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Post-COVID-19 Brain [¹⁸F] FDG-PET Findings: A Retrospective Single-Center Study in the United States

 P. Debs,  N. Khalili,  L. Solnes,  A. Al-Zaghal,  H.I. Sair,  V. Yedavalli, and  L.P. Luna



ABSTRACT

BACKGROUND AND PURPOSE: The pathophysiology of neurologic manifestations of postacute sequelae of Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) infection is not clearly understood. Our aim was to investigate brain metabolic activity on [¹⁸F] FDG-PET/CT scans in patients with a history of coronavirus disease 2019 (COVID-19) infection before imaging.

MATERIALS AND METHODS: This retrospective study included 45 patients who underwent [¹⁸F] FDG-PET/CT imaging for any reason and had, at least once, tested positive for COVID-19 at any time before imaging. Fifteen patients had available [¹⁸F] FDG-PET scans obtained under identical conditions before the infection. A group of 52 patients with melanoma or multiple myeloma who underwent [¹⁸F] FDG-PET/CT were used as controls. Whole-brain 2-sample *t* test analysis was performed using SPM software to identify clusters of hypo- and hypermetabolism and compare brain metabolic activity between patients with COVID-19 and controls. Paired sample *t* test comparison was also performed for 15 patients, and correlations between metabolic values of clusters and clinical data were measured.

RESULTS: Compared with the control group, patients with a history of COVID-19 infection exhibited focal areas of hypometabolism in the bilateral frontal, parietal, occipital, and posterior temporal lobes and cerebellum (*P* = .05 uncorrected at the voxel level, family-wise error-corrected at the cluster level) that peaked during the first 2 months, improved to near-complete recovery around 6 months, and disappeared at 12 months. Hypermetabolism involving the brainstem, cerebellum, limbic structures, frontal cortex, and periventricular white matter was observed only at 2–6 months after infection. Older age, neurologic symptoms, and worse disease severity scores positively correlated with the metabolic changes.

CONCLUSIONS: This study demonstrates a profile of time-dependent brain PET hypo- and hypermetabolism in patients with confirmed SARS-CoV-2 infection.

ABBREVIATIONS: BMI = body mass index; COVID-19 = coronavirus disease 2019; FWE = family-wise error; GLM = general linear model; neuro-PASC = neurologic manifestations of postacute sequelae of SARS-CoV-2 infection; PASC = postacute sequelae of SARS-CoV-2; PCR = polymerase chain reaction; RT-PCR = reverse transcriptase PCR; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2; Tmax = time-to-maximum

As of December 2022, Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) has resulted in >97 million confirmed cases in the United States, with approximately 1 million all-time deaths, the highest among all countries and the sixteenth-highest per 100,000 population worldwide.^{1,2} Knowledge of coronavirus disease 2019 (COVID-19) mainly focuses on the acute illness and related symptoms such as cough, fever, myalgia,

ageusia, and anosmia; nevertheless, the reality of the long-term consequences of COVID-19 is becoming more evident,^{3–5} and many survivors of COVID-19 experience chronic postviral complications.^{3,6}

Evidence of persistent neurologic symptoms following acute COVID-19 is increasing, and this process was recently termed neurologic manifestations of postacute sequelae of SARS-CoV-2 infection (neuro-PASC).^{3,7} The most common neurologic manifestations are “brain fog”, fatigue, headache, numbness/tingling, dysgeusia, and anosmia.^{3,8,9} Although neuro-PASC is more frequent in patients needing hospitalization,^{3,10,11} studies have shown that postacute sequelae of SARS-CoV-2 (PASC) can also impact children, young adults, and those who experience only mild COVID-19 symptoms and do not require respiratory support or hospitalization.^{3,7,12}

The mechanism behind SARS-CoV-2-induced pathologic changes in the CNS is still unclear.^{13,14} Two main hypotheses

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attempt to explain this mechanism: indirect effects via peripheral inflammation and direct effects via SARS-CoV-2 CNS invasion. On the one hand, a cytokine storm (ie, an inflated immune response instigated by the infection) might play an indirect role in the neurologic manifestations of PASC;¹⁰ on the other hand, some reports suggest that SARS-CoV-2 may directly invade the CNS and possibly infect brain cells via the functional receptor human angiotensin-converting enzyme 2.³

