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SHORT COMMUNICATION

Visual interpretation of brain hypometabolism related to neurological long COVID: a French multicentric experience

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Abstract

Background This multicentre study aimed to provide a qualitative and consensual description of brain hypometabolism observed through the visual analysis of ^{18}F-FDG PET images of patients with suspected neurological long COVID, regarding the previously reported long-COVID hypometabolic pattern involving hypometabolism in the olfactory bulbs and other limbic/paralimbic regions, as well as in the brainstem and cerebellum.

Methods From the beginning of August 2021 to the end of October 2021, the brain ^{18}F-FDG PET scans of patients referred for suspected neurological long COVID with positive reverse transcription polymerase chain reaction (RT-PCR) and/or serology tests for SARS-CoV-2 infection were retrospectively reviewed in three French nuclear medicine departments (143 patients; 47.4 years old ± 13.6; 98 women). Experienced nuclear physicians from each department classified brain ^{18}F-FDG PET scans according to the same visual interpretation analysis as being normal, mildly to moderately (or incompletely) affected, or otherwise severely affected within the previously reported long-COVID hypometabolic pattern.

Results On the 143 brain ^{18}F-FDG PET scans performed during this 3-month period, 53% of the scans were visually interpreted as normal, 21% as mildly to moderately or incompletely affected, and 26% as severely affected according to the COVID hypometabolic pattern. On average, PET scans were performed at 10.9 months from symptom onset (± 4.8). Importantly, this specific hypometabolic pattern was similarly identified in the three nuclear medicine departments. Typical illustrative examples are provided to help nuclear physicians interpret long-COVID profiles.

Conclusion The proposed PET metabolic pattern is easily identified upon visual interpretation in clinical routine for approximately one half of patients with suspected neurological long COVID, requiring special consideration for frontobasal paramedian regions, the brainstem and the cerebellum, and certainly further adapted follow-up and medical care, while the second half of patients have normal brain PET metabolism on average 10.9 months from symptom onset.

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Keywords SARS-CoV-2 · COVID-19 · Long COVID · FDG · PET · Olfactory bulb · Limbic regions · Brainstem · Cerebellum

Introduction

Long COVID, defined by the persistence or recurrence of symptoms 3 months after an initial severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, represents a serious public issue since it affects approximately 10–15% of patients, with emerging evidence of brain impairment [1–3]. In such suspected cases, patients can be referred to the Nuclear Medicine Departments for brain ^{18}F-FDG PET scans to contribute to the workup of a differential diagnosis, and to potentially identify the hypometabolic pattern previously reported at the group level in a recent monocentric study for this new entity involving fronto-orbital olfactory regions and other limbic/paralimbic regions, as well as the brainstem and cerebellum [4]. Brain areas that composed this hypometabolic pattern have also been reported in an MRI study measuring cortical atrophy before and after COVID infection [2], as well as in a review of ninety studies [3]. Validation of this long-COVID hypometabolic PET pattern is consequently needed at the individual and multicentric levels to easily apply it in clinical routine for nuclear physicians.

The objective of this multicentre study was to provide a qualitative and consensual description of the brain hypometabolism observed through the visual analysis of ^{18}F-FDG PET images of patients with suspected neurological long COVID.

Materials and methods

From the beginning of August 2021 to the end of October 2021, the brain ^{18}F-FDG PET scans of patients referred for suspected neurological long COVID with a positive reverse transcription polymerase chain reaction (RT-PCR) and/or serology test for SARS-CoV-2 infection were retrospectively reviewed in three French nuclear medicine departments (CHRU of Nancy, Timone Hospital, APHM Marseille and Pitié-Salpêtrière Hospital, APHP, Paris). All patients met the current definition of long COVID by the World Health Organization (https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1), with a PET evaluation performed at least 3 months after the demonstrated infection and while their symptoms persisted. Only patients with suspected neurological long COVID were included, i.e., patients presenting functional complaints of possible brain origin, typically reported in long COVID, i.e., fatigue, pain, memory/cognitive complaints, insomnia, hyposmia/anosmia, dysgeusia/ageusia [5] or signs of dysautonomia (tachycardia, orthostatic intolerance and breathlessness) [6]. No patient presented clinical evidence of other concomitant infectious diseases during the period between their COVID infection and ^{18}F-FDG PET scan after a careful examination by infectious disease specialists (PD, FG, DSC).

