

The diagnostic value of ^{18}F -FDG PET/CT in identifying the causes of fever of unknown origin

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ABSTRACT

Background

This study investigated the clinical significance of ^{18}F -fluorodeoxyglucose positron emission tomography / computed tomography (^{18}F -FDG PET/CT) in identifying the causes of fever of unknown origin (FUO).

Methods

Patients with a fever who received an ^{18}F -FDG PET/CT examination were retrospectively selected. The means of the two groups were compared using an independent-samples t-test.

Results

Among the 89 included patients, 66 were diagnosed using ^{18}F -FDG PET/CT. The sensitivity, specificity and diagnostic accuracy of ^{18}F -FDG PET/CT for the diagnosis of patients with FUO were 84.5%, 25.8%, and 64.0%, respectively. The detection rates of ^{18}F -FDG PET/CT for neoplastic diseases, infectious diseases and non-infectious inflammatory diseases were 100%, 61.3%, and 75%, respectively. The difference in C-reactive protein (CRP) levels between the two groups was statistically significant.

Conclusions

^{18}F -FDG PET/CT has great clinical importance in diagnosing and identifying causes of FUO and improves the accuracy of FUO diagnosis when combined with serum CRP levels.

KEYWORDS: ^{18}F -FDG PET/CT, fever of unknown origin, diagnostic value, biochemical indices, CRP

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Introduction

With the continuous advancement of modern medicine, various causes of fever of unknown origin (FUO) have gradually been

determined.¹ Because of substantial diagnostic difficulties and the long hospital stay, FUO imposes enormous economic and psychological burdens on patients and society. Therefore, effective diagnostic strategies and test methods are critical to improve the accuracy of FUO diagnosis.

The development of ^{18}F -fluorodeoxyglucose positron emission tomography / computed tomography (^{18}F -FDG PET/CT) has not only substantially improved the accuracy and efficiency of the aetiological diagnosis of FUO but also profoundly influenced the determination of causes of FUO.^{2–5} However, because of the high cost of the examination, ^{18}F -FDG PET/CT is not suitable for general screening in the early clinical stages. Therefore, improved timing of the ^{18}F -FDG PET/CT examination will be more conducive to realising its value in the early diagnosis of FUO. Thus, we aimed to retrospectively evaluate the diagnostic value of ^{18}F -FDG PET/CT for determining the aetiology of patients with FUO and the role of clinical biochemical indices in improving the diagnostic efficiency of ^{18}F -FDG PET/CT based on the course of the disease, inflammatory indices and radiological features of patients with FUO.

Methods

Source of patients and definitions

Patients who were admitted to our department of infectious diseases and received an ^{18}F -FDG PET/CT examination between July 2012 and March 2017 were included in this study.⁶ FUO was defined as a body temperature greater than 38.3°C and a fever lasting more than 3 weeks for which the cause could not be conclusively determined by 1 week after conducting a complete medical history enquiry, clinical examination and routine laboratory tests. Patients with nonclassical FUOs who were not definitively diagnosed after a detailed examination were also included in the study. The clinical indices of those patients corresponded to the concept of inflammation of unknown origin (IUO) and included the following conditions: fever lasting for at least 3 weeks, body temperature less than 38.3°C, elevated levels of inflammatory markers (C-reactive protein (CRP) >30 mg/L) and no clear diagnosis after the initial evaluation. The final diagnosis was determined by infectious disease physicians.

Methods and diagnostic evaluation criteria for the ^{18}F -FDG PET/CT examination

A routine ^{18}F -FDG PET/CT examination was performed on all included patients.⁶ ^{18}F -FDG was produced using a MINITrace cyclotron (GE Healthcare, Chicago, USA) and had a radiochemical

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purity >95%. PET/CT was conducted using a Discovery LS PET/CT system (GE Healthcare, Chicago, USA). PET and CT images were analysed using a Xeleris workstation (GE Healthcare, Chicago, USA) and were read independently, layer by layer, by two nuclear medicine physicians with extensive diagnostic experience. According to the metabolic distribution features of ^{18}F -FDG in the lesion area in the PET image, the interpretation of the image was performed together with determination of the maximum standardised uptake value (SUV_{max}). An SUV_{max} >2.5 was used as the standard for a positive PET.^{7–9} Abnormal results on either of these two imaging modalities (PET and CT) was considered positive. Two senior nuclear medicine physicians read all ^{18}F -FDG PET/CT results and made the final diagnosis based on image characteristics and medical history data. The images from inpatients often showed multiple lesions; the conclusion of the ^{18}F -FDG PET/CT examination was thus a comprehensive diagnosis based on all lesions.

