Enfermedades Infecciosas y Microbiología Clínica 41 (2023) 1–2

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

Editorial

PET/CT to diagnose and manage patients with infectious diseases: "*¡vamos a brillar, mi amor!* (Let's shine, my love!)"

PET/TC para el diagnóstico y manejo de pacientes con enfermedades infecciosas: "*¡vamos a brillar, mi amor!* (¡Let's shine, my love!)"

Widely used in the diagnosis and monitoring of oncologic pathologies, ^{18}F-fluoro-2-deoxyglucose positron-emission tomography (FDG PET/CT) is a hybrid imaging technique that combines the good anatomical resolution of computed tomography with "functional" information provided by the accumulation of a tracer analog of glucose, the fluorine-18 cyclotron-produced radioisotope, which is avidly taken up by cells with intense glycolytic activity.[1] It has been shown that cells involved in inflammatory/infectious processes, particularly neutrophils and monocyte/macrophages, express high levels of glucose transport proteins and the hexokinases responsible for its phosphorylation.[2] The accelerated transport of the radiotracer into these cells is proportional to the inflammatory/infectious activity, quantified in values of maximum standard uptake value (SUVmax) and whose expression in imaging corresponds to conspicuous shining areas of the affected zones.

In addition to its usefulness in studying various inflammatory pathologies (such as large vessel vasculitis, sarcoidosis, rheumatic diseases, and inflammatory bowel diseases) and miscellaneous syndromes like fever of unknown origin,[3] in the last two decades we have witnessed a progressive incorporation of FDG PET/CT in the diagnosis and monitoring of many other infectious diseases. Firstly, its potential utility has been reported in infections caused by specific aetiologic agents, such as invasive fungal infections (e.g., invasive aspergillosis, chronic disseminated candidiasis, mucormycosis, histoplasmosis, scedosporiosis, acute pulmonary coccidioidomycosis, etc.)[4] or tuberculosis, where FDG PET/CT has been used for diagnose, staging, response evaluation as well as to potentially predict clinical progression in patients with latent TB infection.[5]

Additionally, this tool has proven practical when there is a need to assess other complex infectious syndromes. There is much literature about its value in the study of musculoskeletal infections like osteomyelitis,[6] spondylitis (both pyogenic and tuberculous),[7] osteoarticular infections related with diabetic foot[8] and infections in prosthetic joints and periprosthetic spaces.[9] Yet, perhaps, a scenario in which this test has shown greater diagnostic yield has been that related to the diagnosis and follow-up of vascular infections, both vascular graft infections[10] and, in particular, cardiac implantable electronic devices infections and prosthetic valve endocarditis.[11] Indeed, its positivity has been incorporated as a major diagnostic criterion for prosthetic valve endocarditis in the modified Duke criteria in the latest guidelines of the European Heart Association.[12]

In the current issue of *Enfermedades Infecciosas y Microbiología Clínica*, it is presented the interesting work by Paula Suanzes et al., which explores the possible impact of the use of FDG PET/CT in the management of *Staphylococcus aureus* bacteraemia (SAB).[13] This microorganism continues to represent the leading cause of gram-positive bacteraemia, being associated with considerable morbidity and mortality. The optimal management of this heterogeneous clinical entity depends, to a large extent, on an accurate diagnosis of disease spread that would help to direct timely surgical maneuvers and/or trigger appropriate antibiotic treatment duration times. For this purpose, in addition to the evident usefulness of a thorough clinical history and physical evaluation, the search for a tool that helps quantify the initial severity of this disease can be compared to that of the "holy grail" for infectious disease specialists. Following this line of thought, additional microbiologic and biochemical data have been incorporated, including the time until blood culture positivity as a predictor of endocarditis and higher mortality,[14] and IL10 measure as a predictor of complicated bacteraemia and unfavorable outcomes.[15] Varying diagnostic scores have also been created to guide transoesophageal echocardiography exploration and facilitate endocarditis diagnoses in specific cases.[16]

The study by P. Suanzes et al.,[13] is a retrospective analysis of consecutive cases of SAB registered in a cohort from a large university hospital, the Vall d'Hebrón University Hospital in Barcelona, between 2013 and 2017. During that period, a highly selected group of patients (39 of 476; 8%) underwent FDG PET/CT as part of a diagnostic work-up for this pathology at the discretion of their treating physicians. The indication for the study was either the search for the initial bacteraemia source when unknown; the investigation of additional metastatic foci; or, finally, the evaluation of possible involvement of intravascular devices or cardiac prostheses. As a result of the test, it was possible to detect the source in 11 of 15 (73%) cases; reach a diagnosis of 30 additional foci in 22 of 39 (56%) patients, and diagnose or rule out infection of an intravascu-