The brain ^{18}F-FDG PET scan was recorded over a 10- to 15-min one-bed acquisition, 30–45 min after the injection of 2 to 3 MBq/kg of ^{18}F-FDG following a sensory rest period. All subjects had fasted for at least 6 h prior to receiving the injection and had blood glucose levels < 10 mmol/L. All PET images were reconstructed with iterative OSEM methods and corrected for scatter, random and attenuation with a CT scan, as usually performed in clinical routine for each department with three distinct cameras (Vereos, Philips® at Nancy; Biograph mCT Flow, Siemens® at Paris; Discovery 710, General Electric® at Marseille). All PET acquisition and reconstruction protocols performed in expert centres for brain ^{18}F-FDG PET imaging were in accordance with the brain ^{18}F-FDG PET European procedure guidelines [7].

Experienced nuclear physicians from each department (AV, AK and EG) had to classify the brain ^{18}F-FDG PET scans according to the same visual interpretation analysis as being normal (or slightly non-specifically impaired), vs. mildly to moderately affected or severely affected within the previously reported long-COVID hypometabolic pattern [4]. This typical hypometabolic long-COVID pattern involves the fronto-orbital olfactory regions, visualized in coronal slices, other limbic/paralimbic regions in axial and coronal slices, the brainstem in sagittal slices and the cerebellum in sagittal and coronal slices [4]. Detailed localizations of these areas are shown with arrows in Fig. 1 for the two grades of severity and the 3 centres. A mild-to-moderate impairment was defined as an incomplete hypometabolic pattern (two or three regions affected) or mild-to-moderate hypometabolism affecting the 4 regions; the impairment was otherwise classified as severe. For this visual analysis, brain ^{18}F-FDG PET images were reoriented to the AC-PC axis, displayed through the French colour scale

by targeting the brain voxel with maximal uptake for normalization in intensity.

Characteristics of patients are presented in Tables 1 and 2. Comparisons between distributions were performed with Mann–Whitney (age and time from symptoms onset in Table 2) or Kruskal–Wallis tests (age and time from symptoms onset in Table 1) for continuous variables and chi-2 tests for discrete variables (sex, visual interpretation and brain areas involved in Table 1; sex in Table 2). A p value < 0.05 was considered significant.

Results

Within the predefined period of 3 months, 10, 29 and 104 patients were referred to the nuclear medicine departments for suspected neurological long COVID in Nancy, Paris and Marseille, respectively (143 patients; 47.4 years old $\pm$ 13.6; 98 women). On average, PET scans were performed at 10.9 months from symptom onset ($\pm$ 4.8). Based on the visual analysis, 53% of the scans were interpreted as normal, 21% as mildly to moderately affected, and 26% as severely affected according to the COVID hypometabolic pattern. Table 1 details the results of this visual analysis per centre, and Table 2 shows the factors potentially influencing the metabolic profile. Importantly, this hypometabolic long-COVID pattern was similarly identified in the three nuclear medicine departments.

Illustrative examples of normal, mildly to moderately affected, and severely affected long COVID-classified cases from the three nuclear medicine departments are depicted in Fig. 1, with no involvement, incomplete or mild/moderate involvement, and severe involvement, respectively, of the olfactory bulbs within the fronto-basal region and connected cerebral regions, including other limbic/paralimbic regions, the brainstem, and the cerebellum. These cases are provided to help nuclear physicians interpret brain ^{18}F-FDG PET scans in cases of suspected long COVID.

