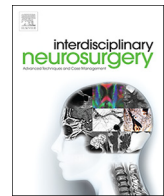




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Review Article

Evaluating the evidence for direct central nervous system invasion in patients infected with the nCOVID-19 virus

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ABSTRACT

The current nCOVID-19 pandemic is raising several questions in the approximately 25% of patients who present with neurological symptoms. While secondary brain injury from the systemic manifestations of the disease account for the majority of non-specific neurological symptoms that include headache, nausea, and progressive confusion, the question that remains unanswered is does the nCOVID-19 virus use the olfactory mucosa as a portal to directly invade the brain? A second question is how common does direct CNS invasion complicate the classical cardiorespiratory severe form of the disease? We know from previous studies that almost all members of the Corona virus family have neurotropism. We also know from the current pandemic that deteriorating consciousness and cerebrovascular accidents are not uncommon. Several previous scattered case reports, and post-mortem examinations of brain tissue, demonstrated nCOVID-19 nucleic acid in the CSF, and brain tissue, of infected and deceased individuals. We performed a PubMed review of the literature to specifically assess the evidence for the direct CNS invasion by the nCOVID-19 virus. This phenomenon would explain the cerebral oedema and encephalitis, that does occur, and bring Neurosurgeons into the management of these patients by for example directed intra-cranial pressure management post insertion of an intra-cranial pressure monitor. Unfortunately, the answers to these questions were not definitively answered by the research reviewed. While suggestive that direct CNS invasion does occur, the exact scale and manifestations of the problem remains, to date, essentially unknown.

1. Introduction

There is no doubt that the primary site of involvement, in patients infected with the nCOVID-19 virus, is pulmonary. One of the first papers comes from Zhonghan Hospital in Wuhan, China, where after retrospectively considering 138 in-hospital patients infected with the virus, concluded fever, dry cough, dyspnoea, myalgia, and fatigue to be the most common presenting symptoms. On chest X-ray imaging all 138 patients demonstrated bilateral patchy shadowing and ground glass infiltrates. From this initial presentation 36/138 (26%) needed treatment in the Intensive Care Unit and the reasons were again largely cardiorespiratory with Type-1 respiratory failure predominating. Besides headache being reported as a minor symptom, this paper does little to support any neurological involvement in the 138 subjects considered [1]. Another review article considered 29 papers on nCOVID-19 and, while giving a convincing argument for and against the controversy about the origin and spread of the virus from Huanan seafood and animal market in Wuhan, focusses almost entirely on the respiratory component of the disease and fails to include any of the neurological characteristics of infection [2].

Despite the research focus in the majority of papers, on the severe respiratory evolution of the disease into a secondary cytokine storm, acute respiratory distress syndrome, and multi-organ dysfunction

syndrome, several papers are now beginning to identify neurological involvement in nCOVID-19 infection. One case report from the United States reports an elderly female patient who presented in an encephalopathic state secondary to respiratory nCOVID-19 infection. While documenting neurological involvement in this patient, the CT brain and lumbar puncture that were performed, identified only a pre-existing porencephalic cyst from a previous stroke and normal cerebrospinal fluid chemistry. The authors concluded that nCOVID-19 does not cross the blood brain barrier and that neurological involvement is almost entirely a secondary injury [3]. Another paper reports neurological involvement in nCOVID-19 infection to be relatively common. In this paper impaired consciousness was noted to occur in 15% of patients, and acute stroke to occur in 6% of patients [4].

But is neurological involvement in nCOVID-19 infection limited only to secondary brain injury from the systemic manifestations of the disease? We sought to review the literature regarding evidence, for or against, the existence of primary CNS infection by the nCOVID-19 virus. The aim of this review was to firstly identify the existence of a primary neurological form of nCOVID-19 secondary to direct infection, and secondly to expand the precise nature of both how the virus accesses the central nervous system, as well as the spectrum of involvement.

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Table 1
Levels of evidence.

