Early evidence of pronounced brain involvement in fatal COVID-19 outcomes

The first cases of COVID-19 in Germany were confirmed in the greater Munich area and isolated in our hospital. Subsequently, more than 690 patients were admitted for inpatient care, 103 of whom were transferred to the intensive care unit (ICU). 63 patients died in hospital. 587 patients recovered and were discharged.

Older patients with comorbidities are considered most at risk of death; however, there are reports of rapid decline and subsequent death in younger patients with no known comorbidities. Pulmonary and heart failure are considered the primary causes of COVID-19-associated death, but the precise pathology of disease progression is unknown. Moreover, recent reports describe irregularities in coagulation for a subset of patients.[1]

Here we report the findings of autopsies of six patients (four men and two women, aged 58–82 years) who died from COVID-19 in April, 2020.

Clinical and pathological findings are summarised in the appendix. The period from onset of symptoms to admission spanned 2–10 days. Five patients were transferred to the ICU within the first 2 days of hospital admission. All patients eventually required ventilation or extracorporeal membrane oxygenation.

The cause of death in the older patients (>65 years), all of whom were admitted with multiple comorbidities, was cardiorespiratory failure. By contrast, all patients younger than 65 years died either of massive intracranial haemorrhage or pulmonary embolism, consistent with COVID-19-associated coagulopathy.[2] These patients exhibited a diffuse petechial haemorrhage in the entire brain. However, both groups showed lymphocytic panencephalitis and meningitis. Our histopathological findings are shown in the appendix. Although entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into the CNS via endothelial cells has been documented with electron microscopy,[3] we observed no conspicuous endotheliitis.

Abundant experimental and animal model evidence of a neurogenic pathway for SARS CoV-2 via olfactory (CN I), trigeminal nerves (CN V), and the brainstem nuclei led us to look for evidence of localised brainstem alterations.[4] In all brains examined, we observed localised perivascular and interstitial encephalitis with neuronal cell loss and axon degeneration in the dorsal motor nuclei of the vagus nerve, CN V, nucleus tractus solitarii, dorsal raphe nuclei, and fasciculus longitudinalis medialis, but no territorial infarctions (appendix).

We do not attribute these findings to the clinically relevant COVID-19-associated severe hypoxia because morphological alterations of brain areas especially prone to hypoxia were consistent with those commonly observed in autopsied brains. Hypoxic alterations of brains in patients with COVID-19 are listed in the appendix.

Whether the observed lesions were a direct consequence of virus infiltration or resulted from an immune response could not be established definitively in this autopsy study and requires further investigations.

All patients had severe viral pneumonia, with a simultaneous heterogeneous occurrence of different disease stages, independent of the duration of the disease or ventilation time. The most prominent changes were those of a diffuse alveolar damage with virus-induced epithelial changes, capillaritis, and organising pneumonia without interstitial collagen deposition.[3,5,6] Intranuclear inclusion bodies were not observed. It is noteworthy that no cellular damage or angiitis were observed in the heart of any patient.

In summary, in addition to viral pneumonia, a pronounced CNS involvement with pan-encephalitis, meningitis, and brainstem neuronal cell damage were key events in all our cases. In patients younger than 65 years, CNS haemorrhage was a fatal complication of COVID-19.

We declare no competing interests.

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See Online for appendix