvenile idiopathic arthritis | None | Yes | Yes | Yes | No | Yes | No | No |
| Systemic juvenile idiopathic arthritis | None | Yes | Yes | No | No | Yes | No | No |
| Juvenile idiopathic arthritis | None | Yes | Yes | No | No | Yes | No | No |
| Systemic juvenile idiopathic arthritis | None | Yes | Yes | No | No | No | Yes | No |
| Rosai-Dorfman disease | None | Yes | Yes | No | No | No | Yes | No |
| Vasculitis (*n*=3) | | | | | | | | |
| Polyarteritis nodosa | Polyarteritis nodosa | No | Yes | Yes | No | Yes | No | No |
| Kawasaki disease | None | Yes | No | No | Yes | Yes | No | No |
| Kawasaki disease | None | Yes | Yes | Yes | No | Yes | No | No |
| Neoplasm (*n*=4) | | | | | | | | |
| Acute myeloid leukaemia | None | No | Yes | No | No | No | Yes | No |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| T-cell lymphoma | None | No | Yes | No | No | No | Yes | No |
| Multiple endocrine neoplasia type 2 | Juvenile idiopathic arthritis | Yes | Yes | No | No | No | No | Yes |
| Neuroblastoma stage 4 | None | Yes | Yes | No | No | No | Yes | No |
| Genetic disorder ($n$=2) | | | | | | | | |
| Chronic granulomatous disease | Crohn's disease | No | Yes | No | No | No | Yes | No |
| Familial Mediterranean fever | None | Yes | No | No | Yes | No | No | Yes |
| Miscellaneous ($n$=5) | | | | | | | | |
| Fibrous dysplasia | None | No | No | No | Yes | No | No | Yes |
| Thoracic spinal fractures | None | No | No | No | Yes | Yes | No | No |
| Inflammatory lymph node | None | No | Yes | No | No | No | Yes | No |
| Polyarthritis | Hypercholesterolaemia | Yes | Yes | No | No | Yes | No | No |
| Posttransplant lymphoproliferative disorder | Congenital kidney hypoplasia | Yes | Yes | No | No | No | Yes | No |

[a] No diagnosis in 32 patients.

[b] Patients scanned twice.

[c] Four patients scanned twice, one patient scanned three times.

difficult cases where a clear diagnosis cannot be achieved despite an extensive work-up, or where exploratory treatment with steroids or antibiotics remains ineffective. In our study only 45% (FUO scans 43%, unexplained signs of inflammation 48%) of the PET scans were considered helpful (Tables 2 and 3). However, if a scan turned out to be helpful, a final diagnosis could be established in 77%. Despite the low percentage of helpful scans, this rate is at least equivalent to those reported in adults. Four prospective [12, 15, 31, 33] and two retrospective [32, 36] studies in adults have provided lower results (19–118 patients, helpful scans 16–41%, respectively), and three small studies ($n$=14–20) have found FDG PET helpful in 50–69% of patients, respectively [16, 34, 35]. In reported studies in adults, the percentage of patients in whom no diagnosis could be established was 42% (range 10–57%), which is comparable to the percentage found in the present study (46%; Tables 1 and 4).

However, comparing published studies is difficult, since different definitions were used, no structured diagnostic protocol was given, and the number of patients differed considerably (range 14–118). Nevertheless, it seems that FDG PET in children provides results similar to those in adults. Indeed, the age of the children did not seem to have any significant influence on the major results in our study, either for the helpful scans ($p$=0.605) or for the positive ($p$=0.189) or nonspecific scans ($p$=0.569). Laboratory parameters including CRP, leucocytes, ESR and thrombocytes also did not predict whether a scan was particularly likely to be helpful, although CRP showed significantly higher values in those with a positive scan.

The main causes of difficult FUO cases that required PET in the evaluation process turned out to be multisystem diseases (about 20%), followed by infection (about 15%) and malignancies (about 8%). These findings are comparable to those of other studies [12, 15, 16, 31–36]. Some studies have showed the promising ability of FDG to detect inflammatory lesions due to infection [17, 37–40], different types of vasculitis [41], malignancies [42, 43], rheumatoid arthritis [44], Still's disease [31, 32] and chronic granulomatous disease [45]. We found that $^{18}$F-FDG is a sensitive tracer for inflammatory processes in children, and that the causes of FUO in children [6–10] are generally similar to those in adults. The variety of diagnoses mentioned in the studies above, and the range of helpful scans (16–69%) reflect the manifold reasons for FUO. This also explains an inherent problem when studying FUO: interpretation of data can be difficult in such a heterogeneous group. The diagnostic dilemma in children with FUO also explains why apparently obvious diagnoses could not be established with standard methodology, since the signs and symptoms did not lead diagnostic suspicion in the right direction in a number of children. In these difficult cases, which are more

likely in children than in adults, PET scans revealed signs that directed the diagnostic work-up further on, leading to previously unexpected diagnoses including EBV infection, pneumonia, osteomyelitis, candida sepsis, sinusitis, leukaemia, and spinal fractures.

