^{68}Ga-NODAGA-Exendin-4 PET Scanning for Focal Congenital Hyperinsulinism: Need for Replication

TO THE EDITOR: ^{18}F-6-fluoro-L-DOPA PET (^{18}F-DOPA PET) scanning has been the mainstay in the diagnosis and localization of focal lesions in patients with congenital hyperinsulinism (CHI) (*1*). Although scan-to-lesion correlation is not completely perfect, the predictive value of ^{18}F-DOPA PET as a clinical tool has been clinically meaningful and reliable, with sensitivity ranging from 75% to 100% (*1*,*2*), enabling significant transformation in the surgical management of focal CHI (*3*,*4*).

^{68}Ga-NODAGA-exendin-4 PET (^{68}Ga-exendin PET) is a new imaging modality that has potential to replace ^{18}F-DOPA PET (*5*). ^{68}Ga-exendin PET has been shown to have greater sensitivity and surgical preference in the localization of focal CHI. This exciting development has the advantage of molecular specificity in targeting glucagon-like peptide-1 receptor in pancreatic β-cells, as well as relatively low radiation (estimated at 0.77 mSV for a 1-y-old child) (*6*), although the short half-life (68 min) of ^{68}Ga requires access to a local production site.

However, our enthusiasm for this new diagnostic development in CHI is tempered by a deeper examination of the data and a review of the trial design to derive divergent conclusions from those reported prematurely and optimistically by the authors (*5*). The prospective arm of the study recruited only 8 patients, with no justification provided on the sample size needed to demonstrate clinical benefit. In comparing ^{68}Ga-exendin PET with ^{18}F-DOPA PET, the order of scanning was not made explicitly clear; considering the reporting and interpretation of nonconcurrent scans (at an interval of 4–72 d) by nonmasked observers, results were undoubtedly influenced by carry-over bias. Unusually, authors added a retrospective arm to the study, citing real-world observations to support doubtful findings from prospective study data but reinforcing observational bias in the process.

Although the authors provided clear descriptions of radiotracer production and PET imaging techniques, the article ignored the need to confirm focal CHI by correlating scan results with histopathologic results on intraoperative pancreatic frozen sections. Further, the authors did not discuss location specificity or the surgical complexity in achieving complete resection of lesions to demonstrate true benefit from shifting reliance on ^{68}Ga-exendin PET as a surgical navigational tool. Therefore, it remains unclear whether ^{68}Ga-exendin PET offered real-world benefit to patients in either prospective or retrospective arms of the study.

The combined experience of specialist CHI centers in the United Kingdom, Germany, and the United States over 14 years has established ^{18}F-DOPA PET as a proven clinical tool in the diagnosis of focal CHI. Notwithstanding this success, as a group we feel it is important to investigate improved imaging techniques that are more accessible, inexpensive, and reliable. However, the development of an alternative imaging modality away from ^{18}F-DOPA PET will require convincing strength of data, which the recently published paper (*5*) does not provide. Clearly, this paper whets the appetite with interesting preliminary information that needs to be replicated in well-designed, prospective multicentered studies with robust patient numbers to demonstrate clear clinical benefit.

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Reply: ^{68}Ga NODAGA-Exendin-4 PET Scanning for Focal Congenital Hyperinsulinism: Need for Replication

REPLY: Science needs differences in opinions to ensure that facts are presented in a truly *reproducible* way. That is why we welcome the comments by Banerjee et al. (*1*), and we have to admit that we actually agree with most of them.

Needless to say, the results of our study must be tested for replicability—as every set of novel data must be tested. Having said that, we would like to highlight that we have never claimed that this study was a registration trial. In fact, we clearly state that these are the first results of clinical imaging of congenital hyperinsulinism with ^{68}Ga NODAGA-exendin-4, and we did raise this issue in the discussion and conclusion sections (*2*).

Pertaining to the comments on retrospectively including 11 patients outside the prospective study, we do agree that there is a possibility of extending the bias. However, as the nature of the study was proof of concept and considering the expertise of the Charité Berlin Centre in treating congenital hyperinsulinism patients from all around the world, we decided to include all available patient data.