The path to resilience and recovery: understanding the epidemiology, neuropathology and treatment of neurologic injury due to the SARS-CoV-2 virus in children

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The lessons from previous coronaviruses outbreaks are sobering reminders of the spectrum of medical and psychiatric morbidity infections on a large scale may cause. Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) in 2002 and 2012, respectively, resulted in a high prevalence of spectrum of psychiatric symptoms in adults and children after hospital discharge. In a meta-analysis of 72 studies, the follow-up interval ranged from 60 days to up to 12 years [1]. During this long postillness phase, the point prevalence of depression was 14.9% and posttraumatic stress disorder 32.2%.

As the neurologic sequelae of paediatric SARS-CoV-2 become clear, the need to identify and treat children at risk for these neurologic and psychiatric complications becomes more urgent. These initiatives cannot rely on an understanding only of the neurobiology of SARS-CoV-2 related neurologic injury. There are a number of reasons for this. First, that information does not yet exist at a level of detail that would allow targeted therapies to be designed. Second, it is not clear which of the mechanisms of neurologic injury due to SARS-CoV-2 are responsible for these sequelae. Third, the heterogeneity of neurologic complications involving the central and peripheral nervous system would make clinical trials unwieldy.

The reviews in this series focus on neurologic manifestations, mechanisms of injury and sequelae of SARS-CoV-2, but these infections occur in the context of huge social upheavals, disrupting access to care and the social networks, which support families. For children in particular, the medical complications of SARS-CoV-2 need to be considered in the context of the social stressors and associated emotional toll caused by the pandemic. Alcamo and colleagues highlight the impact of the SARS-CoV-2 pandemic on overall child health. The increase in child mortality, for example, during the pandemic is due not to the direct effects of SARS-CoV-2, but to its disruption of healthcare systems.

The confluence of medical and social factors SARS-CoV-2 affecting morbidity and outcome informs the review of the worldwide epidemiology of Neuro-COVID by Alcamo and colleagues. Children account for 14.2% of all reported cases in the USA, but (for children under 14 years of age) 2.5% of cases worldwide. This discrepancy highlights the differences in access to testing ability to report cases in different regions. Although more data are being accrued about every aspect of SARS-CoV-2, it is important to note that the current understanding of neurological complications and outcomes in children following SARS-CoV-2 is taken from case series. The achievements of the many organizations involved in clinical research of SARS-CoV-2 are considerable, but, as Alcamo and colleagues argue, understanding the spectrum of neurologic morbidities and differences in new strains of SARS-CoV-2 and adapting with new treatments will require an integrated, global paediatric research platform.

The urgency of the need to define common data elements and definitions for neurologic manifestations of paediatric SARS-CoV-2 extends beyond the requirements of the response to the current pandemic. Alcamo and colleagues summarize the current literature reporting a range of neurologic manifestations ranging from encephalopathy and seizures to headaches, stroke or Guillain-Barre syndrome (GBS) in children with SARS-CoV-2 or

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Curr Opin Pediatr 2021, 33:576–579

DOI:10.1097/MOP.0000000000001079

multisystem inflammatory syndrome in children (MIS-C). But without common definitions of some of these symptoms such as encephalopathy, the true prevalence cannot be known with certainty. In addition, the emergence of Post-Acute Covid Syndrome (PACS), reported in up to 58% of children, means that the data definitions and research infrastructure must be established to support long-term follow-up of this population of survivors. This approach, as this group argues, is also essential to prepare for the next pandemic.

Understanding the variations in neurologic disease phenotype associated with SARS-CoV-2 will be essential for the development of specific neurologic therapies and predicting and preventing long-term morbidity. To achieve this goal, elucidation of the pathophysiology of SARS-CoV2 and its various strains is essential. In their review of the neuropathogenesis of SARS-CoV2 infection, Patel and Bearden summarize the current data on the mechanism of neuroinvasion by the virus. SARS-CoV2 binds to angiotensin-converting enzyme 2 (ACE2) receptors and transmembrane serine protease 2 (TMPRSS2) receptors on cellular surfaces and within the cytoplasm. These receptors are widely distributed in the central nervous system (CNS) with the cell type and region varying depending on the method used for analysis.

The mechanisms by which the virus causes injury and the cell types vulnerable to that injury are coming into focus. The current data suggest that the injury produced by the virus is indirect and mediated by the immune response to SARS-CoV2 infection, not by the virus itself. Animal models suggest that the virus gains access to the CNS via endothelial cells in the olfactory mucosa. However, human autopsy data identify more systemic endothelial dysfunction in multiple organ systems, consistent with the hyperinflammatory and hypercoaguable state seen in some patients with SARS-CoV2 infection. Human data show that in some patients, viral activation of endothelial ACE2 receptors results in astrocyte and microglial-mediated disruption of the blood–brain barrier, enabling viral translocation into the CNS.

Paediatric data from autopsy series are lacking and there are overall gaps in understanding of the developmental changes in the vulnerability of endothelium, glia and the blood–brain barrier to SARS-CoV2 infection. Autopsy series of SARS-CoV-2 are largely from adults and are confounded by the combined effects of systemic effects of mechanical ventilation or extracorporeal membrane oxygenation and SARS-CoV-2. Collectively, these studies have identified astrocyte and microglial activation in the CNS, but this is most likely the sequelae of ischemic injury and not viral infection of the brain parenchyma.