Despite these 2 hypotheses, questions regarding the mechanisms underlying the pathophysiology of neuro-PASC symptoms remain unanswered, and imaging could help elucidate the underlying processes. PET might meaningfully contribute to our understanding of the pathophysiologic changes in patients post-COVID-19 by identifying affected brain regions.¹⁵ The underlying mechanisms can be explored by investigating changes in metabolic parameters, and [¹⁸F] FDG-PET/CT can be a valuable tool for detecting or ruling out severe coexistent processes and highlighting alterations in brain metabolism.¹⁶

Prior studies assessing imaging patterns associated with post-COVID-19 functional symptoms in PET/CT scans have compared whole-brain voxel-based analysis with a local database of healthy individuals to characterize cerebral metabolism patterns.¹⁷⁻²⁰ However, to our knowledge, no prior studies have assessed the potential alterations in brain metabolism in patients without functional symptoms at the time of imaging. We present a retrospective analysis of brain [¹⁸F] FDG-PET scans of patients with a biologically confirmed SARS-CoV-2 infection with and without persistent functional symptoms. On the basis of our clinical observations, we hypothesized that a history of COVID-19 infection may be associated with functional brain involvement that can be identified using [¹⁸F] FDG-PET. We aimed to compare PET scans using whole-brain voxel-based analysis with a local database of patients imaged under similar circumstances to characterize cerebral metabolism patterns, assess temporal evolution, and correlate PET abnormalities with patient characteristics and functional symptoms.

MATERIALS AND METHODS

Patient Selection

Post-COVID Patients. The institutional review board approved this retrospective single-center study and waived the requirement for written informed consent. The study complied with the Declaration of Helsinki and Health Insurance Portability and Accountability Act (HIPPA) regulations.

Forty-five patients underwent whole-body [¹⁸F] FDG-PET imaging between April 2020 and October 2021 at our institution. Inclusion criteria were adult patients older than 18 years of age with at least 1 documented case of SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR) at any time before imaging. None of the patients had an active SARS-CoV-2 infection at time of imaging. We excluded patients with incomplete PET/CT imaging of the entire brain, patients with brain imaging showing major structural abnormalities (eg, tumors, prior surgery, ischemic infarcts, cerebral venous thrombosis) unrelated to the COVID-19 infection, and patients with documented neurologic/psychiatric antecedents or symptoms preceding the SARS-CoV-2 infection (ie, confounding clinical variables). The study flow diagram is shown in the Online Supplemental Data.

Clinical and laboratory data were extracted from the patients' electronic medical records. Variables at the initial infection were age, sex, medical comorbidities, and presenting symptoms. When patients required hospital admission, information regarding supplemental oxygenation, admission to the intensive care unit, and the development of new symptoms was also collected. COVID-19 cases were rated as mild, moderate, or severe according to international guidelines and using the National Early Warning Score 2.²¹ Variables at the time of imaging included the time lag between the first COVID-19 test and the PET/CT scan, any persistent neurologic symptoms, body mass index (BMI), glucose levels, medications, administered [¹⁸F] FDG dose, and administration of any COVID-19 vaccine before imaging. Neurologic symptoms included persistent headaches, memory impairment, difficulty concentrating, fatigue, and insomnia. The presence of neurologic symptoms at the time of imaging was defined as persistent symptoms following COVID-19 infection that were reported in clinical notes dating no more than 7 days before PET imaging.

Patients with Pre-COVID Imaging. Among included patients, 15 had available [¹⁸F] FDG-PET scans obtained under identical conditions before the COVID-19 infection. Information on BMI, glucose levels, medications, and administered [¹⁸F] FDG pertaining to the pre-COVID scan dates was also collected for these patients.

Controls. A group of 52 age- and sex-matched controls who underwent PET/CT imaging for initial staging and were scanned under identical conditions before January 2021 was selected from our institutional database as follows: those with recently diagnosed melanoma or multiple myeloma, oncologically negative brain images, no history of neurologic disorders, and no recent use of psychotropic medications. All scans were obtained before administering any systemic chemotherapy or anticancer drugs. The limit date (December 31, 2020) used to select controls was settled on the basis of the latest epidemiologic data on the pandemic in the United States to avoid any potential bias. Information on controls regarding age, sex, medical comorbidities, medications, BMI, glucose levels, and administered [¹⁸F] FDG dose was subsequently collected from the electronic medical records.

