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THE DIAGNOSTIC ROLE OF 18F-FDG-PET/CT IN PATIENTS WITH CONSTITUTIONAL SYMPTOMS

KONSTİTÜSYONEL SEMPTOMLARI OLAN HASTALARDA 18F-FDG-PET/BT'NİN TANIYA KATKISININ ARAŞTIRILMASI

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ABSTRACT

Objective: The contribution of 18F-FDG-PET/CT to diagnosis and its role in differential diagnosis were investigated in patients examined for constitutional symptoms.

Materials and Methods: The 18F-FDG-PET/CT scan results and clinical data were analyzed retrospectively in 144 patients with constitutional symptoms examined between January 2017 and December 2019 in our outpatient and inpatient clinics in Istanbul University Istanbul Faculty of Medicine Internal Medicine Department. The FDG uptake other than physiological FDG uptake was considered as PET-positive. Clinical, laboratory data, and 18F-FDG-PET/CT scan results were evaluated retrospectively from records. All patients were classified into four categories as malignancies, infectious diseases, rheumatic diseases and other diseases based on their definitive diagnoses. The contribution of 18F-FDG-PET/CT in establishing a definitive diagnosis was investigated.

Results: The 144 patients comprised 85 (59.0%) men and 59 (41.0%) women with a mean age of 58.0±17.2 years. The mean duration of symptoms was 4.01±4.46 months. A definitive diagnosis was established in 95.1% (n=137) of the patients based on physical examination, imaging methods, laboratory tests, and other diagnostic tests. In comparison, no definitive diagnosis was established in the remaining 4.9% (n=7) of the patients. 18F-FDG-PET/CT contributed to diagnosis in 86.8% (n=119) of patients. The patients were classified into four categories based on their diagnoses: (i) malignancies (n=79; 57.7%), (ii) rheumatic diseases (n=22; 16.1%), (iii) infectious diseases (n=19; 13.9%), and (iv) other diseases (n=17; 12.4%). The sensitivity, specificity, and positive and negative predictive values of 18F-FDG-PET/CT in the diag-

ÖZET

Amaç: Konstitüsyonel semptomları nedeniyle tetkik edilen hastalarda 18F-FDG-PET/BT'nin tanıya katkısı ve ayırıcı tanıdaki rolü araştırıldı.

Gereç ve Yöntem: Ocak 2017 ile Aralık 2019 tarihleri arasında İstanbul Tıp Fakültesi'nde konstitüsyonel semptomlarla tetkik edilen ve 18F-FDG-PET/BT çekilen 144 hasta retrospektif olarak incelendi. Görüntülerin değerlendirilmesinde FDG'nin vücuttaki fizyolojik tutulum bölgeleri dışında saptanan tutulumlar pozitif kabul edildi. Tüm hastaların klinik, laboratuvar ve PET/BT görüntüleme sonuçları geriye dönük incelendi. Hastaların son tanıları malignite, enfeksiyon, romatizmal hastalıklar ve diğer olmak üzere 4 grupta toplandı. Hastalarda PET/BT pozitifliğinin tanıya katkısı araştırıldı.

Bulgular: Çalışmaya 59'u (%41) kadın 85'i (%59) erkek olmak üzere 144 hasta dahil edildi. Toplam yaş ortalamaları 58,0±17,2 idi. Hastaların semptom süresi ortalama 4,01±4,46 ay olarak saptandı ve %95,1'inde (n=137) hastalık teşhisi saptanmasına rağmen, %4,9'unda (n=7) herhangi bir hastalık teşhis edilemedi. 18F-FDG-PET/BT bu hastaların %86.8'inde tanıya katkı sağladı. Hastalık teşhis edilebilen olgu grubu incelendiğinde %57,7 (n=79) oranı ile en sık maligniteler; %16,1 (n=22) oranı ile romatizmal hastalıklar, %13,9 (n=19) enfeksiyonlar ve %12,4 (n=17) diğer hastalık gruplarının yer aldığı görüldü. 18F-FDG-PET/BT'nin hastalık teşhisinde %97,5 sensitivite, %31,8 spesifite, %88,8 pozitif prediktif değer ve %70 negatif prediktif değere sahip olduğu görüldü.

