

FDG PET/CT in Pyrexia of Unknown Origin: A Review

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INTRODUCTION

Petersdorf and Beeson in 1961 proposed the definition of pyrexia of unknown origin as "a condition in which a fever of 38.3 °C or higher is observed several times for more than 3 weeks with an unknown cause after in-hospital investigation for 1 week or longer"¹. However with improvements in diagnostic modalities and better understanding of various diseases PUO has been recently redefined as (1) fever ≥ 38.3 °C (≥ 101 °F) on at least two recordings, (2) duration of ≥ 3 weeks, (3) no known immune-compromised state, (4) undetermined diagnosis even after history-taking, physical examination, and the following obligatory investigations: leukocyte count, platelet count, hemoglobin (Hb), electrolytes, creatinine, total protein, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, creatine kinase, ferritin, antinuclear antibodies, rheumatoid factor, protein electrophoresis, urinalysis, blood cultures, urine culture, chest X-ray, abdominal ultrasonography, and tuberculin skin test or interferon- γ release assay². If the diagnosis remains uncertain after these investigations, different algorithms have been set up with an ever-increasing array of invasive and noninvasive diagnostic modalities. 18F-fluorodeoxyglucose positron emission tomography (FDG PET) is one such modality. Whereas conventional imaging modalities depend more on anatomical changes caused by disease processes, PET combines anatomical and functional assessment, thus increasing sensitivity and specificity.

Principles of FDG PET

FDG is a glucose analogue (2-deoxy-2-[18F]-fluoro-d-glucose) in which the positron-emitting radioisotope fluorine-18 replaces the typical hydroxyl group of the glucose molecule. The absorption of [18F] FDG by tissues is a marker for tissue glucose uptake, which is intimately tied to specific types of tissue metabolism. FDG enters cells via glucose transporters and is phosphorylated by hexokinase, however unlike glucose; it is not metabolized by glycolysis and hence accumulates in the cell. The glucose channels GLUT1 and GLUT3 in the cell membrane are enhanced in inflammatory cells, just as they are in malignant cells, and it is hypothesized that this increases glucose utilization³. Activated inflammatory cells consume 10 times more glucose than non-activated inflammatory cells, which is how inflammatory tissue seems to have considerable FDG accumulation.

After injecting FDG into a patient, a PET scanner can provide two-dimensional or three-dimensional pictures of FDG distribution inside the body. The FDG-PET/CT scan identifies a causal focus of persistent fever that other diagnostic imaging modalities miss. Even when identifying a specific disease is difficult, FDG-positive areas have a high probability of containing malignant and inflammatory cells, and thus the pathological diagnosis is confirmed by accurate biopsy and the pathological diagnosis can be confirmed at an early stage, leading to early treatment of the

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PUO⁴. Numerous studies have established the efficacy of FDG-PET or FDG-PET/CT for the diagnosis of PUO based on this mechanism.

Etiology of PUO

The etiology of PUO is divided under various headings, which include infections, malignancy, non-infectious inflammatory diseases (NIID) which include connective tissue disorders, vasculitis, auto inflammatory diseases and other rheumatologically conditions, and miscellaneous. In the developed world, rheumatic diseases and malignancies are more commonly identified as the sources of fever, whereas in developing countries from Africa and Southeast Asia, including India, infectious diseases predominate.

Tuberculosis was the commonest global infectious cause in a comprehensive meta-analysis of 832 instances of FUO eventually attributable to a particular infectious etiology⁵. It is usually extra pulmonary and military tuberculosis which may not be easily detectable and presents as PUO. Other prevalent causes were brucellosis (confined to southern Europe, the eastern Mediterranean and Southeast Asia), endocarditis, and abscesses. Herpes viruses, CMV, Epstein-Barr virus, pneumonia, urinary tract infections, and enteric fever were other major causes.

Adult-onset Still's disease in young and middle-aged adults and giant cell arteritis (GCA) in older individuals are the most common rheumatologic disorders presenting as PUO. GCA accounts for approximately 15 per cent of cases of FUO in older adults⁶. Other rheumatologically causes include systemic lupus erythematosus, vasculitis, and polymyalgia rheumatica. Auto inflammatory diseases like familial Mediterranean fever, TRAPS, HIDS, and CAPS are rare causes of PUO.

The most common malignancies to present with FUO are lymphoma, especially non-Hodgkin, leukemia, renal cell carcinoma, hepatocellular carcinoma, or other tumours metastatic to the liver. A fraction of patients ranging from 9-51% may not get any diagnosis even after extensive evaluation.

