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RAPID COMMUNICATION

Statement on ^{18}F-FDG PET Usage for Large-vessel Vasculitis

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Abstract

In April 2018, the use of F-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) for large-vessel vasculitis (LVV) was finally approved under the Japanese national health insurance system. The use of ^{18}F-FDG PET in LVV differs from the oncological use in several aspects such as the patients' age distribution, precautions regarding the tracer dosage, and the utility for diagnosis and patient management. Considering the higher incidence of Takayasu arteritis in Japan than in western countries, it is expected that young females will undergo ^{18}F-FDG PET for LVV for the diagnosis and the management. The Japanese Society of Nuclear Cardiology (JSNC) has issued this brief statement about the use of ^{18}F-FDG PET for diagnosing/managing LVV, which focuses on the specific characteristics of LVV, imaging protocols, the clinical utility of ^{18}F-FDG PET, and some issues that clinicians should be aware of.

Keywords: ^{18}F-FDG PET, Giant-cell arteritis, Large-vessel vasculitis, Takayasu arteritis
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It is well known that many studies indicate clinical usefulness of F-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) for the diagnosis/management of large-vessel vasculitis (LVV) (1-5). In April 2018, the use of ^{18}F- FDG PET for LVV was finally approved under the Japanese national health insurance system. It should be noted that the revised health insurance system does not allow application of ^{18}F-FDG PET for initial diagnosis of LVV. This revision of health insurance system allows ^{18}F-FDG PET for the assessment of activity and localization of LVV in patients who are already diagnosed as having LVV using other modalities.

Here, the Japanese Society of Nuclear Cardiology (JSNC) summarizes the basic principles underlying the use of ^{18}F-FDG PET to detect/manage LVV, the usefulness of this approach, and several issues that clinicians need to be aware of.

Definition of LVV

In the most recent nomenclature system developed at the Chapel Hill Consensus Conference 2012 (CHCC2012 nomenclature) (6), Takayasu arteritis (TAK) and giant-cell arteritis (GCA) were described as the major two variants of LVV. It should be noted that in addition to large blood vessels, LVV can also affect medium- to small-sized blood vessels and other organs including eyes, ears, lungs, gastrointestinal tract, and skin (7-11).

Takayasu arteritis (TAK)

TAK predominantly affects the aorta. The onset of TAK usually occurs before the age of 50, and the condition mainly arises in females. Recent registration data collected in Japan indicated that the median age at onset was 35 years for females and 43.5 years for males (7). The peak age of onset is around 20 years old in female patients. Pediatric patients, age less than 10, are rare but are present. This younger age distribution is a major difference between TAK and GCA. In fact, TAK can

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Table 1 Dose table for pediatric patients calculated according to the equation presented in the JSNM guidelines

Body weight (kg)	FDG dose (MBq)	Body weight (kg)	FDG dose (MBq)
3 or less	14	32	102
4	16	34	108
6	24	36	112
8	30	38	118
10	38	40	124
12	44	42	128
14	50	44	134
16	56	46	140
18	62	48	144
20	68	50	150
22	74	52-54	158
24	80	56-58	168
26	86	60-62	178
28	90	64-66	188
30	96	68	196

Figures are rounded to the nearest whole number.

occur in childhood or adolescence. This early age distribution should be noted so as to prevent patients from being subjected to an unnecessary radiation burden.

Giant-cell arteritis (GCA)

GCA, which was formerly known as “temporal arteritis”, involves large blood vessels and frequently affects branches of the carotid and vertebral arteries. GCA usually occurs after the age of 50. In a national survey performed in Japan in 1998, the mean age at onset was 71. 5 years, and a slight female predominance (M : F=1 : 1.7) was observed (11). It should be noted that GCA is frequently associated with polymyalgia rheumatica, which also exhibits a specific pattern of ^{18}F-FDG uptake, although this pattern is not described in detail in this statement (12-15).

^{18}F-FDG PET protocol for LVV

Dose of ^{18}F-FDG

There is no generally accepted specific ^{18}F-FDG PET protocol for LVV. According to the Japanese guidelines for ^{18}F-FDG PET for oncological use, patients must refrain from consuming food for more than 4 hours before the scan. For adults, the minimum ^{18}F-FDG dose is 74 MBq, and the maximum dose is 370 MBq. Recently, the European Association of Nuclear Medicine (EANM), the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the PET interest group (PIG), and the American Society of Nuclear Cardiology (ASNC) jointly issued procedural recommendations (16). In these recommendations, the recommended ^{18}F-FDG dose was 2-3 MBq/kg body weight. The JSNC recommend that the Japanese Society of Nuclear Medicine (JSNM) guidelines for ^{18}F-FDG PET should be followed.