Sonuç: Konsitüsyonel semptomları olan hastaların tanısında 18F-FDG-PET/BT, duyarlılığının ve pozitif prediktif değerinin

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nosis of constitutional symptoms were 97.5%, 31.8%, 88.8%, and 70%, respectively.

Conclusion: We found that 18F-FDG-PET/CT is a valuable diagnostic tool in diagnosing patients with constitutional symptoms and provides high sensitivity and positive predictive value.

Keywords: 18F-FDG-PET/CT, constitutional symptoms, diagnosis, malignancy

yüksek olması nedeniyle değerli bir görüntüleme yöntemidir ve tanısal süreçte kullanılması gereken önemli görüntüleme protokollerden biridir.

Anahtar Kelimeler: 18F-FDG-PET/BT, konstitüsyonel semptomlar, tanı, malignite

INTRODUCTION

Constitutional symptoms such as fever, night sweats, weight loss, and loss of appetite can be encountered in numerous malignant diseases as well as infections and inflammatory rheumatic diseases (1,2). Despite the advancements and the easy accessibility of diagnostic methods, diagnostic delay and failure remain to be severe problems. It is essential to consider the diagnostic role of tests and procedures in evaluating patients with constitutional symptoms and suspected malignancy.

The advantage of F18 FDG-PET/CT over other imaging methods is that it allows the whole body to be examined reasonably. In addition, it can be used in staging most cancers, evaluating the response to treatment, and identifying foci of infection (3,4). PET/CT, which is used concurrently with traditional imaging techniques like USG, CT, or MRI, can prevent the findings from being overlooked and reduce false positive and negative results (5).

Moreover, compared to conventional scintigraphic techniques, 18F-FDG-PET/CT can report results with higher resolution and higher sensitivity in chronic low-grade infections and high accuracy in the central skeleton. It also provides a relatively shorter period between the injection of radiopharmaceuticals and the imaging moment (6).

In the studies conducted so far, it has been documented that 18F-FDG-PET/CT contributes to the diagnosis at a rate of 42-67% in patients followed up with a fever of unknown origin (FUO) (7). The purpose of this study was to evaluate the contribution of 18F-FDG-PET/CT in establishing a definitive diagnosis in cases presenting with constitutional symptoms when other diagnostic tests and imaging approaches have failed.

MATERIALS and METHODS

Patients

The study included 144 patients with constitutional symptoms who were examined in Istanbul University Istanbul Faculty of Medicine, Internal Medicine Department. All patients who could not get a diagnosis with conventional imaging techniques, and underwent 18F-FDG-PET/BT imaging were included in the study. Clinical, laboratory data and 18F-FDG-PET/CT results were evaluated retrospectively from patient records.

Basic diagnostic evaluation

Laboratory, imaging, and physical examination findings of all patients were recorded through hospital records (a detailed clinical history including business, travel, and previous partners, and tests for FUO, along with a complete blood test, creatinin and transaminase levels, lactate dehydrogenase, electrolyte levels, C-reactive protein (CRP), sedimentation rate of erythrocytes (ESR), urine tests, abdominal ultrasonography, and chest radiography).

In addition to these, if performed, blood and urine cultures, serological tests for Salmonella, cytomegalovirus IgM, Brucellosis, Epstein-Barr virus, and viral hepatitis A, B, and C, Echocardiography, CT, MRI, and histopathological examinations were recorded.