I	Large randomized clinical control trials with clear cut results or systematic review of these articles
II	Small randomized clinical control trials with unclear results or systematic reviews of these articles
III	Prospective cohort and case-control studies or systematic reviews of these articles
IV	Historical cohort or case-control studies of systematic reviews of these articles
V	Case series, studies with no controls or Expert opinion

(Adapted from: Sackett DL. *Rules of evidence and clinical recommendations on the use of antithrombotic agents*. Chest 1989; 95:2S–4S).

2. Materials and methods

We conducted a PubMed search using keywords “Neurological COVID-19 infection”; “Neurosurgery COVID-19 infection”; “Clinical COVID-19 infection”; “Brain COVID-19 infection”; “Central nervous system COVID-19 infection”. The selection of articles included was subjective based on the discretion of the researchers however favoured articles which specifically concerned neurological/neurosurgical considerations and especially those that dealt with the subject of direct CNS invasion by the nCOVID-19 virus. A paucity of articles specifically considering neurological involvement, and direct invasion of the CNS by nCOVID-19, was noted.

In total 19 articles were selected for inclusion in the review and below are the Study design and Level of evidence for each (Tables 1 and 2).

3. Results

One paper retrospectively reviewed the charts of 214 hospitalized nCOVID-19 infected patients admitted at Union Hospital in Wuhan, China. In this paper the authors compartmentalized the neurological manifestations into 3-categories namely 1. Central nervous system symptoms which included headache, dizziness, disturbance of consciousness, ataxia, and seizures, 2. Peripheral nervous system symptoms namely hyposmia, hypogeusia, hypopsia, and neuralgia, and 3. Symptoms related to skeletal musculature. In total 78/214 (36.4%) subjects had neurological symptoms. What the authors noted was firstly a clustering of neurological symptoms in patients with severe, rather than mild, infections. Comparing the manifestations of these neurological symptoms these included acute cerebrovascular accidents in 5.7% of subjects with severe infection compared to a 0.8% incidence in subjects with mild infection. Impaired consciousness manifested in

Table 2
Studies used for this review article by Study type and Level of evidence.

Wang D et al. (2020)	Retrospective cohort	IV
Nourah S et al. (2020)	Historical systematic review	IV
Filatov A et al. (2020)	Case report	V
Mao L et al. (2020)	Retrospective cohort	IV
Glass WG et al. (2004)	Prospective cohort animal study	V
Li WC et al. (2012)	Prospective cohort animal study	V
Li K et al. (2016)	Prospective cohort animal study	V
Talbot PJ et al. (1993)	Prospective laboratory study	III
Dube M et al. (2018)	Prospective laboratory study	III
Zhou X et al. (2017)	Prospective laboratory study	III
Li YC et al. (2020)	Historical systematic review	IV
Huang C et al. (2020)	Retrospective cohort	IV
Bohmwald K et al. (2018)	Historical systematic review	IV
Hopkins C. (2020)	Expert opinion	V
Desforjes M et al. (2020)	Historical systematic review	IV
Ali A et al. (2020)	Historical systematic review	IV
Lau KK. et al (2004)	Case report	V
Xu J. et al. (2005)	Prospective laboratory study	III
Jin H et al (2020)	Expert opinion	V
Reichard, RR. et al. (2020)	Case report	V
Baig AM. et al. (2020)	Historical systematic review	IV
Moriguchi T. et al. (2020)	Case report	V
Poyiadji N. et al. (2020)	Case report	V

14.8% of subjects with severe infections, as opposed to a 2.4% incidence in subjects with mild infections. The authors concluded not only the high prevalence of neurological involvement, in nCOVID-19 infection, but noted the specific manifestations of this involvement to include cerebrovascular accidents and impaired consciousness [4]. This study only provides evidence for secondary brain injury and does not specifically address the primary concern of this review, namely direct central nervous system infection by the nCOVID-19 virus.