The ^{18}F-FDG doses for pediatric patients must be determined according to the relevant guidelines. Basically, the ^{18}F-FDG dose should be modified according to the patient’s weight, especially for pediatric patients. A simplified dose table based on the JSNM guidelines is presented in Table 1.

Fig. 1 shows the ^{18}F-FDG PET images obtained in a case of young TAK patient before and after treatment with prednisolone. Note clear localization of active disease on the images before treatment (A) which clearly resolved after treatment (B).

Acquisition time

In the EANM/SNMMI/PIG/ASNC joint recommendations (16), it is recommended that images should be acquired 60 min after the injection of ^{18}F-FDG. However, the European League Against Rheumatism (EULAR) recommendations (17) have recently reported that images should be acquired 90 min after the injection of ^{18}F-FDG.

The EANM/SNMMI/PIG/ASNC joint recommendations (16) have summarized the findings of 24 major studies that evaluated the use of ^{18}F-FDG PET in cases of LVV. Among the 24 studies, only 4 involved a waiting time of ≥90 min (the waiting time was 90 min in 3 studies and 120 min in one study). Thus, at present the JSNC recommend that images should be acquired 60 min after the injection of ^{18}F-FDG.

The vascular wall is a relatively thin structure, and PET has a limited spatial resolution. It is therefore strongly recommended that PET/CT fusion imaging should be performed to ensure proper localization of lesions. PET/magnetic resonance imaging (MRI) is another promising modality for imaging LVV. However, due to its limited availability, there is little evidence about its utility. This issue should be studied in a large cohort in future.

Image interpretation

Visual interpretation is simple, but can be affected by inter-observer variance and first impressions (18). To standardize this variance, scoring ^{18}F-FDG uptake in comparison with a reference organ is recommended (19, 20). A four-grade scoring system in which the ^{18}F-FDG uptake of the relevant blood vessel is compared with that of the liver (0: no uptake; +1: positive, but lower than that of the liver; +2: intermediate, similar to that of the liver; and +3: high-grade, between that of the liver and cerebral cortex) is commonly accepted (21). Another scoring system based on the sum of 7 segment scores (for the ascending aorta, aortic arch, thoracic descending aorta, abdominal aorta, supra-aortic trunks, iliac arteries, and femoral arteries) has been reported (22).

In addition, several semi-quantitative parameters, such as

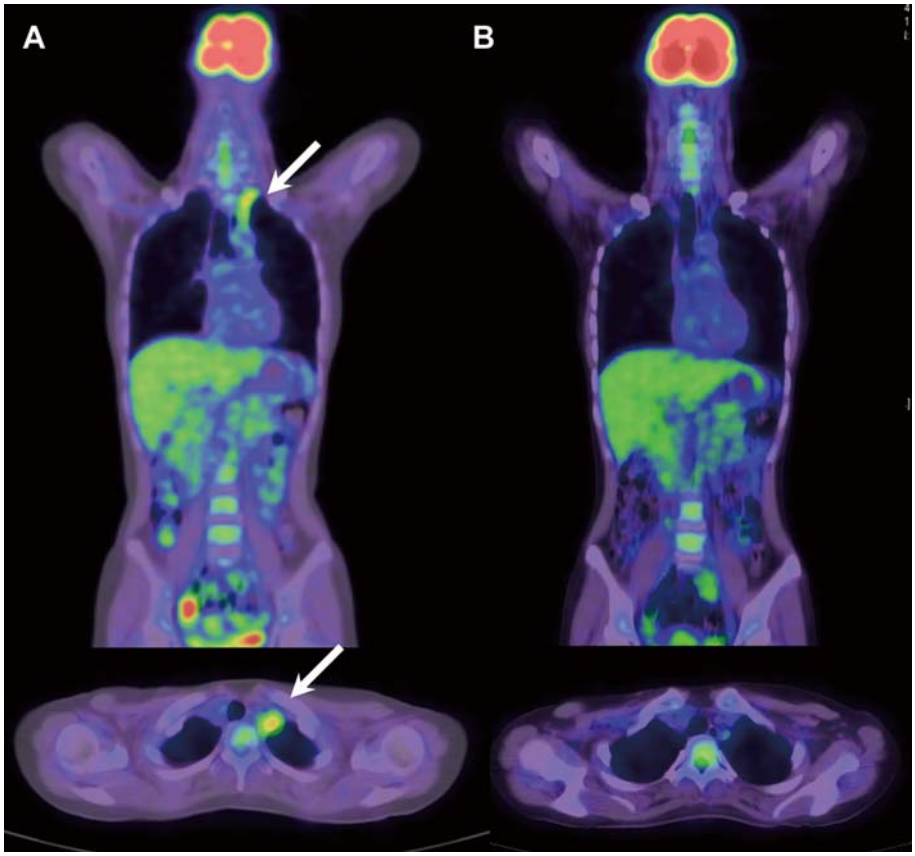

Fig. 1 PET/CT fused images of a young female patient with Takayasu arteritis.
A: before treatment, **B**: after treatment with glucocorticoids.
The arrows indicate the locations of the active inflammation.
Strong ^{18}F-FDG uptake was observed along the proximal left carotid artery before treatment, whereas the ^{18}F-FDG uptake almost normalized after treatment.
This image was kindly provided by Dr. Mitsuaki Isobe.

standardized uptake value (SUV) and the target to background ratio (TBR), which are used in oncological imaging, has been reported for assessing inflammation on ^{18}F-FDG PET. However, there is no consensus regarding which parameters should be used and the optimal diagnostic threshold for LVV (2, 23-30).