Clinical outcome assessment and grouping

We performed a comparative analysis of the ^{18}F -FDG PET/CT results and the final clinical diagnoses and divided the ^{18}F -FDG PET/CT results into true positive, false positive, false negative and true negative groups. Then, the sensitivity, specificity and diagnostic accuracy of ^{18}F -FDG PET/CT were calculated. The diagnostic results of ^{18}F -FDG PET/CT were considered valid when the test results were true positive (effective group) and were considered invalid when the test results were false positive, false negative or true negative (ineffective group).

Statistical analysis

The data were organised using MS Excel. All data were statistically analysed using SPSS 20.0 software (IBM, Armonk, USA). Measurement data are presented as the mean \pm standard deviation. The means of the two sample groups were compared using an independent-samples t-test. Count data are presented as numbers and percentages of patients. A p value <0.05 was considered statistically significant.

Results

Baseline patient data

Eighty-nine patients were enrolled in this study between July 2012 and March 2017, including 46 males and 43 females, with an average age of 59.4 ± 16.4 years. Some patients did not meet the classical FUO definition (25 patients; 28.1%), mainly because the patients' body temperature did not exceed 38.3°C and the fever did not persist for more than 3 weeks. Among them, 18 patients had a long-lasting fever and were orally administered antipyretic drugs, and their fever and body temperature were not recorded in detail or their body temperature was not accurately measured. Seven patients had a fever lasting more than 2 weeks prior to the ^{18}F -FDG PET/CT examination and were unable to be clearly diagnosed through a detailed examination after hospitalisation. Ultimately, 89 patients were included in this study after a comprehensive evaluation. Thirty-one patients (34.8%) were diagnosed with infectious diseases, 15 patients (16.9%) were diagnosed with tumours, 20 patients (22.5%) were diagnosed with non-infectious inflammatory diseases (NIIDs), and 23 patients (25.8%) were unable to be definitively diagnosed after 3–6 months of follow-up visits (Table 1).

Table 1. Comparative analysis of the final diagnosis and ^{18}F -FDG PET/CT

Final diagnosis	Cases	^{18}F -FDG PET/CT positive		^{18}F -FDG PET/CT negative	
		True	False	False	True
Infectious disease, n	31	19	5	7	0
Tumour, n	15	15	0	0	0
NIIDs, n	20	15	3	2	0
Undiagnosed, n	23	0	15	0	8
Total, n	89	49	23	9	8

^{18}F -FDG PET/CT = ^{18}F -fluorodeoxyglucose positron emission tomography / computed tomography; NIIDs = non-infectious inflammatory diseases.

Diagnostic results and grouping of individual ^{18}F -FDG PET/CT

True positive cases

Among the 89 FUO cases, 49 (55.1%) were true positive cases, including infectious diseases (19), tumours (15) and NIIDs (15). Among the 19 patients with infectious diseases, 10 patients had pulmonary tuberculosis, two had tuberculous pleurisy, two had lumbar tuberculosis, two had a liver abscess and remaining three patients each had one of an upper respiratory tract infection, aspiration pneumonia and urinary tract infection (UTI).

Among the 15 patients with tumours, 10 patients (66.7%) were diagnosed with hematologic tumours, including seven with lymphomas and three with myelodysplastic syndrome (MDS), and five patients (33.3%) were diagnosed with other tumour types, including two with lung cancer, one with systemic metastasis after colon cancer surgery, one with adrenal carcinoma and one with appendicular cancer (five patients with tumour lesions were not pathologically biopsied but were diagnosed with malignant tumours after consultation with an oncologist and a radiologist).

