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IMAGE OF THE MONTH

Evaluation of P-glycoprotein function at the blood–brain barrier using [^{18}F]MC225-PET

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P-glycoprotein (P-gp) is an ATP-dependent efflux transporter located at the blood–brain barrier (BBB), involved in the transport of a variety of neurotoxic substances out of the brain. Alterations in P-gp function play an essential role in the pathophysiological mechanisms underlying neurodegenerative disorders. The most widely used tracer to measure BBB P-gp function in vivo is *(R)*-[^{11}C]verapamil [1]. However, *(R)*-[^{11}C]verapamil is an avid P-gp substrate, and its low uptake hampers the measurement of increases in P-gp function. In order to overcome this limitation, [^{18}F]MC225 was developed as a novel PET tracer to measure P-gp function in vivo. [^{18}F]MC225 is a weaker P-gp substrate and has shown higher brain uptake than *(R)*-[^{11}C]verapamil at baseline in preclinical studies [2]. This may facilitate the evaluation of both increases and decreases in P-gp function. In addition, the longer half-life of fluorine-18 enables the use of [^{18}F]MC225 in centers without an onsite cyclotron.

These standardized uptake value (SUV) images show one of the first [^{18}F]MC225 PET brain scans in a healthy human subject in both unblocked (A) and blocked (B) P-gp state. Blocking was achieved by continuous intravenous administration of the specific P-gp inhibitor cyclosporin (2.5 mg/kg/h), starting 30 min prior to the scan. Quantitatively, the whole brain grey matter volume of distribution V_T changed from $V_T = 4.38$ at baseline to $V_T = 5.48$ after cyclosporin administration, showing higher uptake at baseline levels compared with previously described data of [^{11}C]verapamil ($V_T = 1.28$ at baseline, $V_T = 2.00$ after P-gp inhibition) [3], illustrating [^{18}F]MC225 as a promising tracer to measure BBB P-gp function in humans.

This article is part of the Topical Collection on Image of the month.

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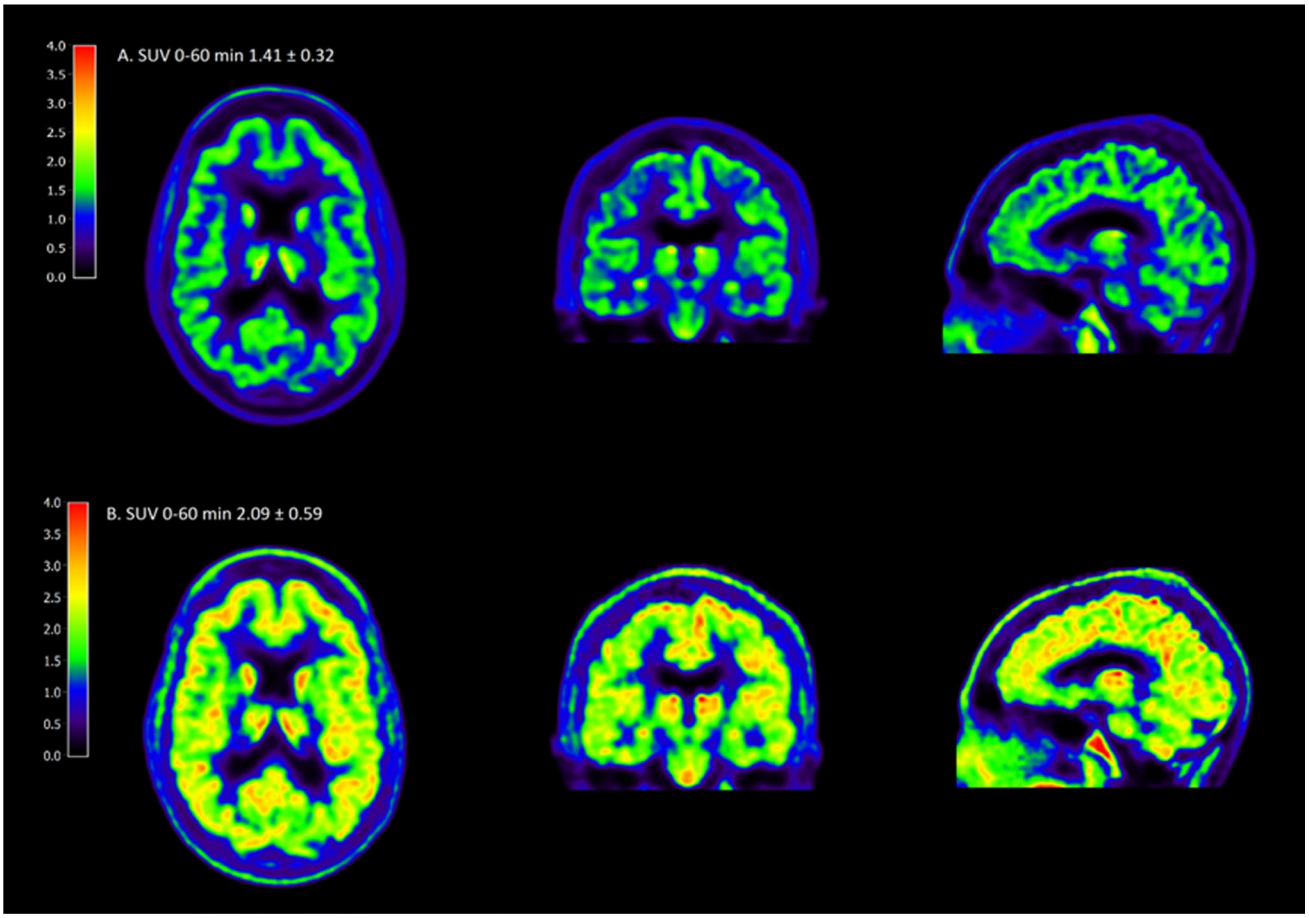

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Declarations

Ethics approval and informed consent All procedures performed involving the human participant were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the patient.

Competing interests GL received a research grant from Siemens Healthineers for appointing a PhD candidate. The other authors declare no competing interests.

References

1. Lubberink M, Luurtsema G, van Berckel BN, Boellaard R, Toornvliet R, Windhorst AD, et al. Evaluation of tracer kinetic models for quantification of P-glycoprotein function using (*R*)-[^{11} C]verapamil and PET. J Cereb Blood Flow Metab. 2007. https://doi.org/10.1038/sj.jcbfm.9600349.
2. García-Varela L, Arif WM, Vállez García D, Kakiuchi T, Ohba H, Harada N, et al. Pharmacokinetic modeling of [18F]MC225 for quantification of the P-glycoprotein function at the blood-brain barrier in non-human primates with PET. Mol. Pharm. 2020 https://doi.org/10.1021/acs.molpharmaceut.0c00514
3. Muzi M, Mankoff DA, Link JM, Shoner S, Collier AC, Sasongko L, et al. Imaging of cyclosporine inhibition of P-glycoprotein activity using 11C-verapamil in the brain: studies of healthy humans. J Nucl Med. 2009. https://doi.org/10.2967/jnumed.108.059162.