18F-FDG-PET/CT imaging

All scans were performed using a 16-slice multi-detector CT integrated PET scanner (Biograph TruePoint TrueV PET/CT; Siemens Healthcare). Patients fasted for at least six hours before 18F FDG injection, blood glucose levels were less than 150 mg/dL, and they had good hydration before the scan. 260-550 MBq (7-14,8 mCi) FDG was given intravenously. After the injection, the patients were kept in a quiet environment for approximately one hour to allow for whole-body biodistribution of FDG uptake. After the patients were positioned, an initial scout image was acquired to define the examination range for the PET/ CT image acquisition. First, a low-dose CT was performed. Emission scans of 18F-FDG-PET/CT were acquired in 3D mode; the scanning from the top of the skull through the upper thighs was performed. If it was clinically required, a scan including the lower extremities, was also done.

All patients with non-physiological FDG uptake were classified as PET-positive. Disease-related and unrelated FDG involvement was evaluated separately according to the definitive diagnosis of PET-positive patients.

Study protocol

The clinical course of the disease was followed up using 18F-FDG-PET/CT, diagnostic tests, other imaging methods, and interventional procedures. Definitive diagnosis was established based on histopathological, microbiological, and serologic investigations and/or long-term clinical and imaging follow-up records. The contribution

of 18F-FDG-PET/CT to the proven diagnosis and its role in differential diagnosis were investigated.

Istanbul Faculty of Medicine Ethics Committee approved the study protocol (Date: 20.12.2019, No: 21).

Statistical analysis

Data were analyzed using SPSS for Windows version 21.0 (Armonk, NY: IBM Corp.). Descriptive statistics were expressed as mean ± standard deviation (SD). Categorical variables were expressed as frequencies (n) and percentages (%). Cross-table statistics (Chi-square and Fisher's exact tests) were used to compare categorical variables. Normally distributed parametric data were compared using Student's t-test and ANOVA, and non-parametric data that did not conform to normal distribution were compared using Kruskal-Wallis tests. The post hoc test was used to compare multiple groups. A p-value of <0.05 was considered significant.

RESULTS

The 144 patients comprised 85 (59.0%) men and 59 (41.0%) women with a mean age of 58±17.2 years (56.4±17.7 years in men and 60.3±16.3 in females). No significant difference was found between male and female patients with regard to age (p=0.195). A definitive diagnosis was established in 95.1% (n=137) of the patients based on physical examination, imaging methods, laboratory tests, and other diagnostic tests. In comparison, no definitive diagnosis was established in the remaining 4.9% (n=7) of the patients.

The mean duration of constitutional symptoms was 4.0±4.4 months. Hepatosplenomegaly was the most common presenting physical examination finding (26.4%, n=38), followed by cardiac findings (18.1%; pathological murmur, swollen neck veins, detection of third and fourth heart sounds, and edema), superficial lymphadenopathy (14.6%), joint findings (9.0%, arthritis, arthralgia), skin findings (8.3%; rash, discoloration), and palpable masses (2.8%) (Table 1).

The LDH level was significantly higher in the malignancy group compared to other groups (p=0.024) (Figure 1). ESR was non significantly higher in the rheumatic diseases group compared to other groups (p=0.051). No significant

Table 1: Distribution of presenting physical examination finding

	n	%
Hepatosplenomegaly	38	26.4
Cardiac findings	26	18.1
Superficial lymphadenopathy	21	14.6
Joint findings	16	9
Skin findings	12	8.3
Palpable masses	4	2.8