[¹⁸F] FDG-PET Imaging and Processing

[¹⁸F] FDG-PET scans were acquired in the same center using an acquisition protocol conforming to guidelines put forth by the American College of Radiology, the American College of Nuclear Medicine, and the Society of Nuclear Medicine and Molecular Imaging.²² Whole-body scans were acquired on a Biograph mCT (Siemens; 36 patients and 47 controls) or a Discovery DRX or DLS (GE Healthcare; 9 patients and 5 controls) with in-line CT for attenuation correction at 60 minutes after the [¹⁸F] FDG intravenous administration in individuals fasting for at least 4 hours with a controlled, normal glycemic level. Brain images were extracted from the whole-body [¹⁸F] FDG-PET/CT as previously described^{20,23,24} and converted to Analyze format for pre-processing in SPM software (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12>).²⁵ The Montreal Neurological Institute 152 brain template was used as the standard template for registering PET/CT images to T1-weighted MR images using the FMRIB

Subjects' baseline characteristics

	Post-COVID (n = 45)	Controls (n = 52) ^a
Age (mean) (range) (yr)	58 (18–87)	57 (24–73)
Male sex (No.) (%)	24 (53.33)	28 (53.85)
[¹⁸ F] FDG administered dose (mean) (SD) (mCi)	12.28 (3.18)	11.88 (2.59)
BMI (mean) (SD) (kg/m ²)	28.62 (7.59)	28.45 (6.36)
Glucose levels (mean) (SD) (mg/dL)	95.13 (22.90)	98.04 (23.82)
Diabetes (No.) (%)	3 (6.67)	6 (11.54)
High blood pressure (No.) (%)	14 (31.11)	21 (40.38)
Delay between positive RT-PCR and imaging (mean) (SD) (mo)	6.57 (4.85)	–
COVID-19 severity mild/moderate or severe (No.) (%)	37/8 (82.22/17.78)	–
Hospitalization (No.) (%)	15 (33.33%)	–
Oxygen supplementation (No.) (%)	9 (20.00%)	–
Mechanical ventilation (No.) (%)	2 (4.44%)	–
COVID-19 vaccine at any time before [¹⁸ F] FDG-PET scan (No.) (%)	28 (62.2)	–
Symptoms (No.) (%)		
Dysosmia/dysgeusia ^b	17 (37.80)	–
Fever	16 (35.6)	–
Chills	6 (13.3)	–
Cough	16 (35.6)	–
Dyspnea	8 (17.8)	–
Chest pain	2 (4.4)	–
Pharyngitis	4 (8.9)	–
Rhinitis	3 (6.7)	–
Headache	4 (8.9)	–
Fatigue	7 (15.6)	–
Muscular pain	1 (2.2)	–
Dysgeusia	1 (2.2)	–
Anosmia/hyposmia	1 (2.2)	–
Diarrhea	4 (8.9)	–
Loss of appetite	2 (4.4)	–
Neurologic symptoms at time of imaging (No.) (%) ^c		
Persistent headaches	3 (6.7)	–
Memory impairment	1 (2.2)	–
Difficulty concentrating	1 (2.2)	–
Fatigue	1 (2.2)	–
Insomnia	1 (2.2)	–

Note:—The en dash indicates not applicable.

^aNo statistically significant difference was observed between patients post-COVID and sex- and age-matched controls ($P < .05$, 2-sample t test for continuous variables, χ^2 test for dichotomous variables).

^bBetween the time of the initial diagnosis and PET imaging. All other symptoms pertain to the time of the initial diagnosis.

^cPersistent symptoms following COVID-19 infection that were reported in the patients' records dating no more than 7 days before PET imaging.

Linear Image Registration Tool (FLIRT; <http://www.fmrib.ox.ac.uk/fsl/fslwiki/FLIRT>).^{26,27} Nonlinear spatial normalization of images to a specific [¹⁸F] FDG-PET template in the Montreal Neurological Institute space was performed using the SPM8 software. The images were then smoothed with a Gaussian kernel with a full width at half maximum of $8 \times 8 \times 8$ mm to increase the SNR.^{28,29} Global activity normalization was performed by proportional scaling (Online Supplemental Data). All images were checked for the presence of nonperfect fits before analysis.