Clinical utility

Detection and diagnosis

Many articles indicate that ^{18}F-FDG PET is very useful method for the diagnosis of LVV (31-37). A recent meta-analysis showed that the pooled sensitivity and specificity of ^{18}F-FDG PET for detecting active TAK were 86% (95% confidence interval [CI]: 0.78-0.93) and 73% (95% CI: 0.63-0. 81), respectively, whereas those of ^{18}F-FDG PET for detecting GCA were 89% (95% CI: 0.78-0.96) and 98% (95% CI: 0.94-0.99), respectively(38). Some studies of TAK have detected significant ^{18}F-FDG uptake in cases without any clinical/serological activity of inflammation (5, 39). Furthermore, it has been suggested that ^{18}F-FDG PET detects TAK earlier than MRI (40). Another study has suggested that ^{18}F-FDG PET can detect active LVV more specifically than MRI (41).

Management

^{18}F-FDG PET is also useful for monitoring and/or management of LVV (20, 39, 42, 43). Many studies have detected significant reductions in ^{18}F-FDG uptake after therapy (2, 43, 44). These results indicate that ^{18}F-FDG PET could be a useful tool for disease management.

However, these studies suffered from a common problem; i. e., the lack of gold-standard criteria for diagnosing inflammation. Some studies used the National Institutes of Health (NIH) criteria, and others used acute-phase parameters, such as the C-reactive protein (CRP) level or the erythrocyte sedimentation rate (ESR). Lee et al. studied the relationships between the ESR, NIH criteria, and ^{18}F-FDG parameters (45). They found that a higher ESR was associated with high ^{18}F-FDG uptake. However, some of the patients with inactive disease (according to the NIH criteria) showed high ^{18}F-FDG uptake.

Another issue regarding these studies is that standard parameters, such as the NIH criteria and acute-phase parameters, are often affected by inter-individual differences, therapeutic interventions, and etc (22, 45).

Points to be noted

Effects of medication

For TAK, glucocorticoids, immunosuppressants (methotrexate [MTX], azathioprine, etc.), and molecule-targeting drugs (tocilizumab [TCZ]) are used. These drugs may have some effects on image interpretation.

Glucocorticoids: Impaired glucose tolerance can lead to a high blood glucose level at the time of ^{18}F-FDG PET imaging, which might result in reduced image quality (46-49). Stellingwerff et al. reported that the diagnostic accuracy of ^{18}F-FDG PET for GCA was improved when patients who were using glucocorticoids were excluded (24). Thus, it is recommended that patients' blood glucose levels should be checked before the injection of ^{18}F-FDG. It should be also noted that the effect to inhibit vascular uptake of ^{18}F-FDG occurs few days after initiation of glucocorticoids therapy (26, 50, 51).

MTX: It is well known that patients with MTX-induced lymphoproliferative disorders exhibit high ^{18}F-FDG uptake (52, 53). Therefore, during image interpretation lymph nodes and organs should be carefully reviewed in addition to blood vessels.

TCZ: It is well known that TCZ affects inflammatory markers related to interleukin-6, such as the CRP level and the erythrocyte sedimentation rate (ESR). This might cause discordance between inflammatory marker data and ^{18}F-FDG PET findings. This knowledge is important when reviewing ^{18}F-FDG PET images. In some cases involving treatment with TCZ medication, ^{18}F-FDG PET might be the only tool for assessing disease activity.

Radiation

As ionizing radiation carries a higher risk of stochastic effect in younger subjects. The risks and benefits of using ^{18}F-FDG PET must be considered more carefully in cases involving young LVV patients. JSNC strongly recommends that the JSNM pediatric imaging guidelines should be followed to optimize the radiation doses administered to young LVV patients.

Conclusion

Although the evidence is not enough compared to the oncological usage of ^{18}F-FDG PET, recent studies indicate that the use of ^{18}F-FDG PET for the diagnosis and management of LVV has clear benefits.

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Conflicts of interest

None.

Abbreviations

CHCC: Chapel Hill consensus conference
GCA: Giant-cell arteritis
LVV: Large-vessel vasculitis
TAK: Takayasu arteritis

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