Fifteen patients with NIIDs were finally diagnosed with adult Still's disease (two), necrotising lymphadenitis (two), and one patient each with polyarteritis nodosa, lymphogenic disease, Sjogren's syndrome, drug-induced vasculitis, retroperitoneal fibrosis, giant cell arteritis, Takayasu arteritis, antineutrophilic cytoplasmic antibody (ANCA) vasculitis, tuberculous rheumatism, hemophagocytic syndrome and polymyositis.

False positive cases

Twenty-three false positive cases were identified (25.8%), including patients with infectious diseases (five), NIIDs (three) and those not clearly diagnosed (15). Among the five patients with infectious diseases, three were diagnosed with viral infections, one was diagnosed with a UTI and one was diagnosed with epididymitis. Three patients with NIIDs were finally diagnosed with ANCA-associated vasculitis, tuberculous rheumatism and non-myopathic dermatomyositis.

False negative cases

Nine false negative cases were identified (10.1%), including infectious diseases (seven) and NIIDs (two). Among the seven patients with infectious diseases, the final diagnoses included

Table 2. Detection rate of ¹⁸F-FDG PET/CT in different types of diagnosed cases

Disease	Fever of unknown origin			Inflammation of unknown origin		
	Effective, n	Ineffective, n	Detection rate, %	Effective, n	Ineffective, n	Detection rate, %
Infectious disease	19	12	61.3	0	1	0.0
Tumour	15	0	100.0	6	0	100.0
NIIDs	15	5	75.0	2	1	66.7
Undiagnosed	0	23	0.0	0	1	0.0

¹⁸F-FDG PET/CT = ¹⁸F-fluorodeoxyglucose positron emission tomography / computed tomography; NIIDs = non-infectious inflammatory diseases.

three patients with a UTI, and one patient each with Epstein–Barr virus (EBV) infection, respiratory tract infection, bullous pemphigoid and brucellosis. The two patients with NIIDs were finally diagnosed with connective tissue disease and vasculitis, separately, after serological tests.

True negative cases

Eight true negative cases were identified (9.0%), none of which were clearly diagnosed. The ¹⁸F-FDG PET/CT did not prompt the identification of an infection or malignant tumour lesions with abnormal uptake. These patients had no diagnosis other than FUO at discharge.

Diagnostic values of ¹⁸F-FDG PET/CT in patients with different disease types

Of the 31 patients with infectious diseases, the detection rate of ¹⁸F-FDG PET/CT was 61.3% (Table 2). Among the 19 patients who were effectively diagnosed using an ¹⁸F-FDG PET/CT examination, 14 had a tuberculosis infection, two had a liver abscess, and one patient each had an upper respiratory tract infection, aspiration pneumonia and a UTI. Among the 12 patients with an ineffective ¹⁸F-FDG PET/CT diagnosis, four had viral infection, four had a UTI, and one patient each had epididymitis, respiratory tract infection, bullous pemphigoid, and brucellosis.

¹⁸F-FDG PET/CT was effective for all 15 patients with tumours, corresponding to a 100% detection rate, including seven patients with lymphoma, three patients with MDS, two patients with lung cancer, and one patient each with colon cancer, adrenal cancer and appendicular carcinoma.

Of the 20 patients with NIIDs, the detection rate of ¹⁸F-FDG PET/CT was 75%. Among 15 patients with an effective ¹⁸F-FDG PET/CT diagnosis, two patients had adult Still's disease, two patients had necrotising lymphadenitis, and one patient each had polyarteritis nodosa, lymphogenic disease, Sjogren's syndrome, drug-induced vasculitis, retroperitoneal fibrosis, giant cell arteritis, Takayasu arteritis, ANCA vasculitis, tuberculous rheumatism, hemophagocytic syndrome and polymyositis. The five patients who were ineffectively diagnosed using ¹⁸F-FDG PET/CT were ultimately diagnosed with ANCA vasculitis, tuberculous rheumatism, non-myopathic dermatomyositis, connective tissue disease and vasculitis.

Among the 89 included patients, 11 patients with IUO were identified. Eight patients had a true positive result, two patients had a false positive result, and one patient had a false negative result and was diagnosed with bullous pemphigoid (Table 3).