DOI of original article: https://doi.org/10.1016/j.eimc.2021.11.013

https://doi.org/10.1016/j.eimce.2022.09.008

lar device in 22 of 26 (85%) patients. The authors concluded that performing FDG PET/CT in patients with SAB could be useful for selected cases following an individualized approach. The study had some limitations, though, including its retrospective, single-center design; a relatively small number of cases evaluated; and no control group. The discretionary indication of the test also raised some additional questions. For example, how many patients considered to have low-risk SAB and without a need for FDG PET/CT were, in the end, cases of complicated bacteraemia with relapse at follow-up? Could these relapses have been avoided if a FDG PET/CT had been performed at the right time? In other words, could systematic FDG PET/CT be a useful tool for an earlier and more accurate detection of patients with complicated SAB, regardless of the initial risk attribution? The study design by P. Suanzes et al. cannot answer these questions. However, other observational studies exploring these issues have presented encouraging results,[17] albeit with obvious methodologic limitations.[18] Of note, some of these studies have found a surprisingly favorable impact on the prognosis of patients with SAB undergoing FDG PET-CT, with significant reductions in 90-day mortality in analyses adjusted for confounders.[17,19] Finally, there is currently a Spanish prospective study underway (Funder: IS Carlos III; ref. PI19/01116) and at least two international clinical trials ("TEPSTAR" study; NCT03419221 and "PET-SAB" study; NCT05361135) that, hopefully, will shed light on the role of FDG PET/CT in the initial evaluation of these patients.

The peculiarity of FDG PET/CT in providing functional images of infectious activity undoubtedly positions the tool as promising for the diagnosis of disease spread. Given the high frequency of SAB and its ubiquity in different healthcare settings, an aspect that is surely relevant to debate in the future will be the accessibility of FDG PET-CT, currently being an expensive examination and only available in tertiary care centers. We will see in coming years if this technique is consolidated in the evaluation of patients with SAB and we will surely witness the progressive expansion of its use in evaluating a large number of infectious pathologies. Paraphrasing the lyrics of a famous Argentine rock band, we will request an FDG PET/CT for our patients with infections and "*¡a brillar, mi amor!*".[20]

