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Neurological infections in 2020: COVID-19 takes centre stage

Although there have been many contributions to advance our understanding of neurological infections in 2020, the year has been dominated by research focused on the neurological consequences of COVID-19. Multidisciplinary studies are ongoing to better differentiate the direct effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) versus its secondary effects (PMC7184392, NCT04386083, and CTRI/2020/07/026339). Nevertheless, it has become clear that there is a striking incidence of neurological involvement in this disease, the symptoms of which span reversible anosmia, stroke-related disability, and death.[1–3]

Dry cough, fever, dyspnoea, nausea, emesis, and fatigue are common symptoms of SARS-CoV-2 infection[1]—a profile shared with numerous viral infections. However, anosmia and ageusia, which have now been documented in ample research,[1,2,4] are symptoms more distinctive of SARS-CoV-2 infection than other common viral infections, and the implications of these symptoms drive our understanding of the unique pathophysiology of COVID-19. In one of the largest studies to date, 3191 individuals infected with SARS-CoV-2 were surveyed to assess the prevalence of anosmia and ageusia. 488 (15·3%) individuals were found to have one or both of these symptoms; in most cases, taste and smell were fully recovered 7 days after onset on average.[1] Smaller studies have shown anosmia to be much more prevalent and the heralding symptom of SARS-CoV-2 infection,[5] therein identifying a potential source of viral replication and CNS invasion.

Subsequently, hypotheses emerged regarding the potential for viral neurotropism and a direct route of entry into the CNS from the olfactory bulbs. In an imaging study[6] of 23 patients with confirmed SARS-CoV-2 infection with clinical anosmia, SARS-CoV-2-related olfactory dysfunction was differentiated from other viral olfactory dysfunction in several crucial ways. Post-viral anosmia in the setting of upper respiratory tract infections is usually related to mucosal congestion and nasal obstruction, resulting in a conductive olfactory loss; however, few patients with SARS-CoV-2-related anosmia had sinonasal symptoms, suggesting that mucosal congestion is an unlikely aetiology for anosmia in these cases.[6] Olfactory epithelium support-cells residing in the olfactory cleft express the angiotensin-converting enzyme 2 receptor, identified as the binding antigen for SARS-CoV-2.[6] Imaging of the olfactory cleft showed olfactory cleft opacification in 17 (74%) of cases.[6] Moving proximally, olfactory nerve filia clumping, suggestive of inflammation, was observed in eight (35%) of patients, and olfactory bulb signal abnormalities, indicating degeneration or microhaemorrhage, were seen in 21 (91%) individuals. Within the CNS, hyperintense T2 or fluid-attenuated inversion recovery signals in the olfactory cortex were found in five (22%) individuals.

An association has been shown between SARS-CoV-2 infection and acute inflammatory demyelinating polyradiculoneuropathy (AIDP),[7] extending the viral pathogenic effects to the peripheral nervous system. In a case series of five individuals with AIDP and SARS-CoV-2 infection, the latency between respiratory symptom and neurological symptom onset was 14–30 days.[7] Most patients presented with the classical findings of AIDP, with ascending paraparesis and hyporeflexia, conduction blocks and increased latency on nerve conduction studies, and albuminocytological dissociation in the

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CSF.[7] However, uniquely to SARS-CoV-2-associated AIDP, patients also showed elevated systemic or CSF levels of IL-6 and IL-8, implicating an overactive inflammatory response in the pathogenesis of AIDP in these patients.

Stroke has been identified as an independent risk factor for death in individuals with SARS-CoV-2 infection.[2] Although it remains unclear whether the incidence of stroke in people with SARS-CoV-2 infection is higher than in those with other severe viral illnesses, SARS-CoV-2-related neurovascular complications appear to have a unique mechanism also tied to inflammation. Neuroimaging has revealed multivascular infarcts in the absence of common cardioembolic mechanisms.[2] Microbleeds are concurrently seen, indicating potential small vessel involvement. Furthermore, vessel wall sequence MRI revealed contrast enhancement of the medium and large arterial vessel walls in these patients.[2] This finding, coupled with the absence of CSF inflammatory markers and SARS-CoV-2-specific IgG antibodies, further supports the hypothesis for a systemic rather than CNS-specific inflammatory response contributing to a hypercoagulable state and endothelial cell dysfunction.[2] An autopsy of one individual additionally showed systemic endotheliitis.[2]

Brain autopsy studies[8] have described pathological changes that have been attributed to the direct effects of SARS-CoV-2 infection in the brain; however, these studies lacked controls. An exception was a brain autopsy study[8] of seven patients with SARS-CoV-2 infection comparing the findings with 13 control patients, defined as SARS-CoV-2-negative patients who died of sepsis or died suddenly without a systemic inflammatory response. The most common brain autopsy findings in patients with SARS-CoV-2 infections are also commonly seen in patients who die of other severe illnesses.[9] Therefore, neuropathological changes such as reactive gliosis, mild chronic perivascular inflammatory infiltrates, and acute hypoxic–ischaemic injury in patients with SARS-CoV-2 infections probably reflect critical illness-related, non-specific changes rather than specific abnormalities induced by the virus.

Through the efforts of researchers worldwide, we have gained foundational insights into the pathophysiology of COVID-19. Indeed, the virus has proven to be of its own kind, displaying a spectrum of potential pathogenetic mechanisms including delayed parainfectious demyelinating and axonal injury, viral invasion, hyperactive inflammatory response, and endothelial dysfunction. With neurological consequences spanning the entire neuroaxis, the importance of continued research efforts to combat this public health crisis cannot be overstated.

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