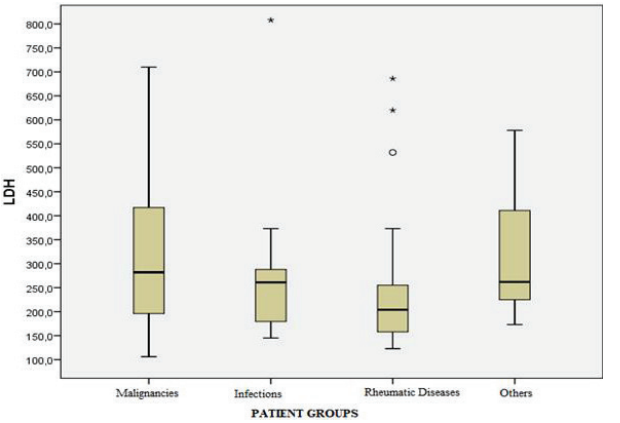

Figure 1: Distribution of LDH in patient groups

difference was found among the groups with regard to the levels of leukocytes, lymphocytes, hemoglobin, hematocrit, mean platelet volume, thrombocytes, C-reactive protein (CRP), albumin, gamma-glutamyl transferase, alkaline phosphatase, iron, total iron-binding capacity, ferritin, calcium, uric acid, and transferrin saturation (p>0.05 for all).

The patients were classified into four categories based on their definitive diagnoses: (i) malignancies (n=79; 57.7%), (ii) infectious diseases (n=19; 13.9%), (iii) rheumatic diseases (n=22; 16.1%), and (iv) other diseases (n=17; 12.4%) (Table 2). Additionally, four patients were found to have two different primary diseases concurrently; one patient had both ovarian cancer and colon cancer, one patient had both Castleman disease and Kaposi's sarcoma, one patient had both lung cancer and gastrointestinal stromal tumor, and the remaining one patient had a graft inflammation associated with nickel allergy.

On PET/CT, non-physiological FDG uptake was detected in 93.1% (n=134) of the patients, and FDG uptake was unrelated to definitive disease involvement in 15 patients. PET-negative patients accounted for 6.9% (n=10) of all patients. The definitive diagnosis was obtained by tissue biopsy in 74 patients, while a laboratory, imaging, and clinical course could diagnose the others.

Moreover, PET had a sensitivity of 97.5%, a specificity of 31.8%, a positive predictive value of 88.8%, and a negative predictive value of 70% (Table 3).

At the end of the study, 94.9% (n=75) of patients with malignancies, 78.9% (n=15) of patients with infectious diseases, 86.3% (n=19) of patients with rheumatic diseases, and 58.8% (n=10) of patients with other diseases showed FDG uptake on 18F-FDG-PET/BT (Figure 2).

DISCUSSION

In internal medicine, diagnosing constitutional symptoms can be challenging since various clinical conditions

Table 2: Distribution of etiologies

	n		n		n		n
Infections	**19**	**Neoplasia**	**79**	**Inflammatory and rheumatic diseases**	**22**	**Others**	**17**
Tuberculosis	10	Non-Hodgkin lymphoma	21	Large vessel vasculitis	6	Primary sclerosing cholangitis, hemolytic anemia, Oncocytoma, Autoimmune Polyglandular Syndrome, Myelodysplastic Syndrome, Subacute Thyroiditis, Macrophage Activation Syndrome (CMV associated), Common Variable Immune Deficiency, Immune Thrombocytopenic Purpura, Primary Myelofibrosis, postinfection polyserositis, Lymphomatoid Granulomatosis, chronic fibrinous pleuritis, nickel allergy, amyloidosis, sarcoidosis, Hypereosinophilic Syndrome	1
Infective endocarditis	3	Lung carcinoma	12	Adult-onset Still's disease, Polymyalgia rheumatica	5		
Mesenteric Panniculitis, graft infection	2	Gastric carcinoma	6	Systemic lupus erythematosus	3		
Prostatic abscess, Bartonella infection	1	Malignant mesothelioma	5	Mixed connective tissue disease, Temporal arteritis, Behcet's disease, Microscopic polyangiitis	1		
		Hodgkin Lymphoma, Multipl Myeloma	4				
		Adenocarcinoma of unknown origin, colon carcinoma, pancreatic carcinoma, renal cell carcinoma, leukemia	3				
		Gastrointestinal stromal tumor, ovarian carcinoma	2				
		Breast carcinoma, gallbladder carcinoma, Warthin Tumor, cholangiocarcinoma, Castleman Disease, Malignant Melanoma, esophageal carcinoma, Kaposi Sarcoma	1				

can cause them. Infections, cancer, metabolic or endocrine disorders, and mood disorders are all possible causes of constitutional symptoms (8). There are still no guidelines in evaluation for the etiology of constitutional symptoms. Metalidis et al. observed that major organic disease and malignancy are extremely uncommon in patients with extensive unexplained weight loss when a baseline screening is completely normal (9). We assessed the contribution of PET/CT to the diagnosis. Our study is the first to evaluate the use of PET/CT as a diagnostic tool in patients with constitutional symptoms.