Single-Subject and Group-Level [¹⁸F] FDG-PET SPM Analyses

Whole-brain 2-sample t test analysis was initially performed at the voxel level using SPM8 software to compare patients with controls and identify clusters of hypometabolism in the patient group. Paired sample t test (single-subject) comparison between patients before and after COVID-19 infection was also performed.

Distinct t -contrasts identified brain areas where glucose metabolism was significantly lower or higher in the patient group than in the control group. Patients post-COVID were further subgrouped according to the time delay between the positive reverse transcriptase PCR (RT-PCR) and PET imaging: 0–2, 2–6, 6–12, and >12 months.

Correlations between metabolic values of clusters and demographic and clinical data were measured for group-level comparisons. A general linear model (GLM) of the preprocessed FDG-PET data of patients taken as 1 group was constructed. Age, sex, COVID-19 severity, presence of neurologic symptoms (eg, syncope, loss of taste and smell, generalized weakness, difficulty concentrating) at the time of infection and at the time of imaging and the time lag between imaging and infection were introduced as covariates of interest centered around condition means in separate GLMs. Separate t -contrasts identified brain regions showing significant positive or negative correlations between the covariates of interest and regional cerebral glucose metabolism. The SPM t -statistic (SPM[T]) maps were acquired at an uncorrected height threshold (voxel-level significance) of $P < .05$, with a correction for multiple comparisons at the level of the cluster using the family-wise error (FWE) rate for a corrected P value $< .05$.

RESULTS

Clinical Characteristics of Patients Post-COVID

The clinical characteristics of the 45 included post-COVID patients are detailed in the Table. No significant difference was found between the post-COVID and control groups in pre-PET glucose levels (mean, 95.13 [SD, 22.90] versus 98.04 [SD, 23.82]); mean BMI (mean, 28.62 [SD, 7.59] versus 28.45 [SD, 6.36]); and administered [¹⁸F] FDG activity (mean, 12.28 [SD, 3.18] versus 11.88 [SD, 2.59] mCi). The mean time delay between positive RT-PCR results and imaging was 6.57 (SD, 4.85) months (range, 1–24 months). At the time of diagnosis, the median National Early Warning 2 clinical score was 2, corresponding to a low-risk grading; 33.3% of patients required hospitalization (15/45), and 4.4% required mechanical ventilation (2/45).

Among the post-COVID patients, fever and cough were the most common manifestations at presentation (16/45, 35.6% each). Dyspnea, fatigue, and chills were reported in 8, 7, and 6 patients, respectively (17.8%, 15.6%, and 13.3%). On admission, 1 patient had loss of taste (1/45, 2.2%), while another had loss of

smell (1/45, 2.2%). A total of 17 patients reported experiencing loss of smell and taste between the initial diagnosis of COVID-19 and their PET imaging (17/45, 37.8%). At the time of imaging, a total of 6 patients (13%) reported ≥ 1 persistent neurologic symptom following COVID-19 infection, including persistent headaches (3/45, 6.7%), memory issues, focus impairment, fatigue, and insomnia (1/45 each, 2.2%) (Table).

Patterns of [18 F] FDG-PET Hypo- and Hypermetabolism

All groups showed comparable global metabolism uptake values (Online Supplemental Data). Specifically, the comparison between the whole post-COVID ($n = 45$), pre-COVID ($n = 15$), and control patient ($n = 52$) groups showed no significant differences ($P = .18$).