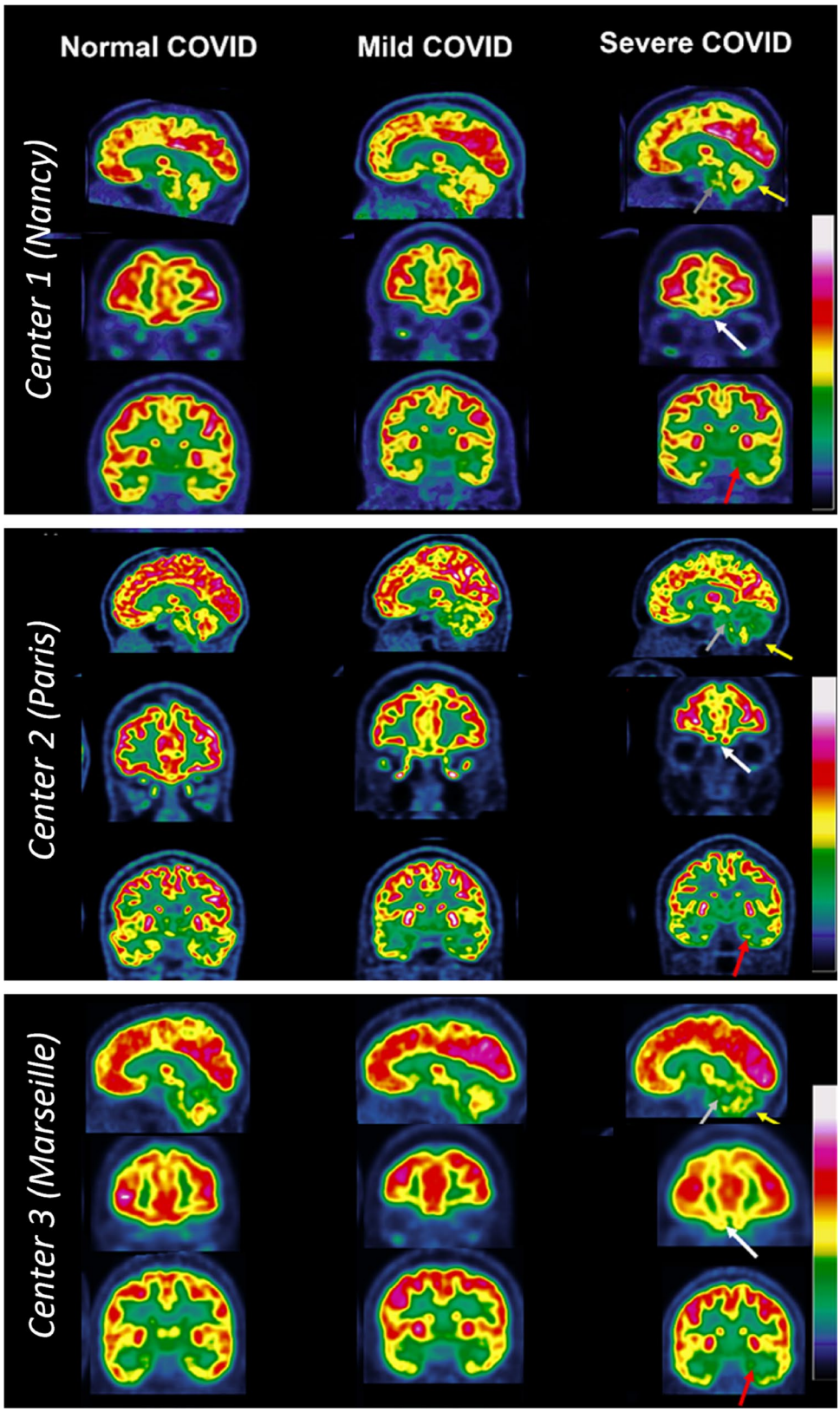
Discussion

This qualitative description provides arguments for a multicentre replication of the hypometabolic long-COVID pattern previously reported at a single-centre level [4]. This pattern can be found at an individual level and helps to objectively assess metabolic abnormalities in patients with suspected neurological long COVID. This strengthens the fact that nuclear neurology can be helpful in routine practice for selected patients, here on average 10.9 months from the initial infection, after clinical evaluation, to identify the possible brain impairment associated with long COVID, beyond its role for differential diagnosis for example for encephalitis or neurodegenerative diseases in this context [8].

