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EDITORIAL

The "complete diagnosis in one day" could be the next goal: the neuro-COVID paradigm

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The incidence of neurological symptoms and neuropsychiatric disorders has increased over time, requiring finer and advanced tools to complement clinical neurological assessment and avoid more invasive bioptic procedures. This valuation is particularly evident following the ongoing COVID-19 pandemic sequelae that, when involving neurological symptoms in an acute phase (neuro-COVID-19) or in a chronic one (after 12 months since the infection—long neuro-COVID-19), encompasses for a wide and unspecific spectrum of manifestations. Indeed, it involves central nervous system (most frequently dizziness, headache, impaired consciousness, acute stroke), peripheral nervous system (most prominently anosmia, dysgeusia, Guillain–Barre syndrome, and Miller-Fisher syndrome), and skeletal muscle systems. Moreover, the mechanisms subtending the brain involvement in COVID-19 infection are still controversial, suggesting different pathways such as blood–brain barrier disruption secondary to viremia, hypoxic injury due to respiratory failure, retrograde trans-cribal route, cytokine storm syndrome, coagulopathy, and/or ACE2 receptors mediate injury.

Several neuroradiological findings have been associated to these manifestations, although data reports are extremely heterogeneous in terms of imaging modality, acquisition protocol, and sample size. Even for these reasons, clinical MR protocols have been proposed in order to address the standardization of the imaging in patients with neurological manifestations of COVID-19 [1]. Moreover, staging scores based on clinical and imaging findings have been suggested to better characterize and classify patients' status and to predict patients' prognosis.

Although it is now clear that an interdisciplinary team should be implemented for treating the wide plethora of symptoms exhibited by neuro-COVID-19 patients, few studies have investigated the role of advanced imaging sequences, e.g., diffusion tensor imaging [2] and of imaging complementarities during staging and follow-up of neuro-COVID patients [3].

Electrophysiology, and mainly electroencephalography (EEG), represents a well-established and widespread tool to support the diagnosis and monitoring of neurological diseases, thanks to an excellent temporal resolution and the possibility to achieve quantitative parameters. In contrast, computed tomography (CT) and especially magnetic resonance imaging (MRI) provide a highly accurate morphological view of the brain, adding new valuable info both in terms of structural and functional information (e.g., structural connectivity revealed by diffusion tensor imaging, functional connectivity achievable by functional MRI, metabolite concentrations revealed by MRI spectroscopy, and perfusion revealed by arterial spin labeling or post-contrast agent scans). Finally, nuclear medicine modalities, and in particular positron emission tomography (PET), have extremely pushed over the functional/molecular possibilities of diagnostic tools, thanks to the possibility to extract metabolic connectivity parameters and mainly to achieve highly specific insights with selective radiotracers. Recently, the possibility to simultaneously combine PET/MRI findings before [4], and EEG/fMRI signals after [5], has boosted brain modeling comprehension, overcoming the disadvantages of a single modality and improving patient compliance. In this direction, mathematical algorithms based on radiomics and artificial intelligence applications have increased the quantitative power of imaging tools, introducing new multifactorial and multidisciplinary classifier to better characterize neurological condition and to predict possible outcomes.

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Nevertheless, probably due to the emergency status requiring an immediate clinical answer, no studies have investigated neuro-COVID alterations with hybrid multimodal technologies, with very few studies reporting findings from advanced MR protocols and with a longitudinal experimental setup.

In a first study on six acute patients with severe COVID-19, images using diffusion tensor imaging, grey matter, and white matter alterations have been demonstrated also in radiological apparently normal brain at conventional MRI, demonstrating a diagnostic role for advanced techniques in neuro-COVID [2].

In a recent study on twenty-six patients with neuro-COVID-19 studied with [18F]FDG-PET, an interesting time-dependent recovery of brain hypometabolism has been demonstrated and correlated with cognitive dysfunction, low blood saturation, and high inflammatory status [6]. Martini et al. paper represents the first longitudinal approach to neuro-COVID-19 spectrum, describing brain metabolism from an acute symptomatic phase to a chronic one with a complete *restitutio ad integrum*. This kind of approach is very useful to understand the neuro-matrix substrate of this unpleasant and unspecific syndrome that it is deeply affecting quality of life, mainly exploring in the same patient the causality relationship between brain alteration and behavior.

While structural alterations have been described to justify specific signs, such as olfactory nerve atrophy in anosmia patients, the correlation between brain structure and function [4], and again brain function and behavior, is less immediate and, mainly, trickier and more complex. The unconclusive literature on brain diaschisis phenomena is only an example about how many ways remain up to now unpaved. Moreover, the inconsistency of inclusion criteria among cross-sectional studies and the lack of standardized longitudinal setup don't allow to discriminate between different progression stages of neuro-COVID-19 symptoms ranging from an acute to a chronic phase, not always restorative.

In this scenario, several issues remain opened, and it is only possible to speculate if bringing together structural, electrophysiological, pathophysiological, and metabolic data, integrated with a rigorous approach based on radiomics and AI; it is possible to have a more complete and informative brain view.

Further studies with a multimodal approach are needed to investigate the impact of hybrid technologies on both neurological manifestation characterization and outcome prediction. Technological improvements are now ready but unexploited. The road is long and the answer needs confirmation from multicenter studies, regarding the acquisition and evaluation of data that need significant statistical weight. However, the best framework appears to be an integration between methods and the creation of extensive networks to acquire homogeneous and standardized data.

Do we have already the instruments to reach this unbelievable goal, i.e., to make a "complete diagnosis in one day"? At present, the answer is certainly negative. Nevertheless, we have information that the pathophysiological basis of each phase of the disease is dependent on different mechanisms, including issues such as blood–brain barrier permeability, blood flow, blood volume, hypoxia, metabolism, hematocrit, diaschisis, and connectivity. We could extract more specific information from each neuroimaging techniques and procedures, integrated with clinical and other neurophysiological data.

As reported above, a complete diagnosis in one day is a very difficult challenge, due to the multiple mechanisms involved. Nevertheless, we also think that the diagnostic tools, necessary to achieve this goal, are already available.

Thus, it is a very hard path, but with very important objectives: to have an earlier final diagnosis, a better prognostic stratification, a finer differential diagnosis, also in terms of acuity and disease activity, and/or a more precise morpho-functional characterization as a basis for customized therapies. In this direction, we are ready to fight.

Declarations

Consent to participate This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare no competing interests.

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