

**MINI REVIEW**

# Definitive pathognomonic signs and symptoms of paediatric neurological COVID-19 are still emerging

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**Abstract**

Children with COVID-19 tend to show milder symptoms than adults during the pandemic, but growing evidence of neurological involvement has emerged. Some studies have reported neurological symptoms in children with COVID-19, which include multisystem inflammatory syndrome, a disease that shares some, but not all, of the characteristics of Kawasaki disease. This review presents, and discusses, the evidence to date. Our initial findings suggest that neurological manifestations can be considered to be the direct result of central nervous system viral invasion or post-infection immuno-mediated disease.

**KEYWORDS**

central nervous system, epilepsy, electroencephalogram, multisystem inflammatory syndrome, neurological involvement

**Key Notes**

- Covid-19 pandemia is an important health problem
- Children can have severe neurological consequences of Covid-19 infections
- Further research needs to understand better the link between Covid-19 and nervous system

Some COVID-19 patients have developed specific and non-specific neurological symptoms that range from moderate to very severe.<sup>1,2</sup> A study suggests that, out of 214 hospitalised adults in Wuhan, China, 36% of them developed neurological symptoms, which may have been the first manifestation of COVID-19, along with respiratory symptoms.<sup>3</sup> However, data on children have been relatively rare.

Reports of neurological complications have increased as the pandemic has continued<sup>4</sup>: the main cerebral events are headaches, fatigue, muscle pain and dizziness. Hyposmia, hypogeusia and visual dysfunction may be the first symptoms.<sup>2</sup> Altered state of consciousness, epilepsy and Guillain-Barré syndrome may also be present, expressed as hypoxia, multiorgan dysfunction, metabolic and electrolyte derangement.<sup>5,6</sup> There has been no evidence of seizure(s) worsening in the general epileptic population.<sup>7</sup> Nevertheless, severe

neurological events may be present and intracerebral haemorrhages have been reported, along with associated risk factors such as hypertension, diabetes and cardiac disease. Strokes due to hypercoagulability, cytokine storm, cardiac embolisms, meningitis, encephalitis and acute necrotising encephalopathy have also been reported.<sup>2,7</sup> The severe acute respiratory syndrome coronavirus 2 has also been detected in cerebrospinal fluid.<sup>8</sup>

This clinical overview provides more information on the neurological manifestations of COVID-19 in children. A literature search through Medline/Pubmed, on COVID-19 disease in children, neurological involvement, multisystem inflammatory syndrome in children and Kawasaki disease, was carried out in the period from 01 February 2020 to 16 December 2020. We have used the following key words for the literature search: 'Coronavirus disease-19', 'COVID-19', 'SARS-CoV-2', 'Kawasaki disease', 'Multisystem Inflammatory

Abbreviation: MIS-C, multisystem inflammatory syndrome in children

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Syndrome', 'MIS-C', neurological involvement. We included original studies, reviews, viewpoints, commentaries, case series and case reports which were relevant to our objectives.

Most of the infections came out as asymptomatic. One study found that the majority of the asymptomatic patients had a mild infection, very few of them required intensive care and their prognosis was good.<sup>9</sup> Another study was conducted on 100 children under 18 years of age, who showed up at an emergency department with COVID-19. Most of them had mild diseases, while severe and critical cases were found in patients with co-existing conditions, and no deaths were reported.<sup>10</sup> A review of 72,314 Chinese patients showed that less than 1% were children under 10 years of age. Most of the children had a mild clinical course and were asymptomatic. Determining the transmission potential of these asymptomatic patients is important when developing measures to control the ongoing pandemic.<sup>11</sup>

The neurological effects of COVID-19 in children have only been discussed in random reports, with little information on possible relationships between COVID-19 and impairment of the central nervous system.

Reports of neurological manifestations have increased as the pandemic has grown and these can be considered as a direct effect of the virus on the nervous system or para-infectious or post-infectious immune-mediated disease.