According to this retrospective review in a predefined period of inclusion, the mild-to-moderate and severe hypometabolic long-COVID patterns represent 47% of patients. Other studies involving long-COVID patients found hypometabolism mainly in the fronto-orbital regions [9, 10] or a similar long-COVID pattern on MRI scans with a more pronounced reduction in grey matter thickness and contrast in the orbitofrontal cortex and parahippocampal gyrus, as well as involvement of the brainstem region [2, 3]. This also means that the previously reported hypometabolic pattern is not visually found in all patients with suspected neurological long COVID. This could explain why this pattern was not found in one series of 14 patients with long COVID that was recently published [11]. Possible explanations include discrepancy between the visual and quantitative analyses, recovery from the initial brain impairment (on average, PET scans are being performed at 10.9 months from symptom onset). Moreover, long COVID is certainly a multisystemic disease, with respiratory and cardiac symptoms that are persistent or fluctuating [1], which could also explain why some patients experiencing long COVID could have symptoms but not brain impairment. We also cannot formally rule out symptoms related to extracerebral diseases other than long COVID. On the other hand, it is particularly interesting to notice that approximately half of patients with symptoms had no brain metabolic abnormalities, demonstrating that the long-COVID hypometabolic pattern is not simply a functional consequence of symptoms, but more probably the signature of a genuine brain impairment.

Of note, the regions affected within the previously reported pattern are known to be related to the typical symptoms presented by patients with long COVID [12], especially olfactory loss, emotional disturbances, memory impairment, motor disorders, impaired balance and dysfunction of autonomous behaviours. Further studies are required to demonstrate such relationships between clinical characteristics and brain PET abnormalities at the individual level, albeit some preliminary relationships with more numerous functional complaints or olfactory test scores have been recently reported [4, 13].

This proposed pattern is easily applicable for visual interpretation, with consideration required for fronto-basal paramedian regions, the brainstem and the cerebellum, which


Normal COVID
Mild COVID
Severe COVID
Center 1 (Nancy)
Center 2 (Paris)
Center 3 (Marseille)

◂**Fig. 1** Typical examples of brain ^{18}F-FDG PET images of patients with suspected long COVID in the three French nuclear medicine departments, all presenting positive RT-PCR and/or serology tests (cases from Nancy in the upper part, Paris in the middle part and Marseille in the lower part of the figure). Patients included in the left column were those with brain ^{18}F-FDG PET images identified as normal by the nuclear physician experts (a 44-year-old woman referred 301 days after COVID infection for the persistence of dyspnoea on exertion and tachycardia without any cardio-pulmonary damage in the upper part; a 35-year-old woman referred 113 days after acute COVID for persistent asthenia, headaches, sleep disturbance, polyarthralgia and memory/concentration impairment in the middle part; and a 50-year-old woman with memory complaints, headaches and anosmia 314 days after infection in the lower part). The middle column includes patients who were classified as presenting a mild-to-moderate long-COVID hypometabolic pattern (a 41-year-old man who presented asthenia, dyspnoea on exertion and cognitive disorder 315 days after acute COVID acute infection in the upper part; a 52-year-old woman referred 342 days after COVID infection for cognitive complaints with language and memory difficulties, asthenia, insomnia and muscular weakness in the middle part; and a 55-year-old woman presenting memory complaints, loss of words, headaches and dyspnoea 168 days after the acute stage of the infection in the lower part); and the right column includes patients who were classified as presenting a severe long-COVID hypometabolic pattern (a 37-year-old-woman presenting cognitive impairment, dyspnoea, orthostatic hypotension, hypersomnia and fever at 253 days since symptom onset in the upper part; a 38-year-old-woman referred for brain ^{18}F-FDG PET 545 days after acute COVID infection, with dysexecutive symptoms, memory difficulties, dizziness, limb paraesthesia, asthenia, myalgia and polyarthralgia in the middle part; and a 20-year-old-woman with persistence of functional symptoms, with asthenia, headaches and memory/concentration impairment 170 days after infection in the lower part). In these patients with a typical severe long-COVID hypometabolic pattern, the brain areas with hypometabolism are identified with arrows: white arrows for the fronto-orbital olfactory regions, red arrows for the other limbic/paralimbic regions, grey arrows for the pons and yellow arrows for the cerebellum

are not classic hypometabolic regions reported in other usual disorders. Even though it was not used for the current study, additional automatic semiquantitative analysis with dedicated software could help to better identify subtle metabolic changes. Further larger studies should evaluate the benefit of adding such automatic analyses in the diagnosis of long COVID.