Table 3. ¹⁸F-FDG PET/CT results in 11 inflammation of unknown origin cases

	Final diagnosis Positive	Final diagnosis Negative	Total
¹⁸F-FDG PET/CT Positive	8	2	10
¹⁸F-FDG PET/CT Negative	1	0	1
Total	9	2	11

¹⁸F-FDG PET/CT = ¹⁸F-fluorodeoxyglucose positron emission tomography / computed tomography.

Differences in indices between the effective and ineffective groups measured via ¹⁸F-FDG PET/CT examination

Among the 89 patients with FUO included in this study, final diagnostic information was directly provided by ¹⁸F-FDG PET/CT for 49 patients. The following laboratory indices were compared between the effective group and the ineffective group: white blood cell (WBC) count, neutrophil granulocyte (NE) count, lymphocyte (LY) count, CRP level, erythrocyte sedimentation rate (ESR), serum procalcitonin (PCT) level, and serum ferritin (Fer) level. According to the statistical analysis, only the difference in CRP level observed between the effective and ineffective groups was statistically significant (Table 4).

Discussion

Among 89 patients with FUO, 66 patients were clearly diagnosed, similar to the reported average value.^{7–13} Based on our data, infectious disease is the main cause of FUO, which is consistent with the results of other studies performed domestically and abroad.¹⁴ The proportion of patients with tumours in this study was slightly higher than the level recently reported in other countries (7%).¹³ Finally, 23 undiagnosed patients were examined in this study, suggesting that the causes of FUO are very complex and the pathogenesis is highly diverse.

The sensitivity of ¹⁸F-FDG PET/CT in the diagnosis of FUO was similar to the results reported by Takeuchi and colleagues.¹⁵ Patients with a persistent fever use various types of antipyretic drugs and have individual differences. The clinical data from 11

Table 4. Comparison of indices between effective group and ineffective group

Indices	Effective group, mean \pm SD	Ineffective group, mean \pm SD	p value
WBC, $\times 10^9/L$	8.90 \pm 6.47	8.00 \pm 4.13	0.433
NE, $\times 10^9/L$	6.63 \pm 6.14	5.77 \pm 3.89	0.423
LY, $\times 10^9/L$	1.31 \pm 0.51	1.42 \pm 0.79	0.452
CRP, mg/L	100.50 \pm 65.26	66.64 \pm 60.92	0.013
ESR, mm/1st hour	59.89 \pm 34.54	45.33 \pm 33.80	0.085
Fer, $\mu g/L$	945.91 \pm 700.47	892.18 \pm 753.48	0.757
PCT, ng/mL	0.15 \pm 0.12	0.15 \pm 0.11	0.802
Days with fever before admission	48.50 \pm 50.80	75.40 \pm 133.00	0.601
Days with fever after admission and before examination	9.31 \pm 7.42	9.55 \pm 7.38	0.744
Days with fever from onset to examination	55.86 \pm 49.66	84.95 \pm 133.16	0.785

CRP = C-reactive protein; Fer = serum ferritin level; ESR = erythrocyte sedimentation rate; LY = lymphocyte count; NE = neutrophil granulocyte count; PCT = serum procalcitonin level; SD = standard deviation; WBC = white blood cell count.

of these patients (approximately 12.3%) who met the diagnostic criteria for IUO were also included.¹⁶ Therefore, in addition to analysing all 89 patients, we separately calculated the sensitivity of the ¹⁸F-FDG PET/CT examination in diagnosing 11 patients with IUO, which was similar to the total sensitivity of ¹⁸F-FDG PET/CT in diagnosing all 89 patients. This finding is consistent with the conclusion reported by Vanderschueren.¹⁶ Therefore, the inclusion of 11 patients with IUO in the current study did not affect the overall research results, and the conclusions drawn in our study are reliable.