References

1. Jamar F, Buscombe J, Chiti A, Christian PE, Delbeke D, Donohoe KJ, et al. EANM/SNMMI guideline for 18F-FDG use in inflammation and infection. J Nucl Med. 2013;54:647–58, http://dx.doi.org/10.2967/jnumed.112.112524.
2. Mochizuki T, Tsukamoto E, Kuge Y, Kanegae K, Zhao S, Hikosaka K, et al. FDG uptake and glucose transporter subtype expressions in experimental tumor and inflammation models. J Nucl Med. 2001;42:1551–5.
3. Treglia G. Diagnostic performance of ^{18}F-FDG PET/CT in infectious and inflammatory diseases according to published meta-analyses. Contrast Media Mol Imaging. 2019;2019:3018349, http://dx.doi.org/10.1155/2019/3018349.
4. Hot A, Maunoury C, Poiree S, Lanternier F, Viard JP, Loulergue P, et al. Diagnostic contribution of positron emission tomography with ^{18}F-fluorodeoxyglucose for invasive fungal infections. Clin Microbiol Infect. 2011;17:409–17, http://dx.doi.org/10.1111/j.1469-0691.2010.03301.x.
5. More S, Marakalala MJ, Sathekge M. Tuberculosis: role of nuclear medicine and molecular imaging with potential impact of neutrophil-specific tracers. Front Med (Lausanne). 2021;8:758636, http://dx.doi.org/10.3389/fmed.2021.758636.
6. Wang GL, Zhao K, Liu ZF, Dong MJ, Yang SY. A meta-analysis of fluorodeoxyglucose-positron emission tomography versus scintigraphy in the evaluation of suspected osteomyelitis. Nucl Med Commun. 2011;32:1134–42, http://dx.doi.org/10.1097/MNM.0b013e32834b455c.
7. Boriani L, Zamparini E, Albrizio M, Serani F, Ciani G, Marconi L, et al. Spine infections: the role of fluorodeoxyglucose positron emission tomography (FDG PET) in the context of the actual diagnosis guideline. Curr Med Imaging. 2022;18:216–30, http://dx.doi.org/10.2174/1573405617666210916121046.
8. Diez A, Fuster D, Morata L, Torres F, Garcia R, Poggio D, et al. Comparison of the diagnostic accuracy of diffusion-weighted and dynamic contrast-enhanced MRI with 18F-FDG PET/CT to differentiate osteomyelitis from Charcot neuro-osteoarthropathy in diabetic foot. Eur J Radiol. 2020;132:109299, http://dx.doi.org/10.1016/j.ejrad.2020.109299.
9. Jin H, Yuan L, Li C, Kan Y, Hao R, Yang J. Diagnostic performance of FDG PET or PET/CT in prosthetic infection after arthroplasty: a meta-analysis. Q J Nucl Med Mol Imaging. 2014;58:85–93.
10. Reinders Folmer EI, von Meijenfeldt GCI, Te Riet Ook Genaamd Scholten RS, van der Laan MJ, Glaudemans AWJM, Slart RHJA, et al. A systematic review and meta-analysis of ^{18}F-fluoro-d-deoxyglucose positron emission tomography interpretation methods in vascular graft and endograft infection. J Vasc Surg. 2020;72:2174–85, http://dx.doi.org/10.1016/j.jvs.2020.05.065.
11. Pizzi MN, Roque A, Fernández-Hidalgo N, Cuéllar-Calabria H, Ferreira-González I, Gonzàlez-Alujas MT, et al. Improving the diagnosis of infective endocarditis in prosthetic valves and intracardiac devices with ^{18}F-fluordeoxyglucose positron emission tomography/computed tomography angiography: initial results at an infective endocarditis referral center. Circulation. 2015;132:1113–26, http://dx.doi.org/10.1161/CIRCULATIONAHA.115.015316.
12. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015;36:3075–128, http://dx.doi.org/10.1093/eurheartj/ehv319.
13. Suanzes P, Willekens R, Puig-Asensio M, Pizzi MN, Roque A, Barios M, et al. Impact of ^{18}F-FDG-PET/CT on the management of *Staphylococcus aureus* bacteraemia: A retrospective observational study. Enferm Infecc Microbiol Clin. 2023;41:3–10.
14. Siméon S, Le Moing V, Tubiana S, Duval X, Fournier D, Lavigne JP, et al. Time to blood culture positivity: an independent predictor of infective endocarditis and mortality in patients with *Staphylococcus aureus* bacteraemia. Clin Microbiol Infect. 2019;25:481–8, http://dx.doi.org/10.1016/j.cmi.2018.07.015.
15. Rose WE, Eickhoff JC, Shukla SK, Pantrangi M, Rooijakkers S, Cosgrove SE, et al. Elevated serum interleukin-10 at time of hospital admission is predictive of mortality in patients with *Staphylococcus aureus* bacteremia. J Infect Dis. 2012;206:1604–11, http://dx.doi.org/10.1093/infdis/jis552.
16. van der Vaart TW, Prins JM, Soetekouw R, van Twillert G, Veenstra J, Herpers BL, et al. Prediction rules for ruling out endocarditis in patients with *Staphylococcus aureus* bacteremia. Clin Infect Dis. 2022;74:1442–9, http://dx.doi.org/10.1093/cid/ciab632.
17. Ghanem-Zoubi N, Kagna O, Abu-Elhija J, Mustafa-Hellou M, Qasum M, Keidar Z, et al. Integration of FDG-PET/CT in the diagnostic workup for *Staphylococcus aureus* bacteremia: a prospective interventional matched-cohort study. Clin Infect Dis. 2021;73:e3859–66, http://dx.doi.org/10.1093/cid/ciaa929.
18. Buis DTP, Sieswerda E, Kouijzer IJE, Huynh WY, Burchell GL, Berrevoets MAH, et al. ^{18}F-FDG-PET/CT in *Staphylococcus aureus* bacteremia: a systematic review. BMC Infect Dis. 2022;22:282, http://dx.doi.org/10.1186/s12879-022-07273-x.
19. Berrevoets M, Kouijzer I, Aarntzen E, Janssen M, De Geus-Oei L, Wertheim H, et al. 18F-FDG PET/CT optimizes treatment in *Staphylococcus aureus* bacteremia and is associated with reduced mortality. J Nucl Med. 2017;58:1504–10, http://dx.doi.org/10.2967/jnumed.117.191981.
20. Solari I, Beilinson S. La bestia pop" [Canción]. En Gulp! Wormo. 1985.

Guillermo Cuervo
Department of Infectious Diseases, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain
E-mail address: glcuervo@clinic.cat