One virology paper, that specifically addresses the neuro-invasive potential of the nCOVID-19 virus, notes that almost all members of the COVID virus family have neuro-invasive ability. The list of COVID viruses that have proven neuro-invasive potential includes the SARS-CoV virus, MERS-CoV virus, HCoV-229E virus, HCoV-OC43 virus, mouse hepatitis virus, and the porcine hemagglutinating encephalomyelitis coronavirus (HEV) [5–10]. The authors of this virology paper note that the high genomic similarity between these proven neuro-invasive viruses and the nCOVID-19 virus makes it highly likely, yet unproven, that the nCOVID-19 virus does directly invade the CNS [11]. Indirect evidence provided by another paper is that regarding symptomatology 8% of patients present with headaches, and 1% of patients present with nausea and vomiting [12]. Another paper also notes that the neuro-invasive ability of the corona virus family has been factually demonstrated in humans. The route of invasion is through the olfactory bulb where it causes inflammatory demyelination [13]. A clinical link to the current nCOVID-19 pandemic is provided in another paper that documents anosmia without congestion, differentiating it from other viral respiratory tract infections characterized by anosmia with congestion, as a common early feature of nCOVID-19 infection [14]. The neurological manifestations thereafter are reported in several papers to include convulsions, deterioration in consciousness, and encephalitis [13,15]. Another meta-analysis failed to find evidence of direct CNS invasion by the nCOVID-19 virus due to no study demonstrating definitive PCR evidence of viral genetic matter in the CSF of infected individuals. While the same paper does acknowledge that neurological symptoms occur in up to 25% of patients infected with nCOVID-19, the authors note that this can be largely explained as secondary brain injury from systemic involvement [16].

Several definitive papers, providing conclusive evidence on the subject under review, have been published. One demonstrated nCOVID-19 nucleic acid on reverse transcriptase PCR in the cerebrospinal fluid of an infected patient [17], and another definitively documented nCOVID-19 viral particles in the brain tissue of deceased patients on most-mortem examination [18]. Another paper, where a post-mortem was conducted on a patient who died of nCOVID-19 complications, confirmed haemorrhagic white matter lesions scattered throughout both cerebral hemispheres. On histopathological analysis the sub-cortical white matter demonstrated macrocytic clustering, axonal swelling, axonal retraction balls, and a perivascular encephalomeningitis [19]. Another paper notes the clinical implications of these studies by noting that in patients who present with neurological symptoms an MRI brain should be performed. The same paper notes that a lumbar puncture should also be performed to specifically evaluate the CSF for nCOVID-19 nucleic acid by PCR [20]. Another paper adds hematogenous dissemination as a plausible route of entry by which the nCOVID-19 virus enters the central nervous system. In this

paper the slower flow of blood in the cerebral circulation is proposed to allow the virus time to damage the capillary endothelium and thereby gain access. The same paper also notes a possible retrograde peripheral neuronal mechanism where, post gaining access to axon terminals in the lungs, the virus uses the neuronal physiology of active transport, synaptic terminal functioning, and retrograde axonal transport, to ultimately access the neuronal cell body [21].

Another paper reports a case of acute necrotizing encephalopathy, in a patient with confirmed nCOVID-19 infection, whose cerebrospinal fluid tested negative for bacteria and other viral pathogens. While highly suggestive, the fact that this patient's cerebrospinal fluid was not tested for nCOVID-19 directly, makes definitive causation inconclusive [22]. Another case report describes a patient who presented with features of meningitis, with no respiratory symptoms, and was subsequently diagnosed with nCOVID-19 infection by nasopharyngeal culture. Unfortunately, in this case, while cerebrospinal fluid was sampled, a traumatic tap limited its use. An MRI was however performed which confirmed haemorrhagic lesions in the thalamii, medial temporal regions, and sub-insular regions bilaterally [23].

4. Conclusion

While indirect evidence suggesting direct CNS infection by the nCOVID-19 virus is definitive, to date no large studies have been performed to prove or disprove the percentage incidence in the current pandemic. Assumptions from the neurotropism of the corona virus family make the possibility of direct CNS invasion likely, as do the findings of several case reports and post-mortem studies mentioned. The authors recommend further attention be given to this very real concern that needs a properly conducted trial to be definitively known.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.inat.2020.100829>.

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