In contrast with adults, children and adolescents with COVID-19 appear to have a milder clinical course. They are often asymptomatic, but anosmia and ageusia have been reported.<sup>12</sup>

Ouhala et al<sup>13</sup> conducted a retrospective, single-centre, observational study in a paediatric intensive and high dependency care unit. They analysed data from 27 confirmed or highly suspected virus cases aged from 1 month to 18 years. The median age at the disease onset was six and 19 of the patients (70%) had comorbidities, including seven of them with neurological comorbidities. The authors reported that five children died, including three with no previous medical problems. They included a previously healthy 16-year-old boy, who was positive to the virus, with no past medical history or respiratory symptoms. He showed up with aseptic meningitis associated with stupor. Magnetic resonance imaging of his brain showed a sphenoidal sinusitis with cavernous sinus thrombosis. In the following days, right hemiparesis related to a left middle cerebral artery stroke appeared, along with loss of consciousness. The patient died from intracranial hypertension and brain ischaemia 17 days after admission. The authors also reported a 6-year-old girl with no past medical history, who presented COVID-19, fever, respiratory distress, stupor and hypotensive shock. The patient developed septic shock due to *Staphylococcus aureus* involvement, followed by acute neurological deterioration related to a massive brain haemorrhage. She died 15 days after admission.

Neurological symptoms, especially meningeal signs, have also been reported in children with COVID-19 and Kawasaki-like disease.<sup>14</sup> Verdoni et al reported that the incidence of Kawasaki disease was 30 times higher after the pandemic started, supporting the hypothesis that an aberrant response of the immune system to the

virus is responsible for a severe form of Kawasaki-like disease in susceptible patients.<sup>14</sup>

Several centres have reported cases of multisystem inflammatory syndrome in children (MIS-C), a new hyper-inflammation syndrome associated with COVID-19 that mimics Kawasaki disease and that mostly occurs 2 weeks after infection.<sup>15</sup> Both Kawasaki disease and MIS-C have been associated with a common trigger that provokes a significant cytokine storm that results in systemic inflammation and multi-organ dysfunction. The common neurological features include headaches, meningeal signs and altered senses. Although the clinical manifestations of MIS-C and Kawasaki disease may overlap, they appear to be distinct clinical entities.<sup>15</sup>

Abdel-Mannan et al<sup>16</sup> studied 27 patients under 18 years of age with MIS-C. They included four previously healthy children, who presented new neurological symptoms involving both the central and peripheral nervous systems, with no respiratory symptoms. These neurological symptoms may be part of the systemic autoimmune-inflammatory disease that leads to an immune-directed attack on the central nervous system. The neurological manifestations included muscle weakness, reduced reflexes, headaches and brainstem and cerebellar signs. All four patients had signal abnormalities in the splenium of the corpus callosum and were admitted to intensive care and then treated for MIS-C. Two patients had cerebrospinal fluid samples taken, that were acellular with normal protein and glucose levels and negative virus results.

The interval between viral exposure and the development of MIS-C varies from 2 to 4 weeks. During this time, the virus may be cleared by neutralising antibodies and immune cells. Therefore, MIS-C is predominantly a post-infectious hyper-inflammatory syndrome that affects multiple organs and is triggered by the virus that causes COVID-19.<sup>17</sup>

Dugue et al<sup>18</sup> reported a 6-week-old baby with COVID-19, with fever, cough and two short episodes of upward gaze and bilateral leg stiffening. A long lasting electroencephalogram showed an excess of temporal sharp waves and intermittent vertex delta with normal sleep-wake cycling. The patient's brain magnetic resonance imaging scan was normal. The baby was discharged the day after admission without further fever or events after 1 week.