Table 3: Distribution of PET results

Clinical variable	**Definitive disease**		**Total**
	+	**-**	
PET-positive n (%)	119	15*	134
PET-negative n (%)	3	7	10
Total	122	22	144

* FDG uptake was unrelated to definitive disease involvement in 15 patients

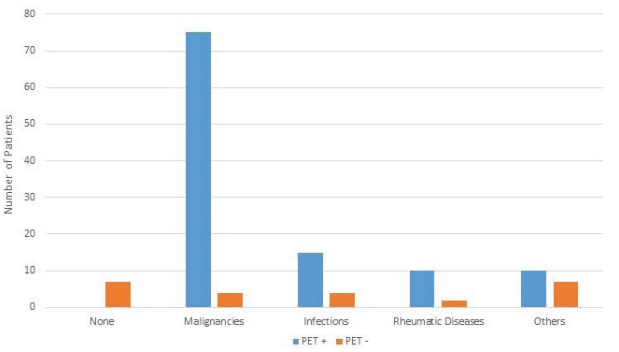

Figure 2: Comparison of PET results among patient groups

Previous studies have shown that high ESR and CRP levels can predict PET/CT positivity, particularly in detecting FUO and inflammatory foci (10,11). In our study, ESR was non significantly higher in the rheumatic diseases group compared to other groups, while CRP level showed no significant difference.

Inflammatory and infectious diseases can be diagnosed using USG, CT, and MRI. Still, these methods cannot diagnose the early stages of the diseases or post-operative pathologies unless a mass has formed (7). On the other hand, patients who cannot be diagnosed using laboratory tests performed concomitantly with physical examination and basic imaging procedures like USG, CT, and MRI require advanced imaging techniques (12).

Nuclear medicine techniques (labeled leukocyte, labeled immunoglobulin, gallium-67 scintigraphy, and PET-CT) showing functional and metabolic changes can often be used as a second-line diagnostic test in diagnosing patients with FUO. Labeled leukocyte, labeled immunoglobulin, and gallium-67 scintigraphy can be used in selected cases due to prolonged processing times, high radiation doses, poor accessibility, and image quality (7). 18F-FDG-PET/CT scintigraphy has recently emerged as an important tool in the detection of inflammatory and infectious foci and in the diagnosis, staging, prognosis, and response to the treatment of malignancies (13-16).

The urinary system, brain, and gastrointestinal tract cannot all be evaluated with 18F-FDG-PET/CT due to urine excretion, increased accumulation, and variable absorption of FDG with peristalsis, respectively (7). Insulin-induced hypoglycemia increases the absorption of FDG in muscle and adipose tissue while decreasing the uptake by the tumor, and the overall tumor-to-background ratio is reduced (17). A study examining 18F-FDG-PET/CT results showed that the diagnostic errors were relatively infrequent (around 2%) but non-negligible (18). The literature indicates that some tumors, including a subset of liposarcomas, diffuse gastric adenocarcinomas, and signet cell colonic adenocarcinomas use substances other than glucose for growth and proliferation, such as glutamine or fatty acids. Thus, their FDG uptake is relatively lower (19). Additionally, some aggressive sarcomas and mucinous tumors might be interpreted as PET-negative when the signal from tumor cells is predominated by low FDG uptake in the surrounding extracellular matrix or mucin production (20). On the other hand, despite having a low proliferation rate, some tumors, including benign oncocytomas (parotid, thyroid, or renal), pheochromocytomas, and hereditary paragangliomas, show a higher FDG uptake on 18F-FDG-PET/CT (21).