The aetiological analysis showed that infectious disease is still the major cause of FUO, and the diagnostic accuracy of ¹⁸F-FDG PET/CT for infectious diseases confirmed the diagnostic value of ¹⁸F-FDG PET/CT. According to Mochizuki, high FDG uptake in tumours and inflammatory lesions is related to a high level of glucose transporter-1 (GLUT-1) expression, again confirming that ¹⁸F-FDG PET/CT is suitable for the diagnosis of infectious diseases.¹⁷ Fourteen of the 31 patients with infectious diseases were conclusively diagnosed with a tuberculosis infection. This proportion is relatively high and consistent with the overall data in China, which has the second greatest tuberculosis infection incidence worldwide.¹⁸ Moreover, the diagnostic accuracy of ¹⁸F-FDG PET/CT for tuberculosis infections was 100%, further confirming the value of ¹⁸F-FDG PET/CT in the aetiological diagnosis of FUO in China.

Among the 49 true positive cases, the sensitivity and diagnostic accuracy rates for 15 tumour cases were consistent with the results

reported in other countries.^{19,20} Based on the results obtained in this study, haematological tumours were more common in patients with tumours (10/15; 66.7%). Imaging manifestations of six patients with lymphoma obtained using ¹⁸F-FDG PET/CT included abnormally high uptake of ¹⁸F-FDG in the lymph nodes, spleen and bone marrow. These abnormally high-uptake foci are very important for the localisation of a puncture biopsy, which is conducive to determining the puncture site.²¹ Abnormal uptake is often lower in patients with NIIDs than in patients with malignant tumours and infectious diseases.²⁰ Because the smallest lesion that can be detected by ¹⁸F-FDG PET/CT is 10 mm, it is not suitable for the diagnosis of ANCA-associated vasculitis and small vasculitis.

According to the current situation in China, when FDG PET/CT is used for infection and inflammation, most of the examined patients were patients presented as FUO or IUO. Their clinical manifestations are lack of specificity, and most of them are rare diseases, thus they become a problem in clinical diagnosis and treatment.²² Currently, each ¹⁸F-FDG PET/CT costs approximately 9,000 yuan in China, which is not suitable for a general examination immediately after admission. The average cost of a routine clinical examination for inpatients with FUO is approximately 4,000 yuan per person, including routine tests, tumour markers, autoimmune antibodies, colour Doppler ultrasound, CT, gastroscopy and fiberoptic duodenoscopy. Although the cost of each test is relatively low, patients require repeated assessments. Furthermore, the economic burden and mental distress caused by a long hospital stay should not be ignored. According to several studies, the application of ¹⁸F-FDG PET/CT in patients with FUO can reduce the time needed for diagnosis and hospitalisation and the treatment costs.²³ Therefore, improved timing of the ¹⁸F-FDG PET/CT examination will enhance its value in the early diagnosis of FUO and may compensate for the cost of the examination.

According to the comparative analysis of the laboratory indices of the effective and ineffective groups, only the difference in CRP levels was statistically significant, indicating that patients with significantly increased CRP levels are more likely to receive an aetiological diagnosis from an ¹⁸F-FDG PET/CT examination. This finding is similar to a conclusion drawn by other international studies.^{24–26} CRP levels are not affected by radiation therapy, chemotherapy or corticosteroid therapy. A CRP level greater than 100 mg/L often indicates a severe disease course and the existence of a bacterial infection, which is consistent with the results from our effective group. Since CRP can be detected 6 to 12 hours after the onset of an inflammatory reaction, it can be used as an indicator for early determination of whether ¹⁸F-FDG PET/CT examination is required.

Our study also has some limitations. This was a retrospective study and, thus, some missing data and data biases were present. Although the sample size was limited, a large amount of data was still produced for an examination of the effectiveness of ¹⁸F-FDG PET/CT.

Conclusion

¹⁸F-FDG PET/CT has excellent sensitivity and diagnostic accuracy in patients with FUO. The combination of ¹⁸F-FDG PET/CT findings with the CRP level not only improves the accuracy of the FUO diagnosis but also represents an index for early decision to conduct an ¹⁸F-FDG PET/CT examination. Therefore, we recommend the use of ¹⁸F-FDG PET/CT combined with measurements of CRP levels in

the early diagnostic strategy for FUO in patients who have not been diagnosed based on routine laboratory and imaging findings. ■

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