Use of FDG PET in PUO

The assessment of the value of FDG PET/CT for diagnosis in the setting of FUO is controversial. The classic diagnostic parameters like sensitivity and specificity are difficult to define due to the abundance of potential differential diagnoses and the lack of a gold standard in PUO.

Therefore, most studies report the proportion of patients in whom FDG-PET/CT was considered helpful in the diagnostic process. However, "helpful" is an undefined term, and investigators have varied interpretations of it. Whether findings that provide direct evidence of a specific disease have been considered helpful (true positive) or findings that rule out malignancy, focal infection, and inflammation (true negative) have also been considered helpful has a bearing on the proportion of PUO that are ultimately diagnosed by PET/CT, thus making comparison difficult.

A meta-analysis of 26 studies involving 1627 cases found that FDG PET/CT was useful in the workup of patients. In these investigations, the commonest cause of FUO was infection (33%), followed by inflammatory disorders (23%), malignancy (14%), and miscellaneous (3%). The proportion of FUO patients who were still unidentified following FDG-PET/CT was 27%. Sensitivity, specificity, positive predictive value, accuracy, and diagnostic yield had median values of 84.5, 60, 83, 73, and 50%, respectively⁷. Another meta-analysis of nine trials with 388 patients found that 62.1% of FDG PET/CT data contributed to the patient's final diagnosis. They found that 32.2% of FDG-PET scans and 62.1% of FDGPET/CT findings contributed to the patient's final diagnosis. For the detection of PUO, FDG-PET had a high pooled sensitivity (0.826) and a moderate specificity (0.578)⁸. A meta-analysis by Kan et al. (based on 23 papers and 1927 cases) of FDG-PET/CT for the diagnosis of FUO and reported a sensitivity of 84%, a specificity of 63%, a positive likelihood ratio of 2.39. The results of these meta-analyses suggest that the sensitivity of FDG-PET/CT is high with moderate specificity for the diagnosis of FUO. Over half of patients with FUO are guided to a final diagnosis by FDG-PET/CT.

FDG-PET/CT has an indirect impact on the diagnosis of FUO by excluding possible causes of FUO and narrowing down the range of diseases. In a study evaluating the clinical impact of FDG-PET/CT on the clinical practice for FUO, 66% of the FUO cases performed by FDG-PET/CT led to a change in the treatment plan, and 25% of them led to improvement of the certainty factor concerning the final cases, even though FDG-PET resulted in moderate sensitivity and specificity for the diagnosis of FUO¹⁰.

A systematic review showed an association between PET and PET/CT results and spontaneous remission in 550

patients with PUO from 13 studies. They found that patients with negative PET/CT results had a 6 times higher average chance of spontaneous remission than those with positive PET/CT results. This finding suggests that a negative PET/CT result can be a predictor of favorable prognosis in patients with undiagnosed classic FUO after a series of unsuccessful investigations¹⁰.

It is evident that FDG PET/CT should be used in patients of PUO but is it cost-effective? This question has been answered by a study conducted by Balink et al who examined the costs of two groups of patients with PUO, one of which had FDG-PET/CT and the other did not (n = 546). A definitive diagnosis was established in 70% of patients with FDGPET/CT compared to 30% of patients in the other group; expenses from diagnostic procedures and hospitalization were reduced in the FDG-PET/CT group due to shorter duration¹¹.

Although it is clear that FDG PET/CT is gradually becoming the first-line investigation for patients with PUO, there are some pitfalls. Firstly, false-negative FDG-PET/CT results can occur in certain diseases like Crohn's disease, systemic lupus erythematosus, liver failure, cytomegalovirus infection, toxoplasmosis, and pyelonephritis^{12,13}. Secondly, physiologically increased uptake of glucose is seen in brown fat, the gut, the salivary glands, and the thyroid gland, making it difficult to distinguish disease from normalcy¹⁴. Thirdly, insulin can increase the uptake of glucose and may result in false-positive results; similarly, corticosteroids, if given before a PET scan, can decrease the uptake in patients with inflammatory conditions like vasculitis¹⁵.

CONCLUSION

In patients with PUO, FDG PET/CT imaging is superior to traditional anatomical imaging like CT scan. For the prognosis of patients, no diagnosis after PET/CT is just as essential as positive finding and diagnosis. However, the availability and expense of this investigative modality are limiting considerations in its better utilization,, particularly in developing countries.

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