Alexander et al<sup>19</sup> described the case of two children with the virus and MIS-C. The 5-year-old boy had no significant past medical history and presented a fever for several days, along with a cough and abdominal pain. He developed cardiopulmonary failure that required extracorporeal membrane oxygenation. After 5 days he had a fixed dilated right pupil and a computed tomography head scan showed a right middle cerebral artery infarction, cerebral oedema and a diffuse contralateral subarachnoid haemorrhage. The reversal of his paralysis revealed absence of brainstem reflexes including doll's eye reflex and extrinsic eye musculature. Brain death was confirmed 3 days later. The 2-month-old boy had undergone a tracheostomy for tracheomalacia. He presented respiratory failure, pneumomediastinum and bilateral pneumothorax and was placed on extracorporeal membrane oxygenation. The electroencephalogram revealed nonconvulsive status epilepticus, while computed

tomography showed bilateral middle and territory infarctions in the posterior cerebral arteries. He kept having poor seizure control, which required several weeks of electroencephalograms and anti-epileptic medication. Interval magnetic resonance imaging showed evolving haemorrhagic infarctions in the bilateral occipito-parietal lobes, left temporal and left frontal lobes. These were believed to be cardioembolic in aetiology. The baby was being weaned off the ventilator at the time of the report.

A multinational multicentre collaborative study<sup>20</sup> reported central nervous system imaging manifestations of the virus in 38 children and described related acute and delayed changes in the central nervous system. Consistent disease patterns emerged and the most common were acute disseminated encephalomyelitis-like abnormalities of the brain and spinal cord and neuritis. The authors identified multifocal T2 bright lesions in brain white matter, vasculitic patterns with ischaemic lesions, enhancing neuritis or polyradiculitis, venous thrombosis, splenic lesions of the corpus callosum, longitudinally extensive myelitis and myositis.<sup>20</sup>

Multiple mechanisms have been described for neurological symptoms, blood circulation, neuronal pathways, immune mediated direct infection injuries and hypoxic damage.<sup>5</sup>

There are many reasons why the virus can invade the brain. First, axonal transport is a common route of infection and this happens when the virus enters the eyes, nose, mouth and infects nearby olfactory or trigeminal nerves.<sup>21</sup> Secondly, the virus enters the cells via the angiotensin converting enzyme receptors, expressed in the lungs and the brain.<sup>22</sup> Thirdly, the latest virus damages the brainstem and could lead to respiratory failure.<sup>23</sup> Fourthly, common symptoms, like loss of smell and taste, could be caused by damage to brain's olfactory system.<sup>24</sup>

Laboratory studies have demonstrated the possible mechanisms for neurological manifestations of COVID-19. These show that the main host-cell receptor of the virus is the angiotensin converting enzyme 2, which is expressed in both neurons and glial cells, causing direct viral invasion of the central nervous system.<sup>25</sup>

The potential role of microvascular pathology in the neurological involvement of the virus has been reported. Once the airway epithelia and lung cells have been invaded, the viral infection can spread via olfactory, trigeminal and vagus nerves, via meningeal vasculature, via the blood brain barrier and via the lymphatic system.<sup>26</sup>

In conclusion, the fact that specific antibodies suggesting acute infection or viral isolation have been found in cerebral spinal fluid could indicate that we are dealing with a neurotropic virus that may lead to multiple neurological involvement.<sup>4</sup> Both Kawasaki disease and MIS-C have been associated with a common trigger that provokes a significant cytokine storm that results in systemic inflammation and multi-organ dysfunction, including neurological symptoms.

The number of paediatric viral infections leading to neurological disease will probably remain small, but as COVID-19 spreads, reports of children developing systemic inflammatory responses that require intensive care may increase.

Even children with mild acute infections may face a high risk of secondary inflammation. The combination of central and peripheral

nervous system profiles are rare in paediatrics, but can be seen in MIS-C.

Neurological manifestations can be considered to be the direct result of central nervous system viral invasion, parainfection or post-infection immuno-mediated disease. The different severity level of neuroinvasion, neurotropism and neurovirulence in neuro COVID-19 patients may result from an interaction between viral and host factors.<sup>27,28</sup>

Close fetal observation is also required to monitor even minor abnormalities in psychomotor development.

Paediatric neurological COVID-19 still needs to be clarified as the knowledge of definitive pathognomonic signs and symptoms is still emerging.

## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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