Orbito-Frontal Cortex Hypometabolism in Children With Post-COVID Condition (Long COVID)

A Preliminary Experience

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Abstract: We describe 3 children with new-onset neurocognitive problems after coronavirus disease 2019 (COVID-19), that showed, at the brain [18F]-fluorodeoxyglucose positron emission tomography/computed tomography, hypometabolism in the left orbito-frontal region. The voxel-wise analysis confirmed a cluster of hypometabolic voxels in this region with a peak at −18/46/−4mm (179 voxels, T-Score 8.1). These findings may explain neurocognitive symptoms that some children develop after COVID-19 and require further investigations.

Key Words: long covid, children, brain, PET, orbito-frontal cortex

There is increasing recognition that SARS-CoV-2 can not only cause severe acute disease [coronavirus disease 2019 (COVID-19)] but a subgroup of patients may develop a chronic condition that impacts daily functioning for months after the initial infection. This condition, commonly referred to as long Covid or post-Covid condition (PCC), is well characterized in adults, where there is evidence from several international independent cohorts that up to 30%–50% of the patients can be affected. Recent studies are providing evidence that adult PCC can have immunologic dysfunction with or without evidence of organ involvement. Although PCC is a multisystem disease, cardiac, lung, and more recently brain pathologic findings at third level imaging studies have been demonstrated.

The latest studies have shown that also a subgroup of children do not fully recover from SARS-CoV-2 infection but develop persisting clinical symptoms, such as fatigue, post-exertional malaise, arthralgia, headache, chest pain and neuropsychiatric problems, including sleep disorders, alterations in mood, memory and concentration. However, available studies have mostly focused on surveys and self-reported symptoms, whereas investigations on pathophysiology are scarce. Indeed, central nervous system functional imaging may be particularly relevant, since children may develop neurocognitive symptoms and it is still unclear if they have a psychological or a more organic substrate. Most importantly, recent adult studies have documented functional and morphological changes in the brain of adults affected by COVID-19.

In this study, we present preliminary findings of a small group of children with new, chronic neurocognitive problems never referred before COVID-19, evaluated by the brain [18F]-fluorodeoxyglucose positron emission tomography/computed tomography ([18F-FDG PET/CT).

METHODS

Study Population

This study is part of a larger observational study of children younger than 18 years of age assessed in the out-patient pediatric post-Covid center of our institution, after a microbiologically confirmed diagnosis (based on SARS-CoV-2 detected on nasopharyngeal swab by real-time polymerase chain reaction) of SARS-CoV-2 infection. Therefore, we assess both children that fully recovered and those with persistent symptoms after the infection. Specifically, the following definition of long Covid (or PCC) is used in our center, according to a Delphi consensus: “Post-COVID-19 condition occurs in young people with a history of confirmed SARS CoV-2 infection, with 1 or more persisting symptoms for a minimum duration of 12 weeks after initial testing that cannot be explained by an alternative diagnosis. The symptoms have an impact on everyday functioning, may continue or develop after COVID-19 infection, and may fluctuate or relapse over time”.

As part of our protocol (available elsewhere, we propose brain [18F-FDG PET/CT imaging for children with neurocognitive signs or symptoms lasting for more than 3 months and which have a negative impact on their routine. The protocol is approved by the ethics committee of our Institution (ID 3078). Written informed consent was obtained from all participants or legal guardians.