At present, $^{18}$F-FDG seems to be the best radioactive tracer in FUO and unexplained inflammation. It provides more sensitive results within a few hours than other tracers such as $^{67}$Ga-citrate [16, 31] or $^{111}$In-labelled leucocytes [46–48]. While being sensitive for the detection of metabolic accumulation, FDG PET/CT provides a noninvasive tool, even when MRI or sonography does not show any correlate to inflamed areas. The lack of specificity mainly due to false-positive results must be accepted when using FDG. When a final diagnosis could be established, FDG PET seems to be a reliable tool for monitoring the inflammatory activity during therapy of the disease (Fig. 1; $n$=30 follow-up scans).

PET/CT was superior to PET. We confirm the findings of others who have shown that CT images are mainly helpful by exactly localizing the site of the inflammatory focus seen on the FDG images, leading to better specificity [27, 49]. It is difficult to determine how much the CT contributed to the final diagnoses in the patients. However, morphological alterations due to advanced inflammatory processes, which could possibly have been seen on the CT scans, were only occasionally found in our paediatric patients. In this study the FDG component thus contributed the major part to the final diagnosis. Other benefits of PET/CT include the shorter duration of the investigation which makes sedation unnecessary [27]. Moreover, CT is helpful in identifying foci with physiological uptake. A disadvantage is the higher radiation exposure due to CT [27, 28], which should be kept as low as possible taking into account the increased radiosensitivity of certain tissues especially in children (e.g. thyroid gland and gonads) [50–52]. Low-dose CT in our PET/CT scanner means an additional estimated exposure of approximately 1–2 mSv to the $^{18}$F-FDG component of approximately 5 mSv. This results in an estimated effective radiation dose to children of 7 mSv, which is approximately equivalent to 3 years natural exposure in Germany. The radiation exposure of a diagnostic thorax CT scan alone in children is comparable to the FDG component of approximately 5 mSv.

Calculating formal sensitivities and specificities in patients with FUO or unclear signs of inflammation is difficult or even misleading for several reasons [1, 32]. First, there is no true gold standard and therefore there is no reliable tool for interpretation of the results [1, 32]. Second, a final diagnosis cannot be established in a relative high number of patients [1, 12] (46% in our study), and hence one cannot always compare diagnoses to PET results. Third, in 55% of all our PET scans there were nonspecific signs of inflammation (Table 3), e.g. uptake in lymphatic tissue or bone marrow. It is often difficult to differentiate between physiological and pathological uptake. Therefore, these findings are not necessarily followed up properly and may formally be false-positive findings. In addition, activation of the immune system is likely in FUO but may represent either a secondary phenomenon (e.g. during infections) or a primary pathology (e.g. in Still's disease). Physiological uptake in Waldeyer's ring, thymus or bone marrow is very characteristic in children [28, 53]. We considered such uptake noncontributory and irrelevant to the diagnosis if it was not further considered helpful in the diagnostic work-up.

We agree with Meller et al. [1] who concluded that it seems most useful to ask how often a technique essentially helps in establishing the final diagnosis in patients with FUO, because calculations of formal sensitivities and specificities are not reliable. Our study focused on the clinical benefit and the diagnostic value of FDG PET and PET/CT scans in children with inflammatory processes that are difficult to characterize. It is conceivable that performing PET scans in children is justified in spite of the risks. Regarding the complex circumstances in unexplained inflammatory processes in children, 45% of helpful scans are certainly of clinical relevance in cases that are difficult to characterize. In our opinion PET and PET/CT should not be suggested as a first-line diagnostic approach in children because of the radiation exposure, but could serve as a reliable noninvasive tool with satisfactory results if previous diagnostic approaches have been unsuccessful.

## Conclusion

This is the first study with a relatively large number of children demonstrating that $^{18}$F-FDG PET and $^{18}$F-FDG PET/CT may be promising diagnostic tools in the evaluation of children with FUO and unexplained signs of inflammation. Of all the PET and PET/CT scans in paediatric patients with FUO or unexplained signs of inflammation, 45% were helpful. A diagnosis was established in 54% of all patients. Among patients with a final diagnosis, scans were found to have been contributory in 73%. It is therefore justified to perform FDG PET scans in children, because traumatic investigations are avoided and diagnostic latency may be shortened, and therefore appropriate therapy can be introduced at an early stage of the disease. On the other hand this has to be balanced against the radiation exposure associated with this technique. The combination of PET with low-dose CT seems to be superior to PET without CT because a morphological correlate to inflamed areas can be established, leading to increased accuracy. However, for final validation, prospective multicentre studies using a structured protocol in a large

population of children with FUO and unexplained signs of inflammation are required.

**Conflicts of interest** None.

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