The interaction of SARS-CoV-2 with cell barriers is particularly salient for understanding the risks of this infection to the foetus. As summarized by Patel and Bearden, the data on foetal transmission are limited but suggest that complications during pregnancy are due to maternal illness produced by SARS-CoV-2 rather a direct effect of the virus. Overall, vertical transmission from mother to foetus appears very rare, but we are early in our understanding of these risks, and little is known as yet about the long-term neurodevelopmental outcomes of infants exposed to SARS-CoV-2 *in utero*.

The objective of better phenotyping both of SARS-CoV-2 neurologic complications and the mechanisms of these injuries is to predict and effectively treat them. Simon and Schober focus on approaches to treatment in their review of this literature. Although the case fatality rate for oSARS-CoV-2 infection in children is lower in comparison to adults, children now account for over 20% of new reported cases.

The impact of acute and long-term neurologic morbidity is not yet clear, but one-third of children hospitalized with SARS-CoV-2 are critically ill and approximately one-fifth of hospitalized children have neurologic symptoms. Importantly, the neurologic symptoms reported are subject to the caveats raised by Alcamo and colleagues regarding variable data definitions and potential of bias towards data collection in more resource-rich regions. Indeed, the importance of a common data structure is exemplified by the finding that severe encephalopathy (a term with broad and variable definitions) is the most common neurologic finding in critically ill children. With this caveat, the occurrence of neurologic disease is associated with high mortality. Children with preexisting neurologic disorders are vulnerable to neurologic complications of SARS-CoV-2.

The diversity of neurologic complications, including stroke, acute disseminated encephalomyelitis, fulminant cerebral oedema, status epilepticus, myelitis, headache, anosmia, encephalopathy or GBS means that no single approach to neuroprotection is feasible. Simon and Schober emphasize the importance of neuroimaging and electroencephalogram (EEG) and treatment with supportive care using immunomodulation depending on the nature of the neurologic insult. There are no trials comparing different therapies and the combination currently used for treatment of MIS-C of steroid, intravenous immunoglobulin (IVIG) and aspirin is also thought to provide protection in

children with neurologic complications of MIS-C. Overall, specific neuroprotective therapies for children with SARS-CoV-2 are lacking and advances in this area require both earlier identification of neurologic morbidities and understanding of the mechanisms of neurologic injury due to this virus.

Arguably, SARS-CoV-2 also poses a unique risk for creating a pool of children with a long-term risk for psychiatric disorders. The onset of the majority of mental health disorders, including depression, anxiety and attention deficit disorder with hyperactivity (ADHD), occurs during childhood [2]. In the U.S. among children aged 3–17 years, approximately 4.4 million have diagnosed anxiety and 1.9 million diagnosed depression. For adolescents in particular, the closure of schools during the pandemic poses an additional risk, as data from the National Survey on Drug Use and Health show that around one-third of this age group receive treatment for mental health issues only at school [3]. For children from racial or ethnic minority groups, from low-income households or those with public insurance, this deprives them of access to these services, as they are more likely to receive care only in an educational setting.

Children who survive the medical complications of SARS-CoV-2 and who receive the type of care described in these papers remain vulnerable to mental health sequelae. Mass disasters and economic recession increase the risk for mental health disorders [4]. Up to 40% of quarantined children in the Kingdom of Saudi Arabia from March to June 2020 exhibited signs of mild or potential PSTD within 2 months of quarantine [5]. Formulated this way, as a combination of a disease process with a complex, undetermined mechanism of action resulting in long-term neurologic sequelae and occurring in the context of world-wide medical and economic crisis, the impact of SARS-CoV-2 may be regarded as a form of 'toxic stress'. This term refers to the biological changes caused by early life adversity without mitigation by emotional or social buffers [6]. In this framework, adverse childhood experiences may result in long-term maladaptive behaviour. Whether this occurs is in part a function of the social and emotional skills children are taught.

The neuroscience of toxic stress is complex, and no single pathway can recapitulate the biologic substrates of the changes in CNS circuitry or neurochemistry caused by this exposure. For example, this exposure may result in greater activity or size of the amygdala or change in the connectivity in reward processing regions, including the temporal pole and prefrontal cortex [7,8]. Prevention or treatment of toxic stress through building stable and nurturing relationships (SSNRs) represents a paradigm shift in paediatric care as means to foster resilience and diminish the effects of adverse early-life experiences [9]. The scale of the medical, economic and psychological impact of SARS-CoV-2 on children and their families is well suited to adapting the recommendations from the American Academy of Pediatrics for the treatment of toxic stress to the treatment of SARS-CoV-2. In addition to treating the diverse clinical neurologic complications of SARS-CoV-2, this approach emphasizes the benefits of a relational health framework. The scope of this framework is broad and seeks to promote stable and supportive families and communities. In practice, these efforts may range from parent education, early intervention, screening for depression, promotion of antiracism or addressing food insecurity [9].

Although the full social, economic and medical impact of SARS-CoV-2 is still evolving and is of particular concern to paediatric practitioners caring for a vulnerable population, there are many grounds for optimism. There are numerous gaps in knowledge identified by the authors of these reviews, but the breadth and depth of the data they discuss here has been generated (and therapies developed) at an unprecedented pace. The long-term mitigation of the neurologic and psychiatric sequelae of SARS-CoV-2 will require medical interventions based on advances in the understanding of SARS-CoV-2 neuropathogenesis, changes in public policy and a global research platform, which also incorporates data from under-resourced regions. Despite these challenges, the studies reviewed here should give some reason to believe these lofty goals can be achieved.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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