In any case, this pattern is clearly different from patients with neurodegenerative and psychiatric diseases in our experience, especially considering the associated resting-state metabolic impairment at individual level of the brainstem and the cerebellum [7, 14]. The exam could reassure half of the patients who have normal scans, and for which a brain impairment was suspected by the clinical physician. On the other hand, it can contribute to the social and medical recognition of a patient's disability by the health care system, especially when all other medical examinations fail to show an objective abnormality. In such cases of brain involvement observed with ^{18}F-FDG PET, adapted follow-up and medical care should be proposed. Typically in our centers, the patients stopped their medical vagrancy, received cognitive re-education counselling and were referred for further investigations and support, including speech therapists and psychomotor therapists.

In conclusion, the proposed PET metabolic pattern is easily identified upon visual interpretation in clinical routine for approximately one half of patients with suspected neurological long COVID, requiring special consideration for frontobasal paramedian regions, the brainstem and the cerebellum, and certainly further adapted follow-up and medical care, while the second half of patients have normal brain PET metabolism on average 10.9 months from symptom onset.

Table 1 Results of the visual analyses among the centres

	Nancy ($n=10$)	Paris ($n=29$)	Marseille ($n=104$)	p values
Age (years old)	40.3 ± 8.9	47.3 ± 12.4	48.1 ± 14.2	0.11
Women	5 (50%)	26 (90%)	67 (64%)	0.02*
Time since symptom onset (months)	11.9 ± 4.0	14.4 ± 4.9	9.9 ± 4.4	< 0.01*
Visual interpretation				0.11
Normal	6 (60%)	14 (48%)	56 (54%)	
Mild to moderate	2 (20%)	11 (38%)	17 (16%)	
Severe	2 (20%)	4 (14%)	31 (30%)	
Brain areas involved				
Fronto-orbital and olfactory regions	4 (40%)	9 (31%)	45 (43%)	0.49
Other limbic and paralimbic regions‡	4 (40%)	13 (45%)	43 (41%)	0.94
Brainstem	2 (20%)	13 (45%)	31 (30%)	0.22
Cerebellum	2 (20%)	8 (28%)	34 (33%)	0.65

* p value significant for the comparison among the 3 centres

‡ including amygdalae, hippocampal and parahippocampal regions

Table 2 Factors potentially influencing the metabolic profile of the brain ^{18}F-FDG PET images

	Normal/Abnormal	Moderate/severe	Fronto-orbital and olfactory region involvement (y/*n*)	Other limbic and paralimbic region involvement (y/*n*)	Brainstem involvement (y/*n*)	Cerebellum involvement (y/*n*)
Age (years)	46.7 ± 13.1/48.2 ± 13.2 $p = 0.52$	50.2 ± 14.4/46.5 ± 14 $p = 0.23$	47.9 ± 14.6/47.0 ± 13.0 $p = 0.68$	48.4 ± 14.1/46.6 ± 13.3 $p = 0.53$	45.3 ± 13.3/48.4 ± 13.7 $p = 0.15$	45.7 ± 13.7/48.1 ± 13.6 $p = 0.27$
Sex (women)	72%/64% $p = 0.29$	77%/54% $p = 0.06$	60%/74% $p = 0.08$	60%/75% $p = 0.06$	63%/71% $p = 0.33$	61%/72% $p = 0.22$
Time since symptom onset (months)	10.6 ± 4.9/11.3 ± 4.6 $p = 0.48$	12.0 ± 3.8/10.7 ± 5.2 $p = 0.07$	11.0 ± 4.6/10.9 ± 4.9 $p = 0.89$	11.4 ± 4.6/10.6 ± 4.9 $p = 0.37$	11.3 ± 5.1/10.8 ± 4.6 $p = 0.94$	10.7 ± 5.0/11.0 ± 4.7 $p = 0.49$

p values for the comparison between two groups. y/n: yes/no

Author contribution All authors contributed significantly to the analysis and interpretation of the data (AV, AK, EG), the writing of the manuscript (AV, EG) and the revision of the manuscript (AK, PD, FG, DSC, EG).

Availability of data and material The data that support the findings of this study are available upon request from the corresponding author (EG).

Code availability Not applicable.

Declarations

Ethics approval and consent to participate The retrospective observations required no ethical approval other than informed consent. Informed consent was obtained from all individual participants included in the study.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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