PET Metabolic Profile of Post-COVID Scans Compared with Controls

Clusters of significant hypo- and hypermetabolism in the whole group of post-COVID patients and subgroup analyses are reported in the Online Supplemental Data. In comparison with the 52 controls, post-COVID patients presented with significant hypometabolism (P -voxel $< .05$ uncorrected, P -cluster $< .05$, FWE-corrected) involving the bilateral parietal lobes, including the precuneus regions (time-to maximum [Tmax] = 3.90); frontal lobes, including the anterior cingulate (Tmax = 2.40) and prefrontal cortices (Tmax = 3.04); occipital lobes (Tmax = 3.90); right temporal lobe (Tmax = 2.64); and right cerebellum (Tmax = 2.74). The whole group of post-COVID patients did not exhibit brain regions of statistically significant relative hypermetabolism compared with controls. In addition, cross-sectional imaging subgroup analyses showed more severe and extensive brain hypometabolism during the first 2 months after the infection onset, followed by a progressive return to normal metabolic activity. At 6–12 months, patients showed a near-complete recovery of brain abnormalities, with residual limited hypometabolic clusters in the anterior cingulate cortex, posterior inferior frontal gyri, right frontal operculum, and right temporal-insular region. The significantly reduced metabolism disappeared at 12 months. Hypermetabolism involving the brainstem, cerebellum, limbic structures (ie, amygdala and hippocampus bilaterally), a smaller region of the frontal cortex, and periventricular white matter was observed only at 2–6 months after infection (Online Supplemental Data).

PET Metabolic Profile of Patients Post- versus Pre-COVID

At the group level, SPM paired samples t test comparison between PET scans of patients pre- and post-COVID ($n = 15$, P -voxel $< .05$ uncorrected, P -cluster $< .05$ FWE-corrected) did not show statistically significant clusters. However, at 2–6 months after the infection onset, post-COVID patients presented with a significant decrease in regional glucose consumption in the bilateral parietal lobes, posterior frontal lobes including the frontal eye fields and the left cingulate cortex, and occipital lobes compared with their pre-COVID scans ($n = 6$). Moreover, significant hypermetabolic areas were found in the bilateral limbic structures (anterior hippocampi and amygdala), brainstem, ventral thalami, left inferior frontal lobe, and left cerebellum during the 2- to 6-month interval (Online Supplemental Data).

Correlations between Brain Hypometabolism and Clinical Variables

Age, neurologic symptoms at the time of imaging, and SARS-CoV-2 infection-severity scores were all significantly associated with the widespread extension and severity of brain metabolic patterns seen on post-COVID versus control scans. Precisely, older age, the presence of neurologic symptoms, and worse disease severity scores were positively correlated with the degree of hypometabolism in the bilateral parietal, posterior frontal, and temporal lobes, as well as the degree of hypermetabolism in the central cerebral and subcortical regions (Online Supplemental Data). In addition, SARS-CoV-2 infection severity scores were also significantly associated with the widespread extension and severity of brain metabolic patterns seen on post- versus pre-COVID scans (Online Supplemental Data).

DISCUSSION

This whole-brain voxel-based PET study demonstrates brain metabolic abnormalities in patients with a history of biologically confirmed SARS-CoV-2 infection. Voxel-based brain analysis supported the recent hypothesis on SARS-CoV-2 infection-related brain metabolic impairment and provided new insights into the pathophysiology of COVID-related brain abnormalities. Cross-sectional subgroup analyses suggest that the brain metabolism remains mildly altered 6 months after disease onset and gradually improves after 6–12 months. Moreover, the significant brain hypermetabolism observed between 2 and 6 months after infection in subcortical brain regions, including the limbic structures (eg, hippocampi and amygdala), in patients post-COVID compared with both the control group and the pre-COVID imaging data set suggests that brain inflammation peaks and subsequently recovers after this time window.

A gradual change in the severity and extent of hypometabolism from a widespread pattern in < 2 months to a limited involvement of the anterior cingulate cortex, right orbitofrontal cortex, bilateral posterior gyrus rectus, right insula, and medial temporal lobes was observed between 6 and 12 months postinfection. However, no significant hypometabolism was noted in these particular regions in the 0- to 2- and 2- to 6-month subgroups, raising the possibility that these regions might be preferentially impaired in the later stages of the disease. Conversely, significant areas of hypermetabolism involving the brainstem, cerebellum, and limbic structures were observed in the 2- to 6-month period subgroup. One explanation for this finding is that the regions of hypometabolism involving the frontoinsular areas and limbic system after 6 months may result from a peak in the active inflammation involving the central regions of the brain between 2 and 6 months after disease onset. Correspondingly, prior studies have reported a predominant involvement of the brainstem, cerebellum, and limbic structures (amygdala and hippocampus bilaterally) as hypermetabolic hallmarks.^{17,20,30} Most interesting, this metabolic pattern was observed in our nonselected whole-patient group regardless of the individual's neurologic symptoms or lack thereof, highlighting some degree of abnormal cerebral metabolic activity possibly occurring even in the absence of clinical symptoms or during the subclinical phase of the infection. Yet, because previous prospective studies

had focused on comparing clinically symptomatic patients with healthy controls without including asymptomatic post-COVID patients, it remains unclear to which degree clinical symptoms correlate with specific abnormal brain metabolic patterns.¹⁷⁻²⁰

