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CLINICAL INERTIA IN THE MANAGEMENT OF PATIENTS WITH POST-COVID 19 NEUROLOGICAL SYNDROME: A PROBLEM WITHOUT CURRENT EVIDENCE

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Clinical inertia is defined as the failure to escalate the goal in the management of a disease, and becomes an ambiguous scenario for decision making by a physician and a medical multidisciplinary team[1]. This means that treatment is not initiated or intensified in patients who need it. The absence of evidence is a factor that substantially influences the physician's insecurity in establishing a therapeutic regimen or following an algorithm to make a decision, and facilitates falling into clinical inertia[1]. Accuracy in the management of neurological diseases is crucial in the outcome and prognosis in the short- and medium-term, due to the fact that neural tissue is difficult to recover. Therefore, clinical inertia in neurology is a delicate issue that deserves to be kept in mind and discussed from the perspective of evidence-based medicine, evidence-based practice, and the dynamics of quality health care [2]. Post-COVID 19 neurological syndrome is a condition that has not been studied sufficiently to establish recommendations based on the highest level of evidence until now [2]. In addition, as time goes by, new clinical phenotypes are being described [3].

This syndrome is defined as the appearance or persistence of neurological signs or symptoms after the acute phase of COVID-19 (with some cut-off scores being considered as from 21 days after the appearance of the symptoms of the acute phase of the disease, and up to 6 months after the resolution of the disease), which decrease the functional capacity and affect the quality of life of the individual [4]. This pathological condition, justified on the basis of some cellular, molecular, immune-mediated and epigenetic mechanisms [5], facilitates the appearance of an unspecific neurological syndrome and can trigger major complications, such as neurovascular disorders, neurometabolic disorders, status epilepticus, Guillain Barre syndrome, encephalitis, neuropsychiatric disorders, among others [2,6]. It has been indicated that approximately 30% of patients with COVID-19 develop post-COVID-19 neurological syndrome with a diversity of symptoms affecting the integrity and quality of life of those affected Table 1 [6].

Table 1. Summary of the prevalence of neurological manifestations during the post-COVID 19 neurological syndrome [4,6].

Symptom	Prevalence	
	3 – 6 months	≥ 6 months
Anosmia	10%	10% - 12%
Anxiety	20% – 22%	< 40%
Brain Fog	< 30%	40%
Cognitive Dysfunction	55%	60%
Depression	< 10%	25%
Dysgeusia	< 10%	< 10%
Fatigue	30%	< 50%
Headache	< 10%	22% – 23%
Hypersomnia	3.6%	-
Insomnia	< 20%	32% – 35%
Memory Issues	< 30%	30%
Myalgia	< 20%	20%
Nightmare	< 1%	-

So far, the pathophysiology of post-COVID 19 neurological syndrome is associated with the invasion of SARS-CoV 2 in the central nervous system, triggered by the presence of co-receptors in common between the virus and the nervous tissue (neurons, astrocytes, oligodendrocytes and microglia), such as angiotensin-converting enzyme II (ACE2) and neuropilin-1 (NRP-1) [5]. The distribution of ACE2 at the level of the cerebral cortex, several nuclei, brain gyri, medulla, and brain stem, would explain the selective neurotropism of this viral agent and the ability to induce neuroinflammation in multiple regions of the central nervous system simultaneously, which manifests itself with the unspecific neurological syndrome [5,6]. Amongst the different pathways previously indicated, the NRP-1 in the olfactory cells is one of the strongest ways in which the virus attacks the nervous system. This is especially due to the fact, as previously described, that there is an interaction between blocking the vascular endothelial growth factor-A (VEGF-A)/NRP-1 signaling pathway, reducing pain perception (manifesting in the asymptomatic contagious phenotype or in the first phase of acute disease, and inducing anosmia. Subsequently, activation of signaling cascades for the expression of proinflammatory proteins such as interleukin-6 (IL-6), IL-12, IL-15, hypoxia-inducible factor 1-alpha (HIF-1α) and tumor necrosis factor alpha (TNF-α), causing T cell dysfunction, altered adaptive autoimmunity, microglia activation, hypoxia, microvascular thrombosis, altering cerebral perfusion pressure and silent cerebral edema. Such factors perpetuate the injury [5]. This, together with comorbidities, extracranial target organ damage, pharmacological interaction and epigenetic factors, generate infectious toxic encephalopathy and persistent neuroinflammation with long-term cellular damage [5-7]. The outcome and prognosis of these patients will depend on the magnitude of the multiorganic involvement during the acute phase of the disease, prolonged hospital stay or events not evaluated long after hospital discharge, so it is difficult to define what will be the course of the disease, especially in those with a history of neurological diseases.

Yong SJ [7] synthesized evidence demonstrating the presence of SARS-CoV 2 in the brain stem in autopsies performed in deceased patients with neurological manifestations, positing that multiple, specific and persistent involvement over time of some nuclei at the level of the brain stem (what Yong SJ calls low-grade dysfunction of the stem in long COVID) [7] such as the nucleus solitarius tractus, raphe nuclei, substantia nigra, reticular activating system, ventral tegmental area, dorsal motor nucleus of the vagus, among others; plausibly explain the occurrence of neuropsychiatric symptoms such as anxiety, depression, cognitive impairment, brain fog, insomnia, headache, ageusia and functional gastrointestinal disorder. At the level of the bulb and pons, the involvement of the parabrachial nucleus, Kölliker-Fuse nucleus, Pre-Botzinger complex, and Botzinger complex, could even explain the presence of the tachycardic phenotype of post-COVID 19 cardiovascular syndrome, dyspnea and palpitations, in the absence of evidence of cardiac or pulmonary injury to explain such manifestations [7]. In these terms, the lack of diagnostic tools allowing a panoramic evaluation of the nervous system's integrity would confuse the treating physician, redirecting the therapeutic management to another organ.

Unfortunately, there are also no drugs with solid evidence aimed at controlling neuroinflammation or neuroimmune modulation. This would immediately direct to the error of clinical inertia in the management of post-COVID 19 neurological syndrome. Studies that have described the manifestations and severity of this syndrome have found that headache, fatigue, brain fog, memory problems, attention disorders, and sleep disturbance are the most frequent neurological and psychiatric symptoms, considerably affecting quality of life [6,8]. The vast majority of these studies consist of case series, small samples, and those with a higher level of evidence (cohort studies), on average follow up for 6 months [6,8]. However, almost all authors conclude that patients with post-COVID 19 neurological syndrome have high levels of neuroticism.

Due to the complexity of the pathophysiology of neuroinvasion and the role that the central nervous system plays in maintaining the functional capacity and quality of life of the human being [9], it is imperative to develop preventive, diagnostic and therapeutic interventions, as well as strategies for the identification of risk factors, to control the potential burden of disease that this syndrome will generate in the coming years. The real gap in the current evidence that predisposes to clinical inertia is found in the general management guidelines for post-COVID 19 syndrome [9,10], which focus on the standard approach to central and peripheral nervous system complications, based on expert recommendations or low-quality evidence. This results in inadequate management of the patient with post-COVID 19 neurological syndrome, and patients who need it are not treated more aggressively, compromising their functional and global neurological prognosis.

In conclusion, there is still a large gap in the evidence on post-COVID 19 neurological symptoms, which may facilitate the existence of clinical inertia in these patients. It is necessary to develop studies aimed at answering the questions that hinder an accurate and quality approach to those affected with this condition.

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