In a meta-analysis that investigated 823 individuals with FUO, the contribution of 18F-FDG-PET/CT to the diagnosis ranged from 42% to 67% (7, 22). Schönau et al. observed that 18F-FDG-PET/CT was useful in the diagnosis of 136 out of 240 (71.6%) patients with FUO or inflammation of unknown origin (11). Sonoda et al. reported that the contribution of 18F-FDG-PET/CT to the diagnosis was 79% in 231 patients (23). In comparison to the previous studies, our study indicated that the contribution of 18F-FDG-PET/CT to the diagnosis was remarkably higher (86.8%), while this rate was 78.9% (15/19) in the detection of infectious diseases.

It is known that 18F-FDG-PET/CT can detect tissues with high FDG uptake in individuals with suspected malignancy. Therefore, it has a wide variety of uses in the diagnosis, staging, prognosis, and evaluation of the effectiveness of treatment for malignancies (24). In a study by Cengiz et al., 121 patients with an unknown primary malignancy underwent diagnostic PET/CT scanning, and primary malignancy focus was detected in 59 (49%) of the patients (25). A previous review reported that PET/CT had a sensitivity of 88% and a specificity of 84% for diagnosing oncological diseases (26). In our study, 18F-FDG-PET/CT contributed to the diagnosis in 75 out of 79 patients diagnosed with malignancies, and thus provided a sensitivity of 95%. Including patients with FUO and constitutional symptoms may have led to the increased prevalence.

The effectiveness of 18F-FDG-PET/CT in detecting rheumatic diseases and its superiority to other imaging techniques have been shown in numerous studies (27,28). In a study by Bleeker-Rovers et al., high FDG uptake was observed in periaortitis caused by Takayasu's arteritis, Wegener's granulomatosis, polymyalgia rheumatica, giant cell arteritis, and infectious vasculitis. The study also noted that 18F-FDG-PET/CT had a specificity of 89% and a sensitivity of 77-100% for identifying vasculitis (29). In contrast, it has also been reported that if the giant cell artery is restricted to the temporal arteries alone, the sensitivity of 18F-FDG-PET/BT may remain low due to the small arterial diameter and significant background FDG retention in the brain (30). In a study by Umekita et al., 18F-FDG-PET/CT was shown to be more effective than CT and MRI for the diagnosis of Takayasu's arteritis, particularly in early-stage lesions (29). In our study, 18F-FDG-PET/CT contributed to the diagnosis in 19 out of 22 rheumatic diseases (86.4%) and all eight vasculitis patients (100%). These findings indicate that 18F-FDG-PET/CT is highly effective in identifying vasculitis.

Previous studies have primarily focused on the diagnostic effect of 18F-FDG-PET/CT in FUO patients (31). In contrast, the present study included patients with constitutional symptoms other than fever, which makes our study different from other studies. It is considered that malignancies are observed to be much higher than in other patient groups as a result of FUO and/or constitutional symptoms. A 2022 review indicated that 18F-FDG-PET/CT is superior

to conventional CT or other nuclear imaging techniques in individuals examined for FUO (32). In our study, the contribution of 18F-FDG-PET/CT in diagnosis was highlighted in patients with constitutional symptoms.

On the other hand, we also found that diseases other than vasculitis in the rheumatic diseases group and particularly benign disorders in the other diseases group did not show FDG uptake, which explains our study's low negative predictive value.

In conclusion, constitutional symptoms are not specific to any disease and may be the only findings of a serious underlying disease. Regardless of the presence of FUO, using 18F-FDG-PET/CT in such patient groups contributes significantly to the diagnosis.

Ethics Committee Approval: This study was approved by Istanbul University, Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 20.12.2019, No: 21).

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