To the best of our knowledge, no regional brain metabolic studies assessing intrasubject variability in patients before and after COVID-19 infections have been previously published. Therefore, we believe this approach reduces the potential bias of pre-existing regional metabolic changes in these individuals. Even though no significant regional metabolic changes were observed in the whole-group level analysis at the statistical threshold used, significant regional [¹⁸F] FDG-PET hypometabolism and hypermetabolism in the post-COVID subgroup of patients ($n = 6$) imaged between 2 and 6 months after COVID-19 infection onset were noted. The lack of significant findings on [¹⁸F] FDG-PET in the whole patient group and other subgroups might be partly due to the FWE at the cluster level used and the small sample size, because the FWE rate may be considered conservative for group-level analyses with small sample sizes.

Correlation analyses revealed a relationship between regional cerebral glucose metabolism and age, neurologic symptoms at the time of imaging, and SARS-CoV-2 infection severity. This is consistent with previous studies documenting a correlation between the severity of SARS-CoV-2-related loss of smell and metabolic changes and an inverse correlation between an increased number of functional symptoms with alterations in the brainstem and cerebellum metabolism.^{19,31} In addition, increased age has been reported as a predictor of more severe outcomes, explaining the correlation between age and the observed metabolic derangements.^{32,33} Moreover, neurologic symptoms at the time of imaging also correlated with brain metabolic changes, in line with a study by Goehring et al³⁴ showing correlations between metabolism in the orbitofrontal, internal temporal area, and the pons ROIs and multiple cognitive assessment scales. Also, the presence of persistent neurologic symptoms such as headaches, memory and concentration impairment, fatigue, and insomnia was positively correlated with decreased metabolism in the parietal lobes. As previously assessed, the strong correlation between changes in cerebral metabolism, specifically in the frontoparietal regions, and the cognitive functions served by those regions in COVID-19 encephalopathy suggests that these changes are interdependent.^{30,35}

Limitations must be considered for the interpretation of this study. First, this retrospective, observational study evaluated a small group of patients who underwent FDG-PET imaging for other clinical indications, most of which were oncologic. Patients with brain lesions who underwent chemotherapy or radiation therapy to the head and neck area were excluded to reduce the confounding effect of such comorbidities. Second, patients selected for the control group were diagnosed with either multiple myeloma or melanoma, which could have affected the study results. Enrolling disease-free patients was not possible due to the retrospective nature of the study, because patients usually undergo PET imaging for a clinical indication. To minimize bias, we selected patients who had recently been diagnosed, were not experiencing symptoms, had not commenced any treatment, and did not show evidence of brain abnormalities on imaging. Nonetheless, both melanoma and multiple myeloma can have

direct and indirect effects on brain metabolism and could, therefore, affect the validity of our results. Third, the inclusion of patients who have had at least 1 dose of the COVID-19 vaccine before PET/CT may have impacted the clinical disease course and clinical-imaging correlations. Fourth, the 15 patients with pre-COVID imaging could have potentially had another earlier undocumented COVID-19 infection before the pre-COVID imaging, thus affecting the validity of that comparison.

CONCLUSIONS

The present study demonstrates a pattern of reversible brain PET hypo- and hypermetabolic changes in patients with confirmed SARS-CoV-2 infection. The degree of observed alterations appears to be transient and positively correlates with older age, neurologic symptoms at the time of imaging, and worse disease severity scores. Even so, metabolic changes were detected in asymptomatic patients and patients without symptoms strongly suggestive of COVID-19. Brain imaging could potentially serve as a tool to identify asymptomatic cases whenever incidental [¹⁸F] FDG-PET/CT findings suspicious for SARS-CoV-2 are detected and to further understand the pathophysiology behind the neurologic symptoms observed with long COVID. Future studies must clarify how PET imaging can be used as a potential biomarker to follow-up patients clinically, monitor disease progression, and assess recovery.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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