Brain Imaging

Brain [18F-FDG PET/CT scans were carried out using the Biograph mCT64 PET/CT scanner (Siemens Healthineers) in a three-dimensional acquisition mode. Each patient fasted 6 hours before the radiotracer injection. FDG PET acquisition started 40 minutes after a slow intravenous bolus injection of [18F-FDG (3.7 MBq/kg), while the subject rested quietly in a dimly-lit and silent room. PET images were reconstructed using an iterative time of flight algorithm with CT-based attenuation correction as well as scatter and random corrections. All scans were acquired and reconstructed with the same technical parameters. After a visual analysis of patient images, a voxel-wise comparison using Statistical Parametric Mapping version 8 (SPM8, Wellcome Department of Cognitive Neurology, London, UK) was performed to identify regional [18F-FDG PET hypometabolism. SPM8 was also employed for the spatial normalization of the Montreal Neurological Institute (MNI) space and spatial smoothing with an 8mm Gaussian kernel. Patient images were compared with those of 19 healthy controls, selected from a previously gathered database. Statistical analysis was carried out through an unpaired
| TABLE 1. Main Clinical and Demographic Characteristics of the Three Evaluated Children |
|----------------------------------------------------|-------|-------|
| **Patient 1**                                      | **Patient 2** | **Patient 3** |
| Age                                                | 13    | 14    | 13    |
| Gender                                             | Female | Male  | Female |
| COVID-19 vaccination before infection              | Not vaccinated | Not vaccinated | Not vaccinated |
| Severity of acute disease                          | Mild   | Mild  | Mild  |
| Signs and symptoms                                 | Yes    | Yes   | Yes   |
| Fever                                              | Yes    | Yes   | Yes   |
| Days of fever                                      | 7      | 2     | 2     |
| Cough                                              | No     | No    | No    |
| Gastrointestinal                                   | No     | No    | No    |
| Headache                                           | Yes    | No    | No    |
| Anosmia                                            | No     | No    | Yes   |
| Dysgeusia                                          | No     | Yes   | Yes   |
| Memory problems                                    | No     | No    | No    |
| Concentration problems                             | No     | No    | No    |
| Fatigue                                            | Yes    | No    | No    |
| Pain (muscle/joints)                               | Yes    | No    | No    |
| Rash                                               | Yes    | No    | No    |
| Distance from acute infection (in days) at PET scan | 100   | 150   | 185   |
| Time from SARS-CoV-2 infection to onset of neurologic symptoms (weeks) | 0     | 4     | 6     |
| Persisting symptoms                                | Yes    | No    | No    |
| Memory Problems                                    | Yes    | No    | No    |
| Concentration problems                             | Yes    | No    | No    |
| Headache                                           | Yes    | No    | No    |
| Olfactory disfunction                              | Yes    | No*   | Yes†  |
| Fatigue                                            | Yes    | No    | No    |
| Pain (muscle/joints)                               | Yes    | No    | No    |
| Rash                                               | Yes    | No    | No    |
| Other                                              | Post Exertional Malaise | Dysgeusia | Dysgeusia† |

*Distortion of smell perception; feeling disgusting his sweat and smells of his best friends; feeling nauseated feeling sweat smell in the gym where he was used to attend since years; nauseated by the smell of his mother’s breath. All these issues limited his confidence in social relationships.

†Distortion of most smells. Complete loss of taste of several usual meals including chocolate, with negative impact on daily eating habits and indirect impact on family dynamics.

The voxel-wise analysis, using $P$ values of <0.001, showed lower $^{18}$F-FDG-PET uptake in the left frontal cortex compared to healthy controls (Figs. 1 and 2). In particular, a cluster of hypometabolic voxels was found in the left orbito-frontal region, with a peak at $-18/46/-4$ mm (179 voxels, T-Score 8.1).

DISCUSSION
In this study, we provided preliminary evidence of orbito-frontal cortex hypometabolism in a small group of children experiencing chronic neurological symptoms lasting for more...
than 3 months after SARS-CoV-2 infection. The metabolic pattern observed in our patients significantly differed from a cohort of the healthy, age-matched control group, as demonstrated by SPM analysis. These data are in line with more robust evidence from neuroradiological follow-up studies of adults assessed after COVID-19. Recent studies, in fact, have documented similar or even more significant changes in brain structure as demonstrated by a UK biobank study.²

Our findings are relevant for a number of reasons. So far, there has been debate about the real incidence of pediatric long Covid since studies have documented wide variability in the rate of children presenting with persisting symptoms and some authors have argued that some may suffer from psychological consequences of pandemic restrictions rather than a consequence of the viral infection.³ These uncertainties may limit access to diagnostics and care, and also lead to less funding for studying PCC in children. Therefore, objective data of organ involvement, as also previously described in children with abnormal lung perfusions,⁶ provides the scientific community with a new perspective about the real impact of PCC in children. Indeed, this may raise interest towards this condition, which in turn can stimulate funding, research, understanding and, ultimately, pediatric care. Importantly, further studies are needed to better understand which children suffer from neuroradiological defects and ongoing inflammation in an adolescent with post-acute sequelae of SARS-CoV-2 infection. Lancet Child Adolesc Health. 2021;5:677–680.

In conclusion, we provided evidence of orbitofrontal cortex hypometabolism in children with persistent neuropsychiatric symptoms after SARS-CoV-2 infection, highlighting the need to implement research and raising funds for children with long COVID.

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