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VIEWPOINT

COVID-19 and the Pediatric Nervous System: Global Collaboration to Meet a Global Need

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has affected mortality and morbidity across all ages, including children. It is now known that neurological manifestations of COVID-19, ranging from headaches to stroke, may involve the central and/or peripheral nervous system at any age. Neurologic involvement is also noted in the multisystem inflammatory syndrome in children, a pediatric condition that occurs weeks after infection with the causative virus of COVID-19, severe acute respiratory syndrome coronavirus 2. Knowledge about mechanisms of neurologic disease is scarce but rapidly growing. COVID-19 neurologic manifestations may have particularly adverse impacts on the developing brain. Emerging data suggest a cohort of patients with COVID-19 will have longitudinal illness affecting their cognitive, physical, and emotional health, but little is known about the long-term impact on affected children and their families. Pediatric collaboratives have begun to provide important initial information on neuroimaging manifestations and the incidence of ischemic stroke in children with COVID 19. The Global Consortium Study of Neurologic Dysfunction in COVID-19-Pediatrics, a multinational collaborative, is working to improve understanding of the epidemiology, mechanisms of neurological manifestations, and the long-term implications of COVID-19 in children and their families.

Keywords: Neurological manifestations, Pediatrics, COVID-19, Child development

Coronavirus disease 2019 (COVID-19), the disease caused by infection with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic in March 2020. Since that time, worldwide cases number greater than 100 million and deaths greater than 2.1 million. In the United States, as of January 17, 2021, more than 24 million COVID-19 cases and more than 395,000 deaths have been reported. Among children, more than 2.2 million cases had been reported as of January 7, according to the American Academy of Pediatrics. As cited in the Centers for Disease Control and Prevention (CDC) Web site, Kim et al. [1] reported that one third of children hospitalized with COVID-19 required critical care. At least 188 children have died in the United States alone [2, 3].

Although acute COVID-19 most commonly presents with respiratory symptoms, it can also affect the central and peripheral nervous systems [4]. Indeed, the neurologic system is one of the possible organ systems involved in the COVID-19-associated multisystem inflammatory syndrome in children (MIS-C) as defined by the CDC. A recent case series of nearly 1700 hospitalized patients with COVID-19 under the age of 21 reported that 22% had neurologic manifestations. In this series, half of the patients with life-threatening neurologic manifestations had MIS-C [5].

Knowledge about long-term outcomes of COVID-19 in pediatrics is scarce. In adults, persistent neurobehavioral symptoms ("long-COVID") after SARS-CoV-2 suspected or confirmed infection was noticed early, partly because adults used social media for self-reporting. In contrast,

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to our knowledge, only five pediatric cases of long-term academic impairment have been published [6]. Adult patients with long-COVID may or may not have been initially hospitalized, as shown by data collected either from social media-circulated surveys, national health systems, and/or discharge records. The prevalence of disabling cognitive and emotional disabilities ranges from 30 to 55% and significantly impairs or delays return to previous activities [7–9]. Such high prevalence, together with the potentially greater impact of SARS-Co-V-2 pediatric infection during critical neurodevelopmental periods on children and their families, heightens the importance of conducting long-term studies of pediatric COVID-19 neurologic outcomes.

Here we review the rapidly evolving mechanistic understanding of neurologic manifestations of COVID-19, with a focus on risks posed to the developing nervous system and on long-term consequences on cognition and emotional health in children. To increase knowledge about long-term neurologic outcomes in children, we created an international research initiative titled Global Consortium Study of Neurologic Dysfunction in COVID-19 (GCS-NeuroCOVID)-Pediatrics.

Neurologic manifestations related to COVID-19 may be categorized as follows: (1) nonspecific (e.g., headache), (2) primary infectious (e.g., meningoencephalitis), (3) postinfectious (e.g., Guillain-Barré), or (4) chronic or late sequelae (e.g., cognitive dysfunction).

In adults, the reported prevalence of acute neurologic symptoms (e.g., headaches, anosmia, seizure) and conditions (e.g., encephalopathy, stroke, delirium, encephalitis) ranges widely, from 4.4 to 100% of COVID-19 cases [10–12]. Anosmia and dysgeusia, relatively specific manifestations of COVID-19 that affect between 40 and 90% of adult patients, are considered neurologic in origin, although definitive proof is lacking [13–15]. Anosmia occurs in at least 5–20% of pediatric patients [16, 17]. Table 1 lists the larger case series and cohorts on hospitalized children with COVID-19 published thus far. In a recent systematic review, Panda et al. [18] reported that of nearly 3700 cases in patients younger than 18, 17% had nonspecific neurologic manifestations, such as headache, fatigue, and myalgia, and 1% presented with encephalopathy, seizures, and meningeal signs. Most of the patients from this review were from a single large US-based cohort study by the CDC [19]. LaRovere et al. [5] reported 22% prevalence of neurologic manifestations in 1695 patients younger than age 21 admitted to US hospitals. Using a global health collaborative database to extract electronic records on nearly 1400 pediatric patients, of whom 20% were admitted, Ranabothu et al. [20] reported similar rates of neurologic involvement: headache in 4%, anosmia in 2%, seizures in 0.7%, and stroke in 0.7% of cases. Postinfectious conditions, including MIS-C, atypical Kawasaki disease, and febrile inflammation, have raised new concerns about serious neurological manifestations and consequences of COVID-19 infection in children. In a review of MIS-C case series, an average of 22% of patients had neurologic manifestations [21]. We are not aware of large studies comparing neurologic manifestations and outcomes in children with MIS-C or acute COVID-19 over time.

Data on COVID-19-related neurological manifestations are constantly evolving. Recently published cohort studies include data on stroke prevalence and neuroradiological findings in children with COVID-19-related conditions. Strokes affect 1–5% of adults hospitalized with COVID-19 [30]. Case reports of thrombotic and hemorrhagic stroke in children with acute COVID-19 are growing [20, 29, 31, 32]. LaRovere et al. [5] reported a total of 12 cases of ischemic or hemorrhagic stroke in 1695 hospitalized pediatric patients with COVID-19. A recent 42-center survey published by the International Pediatric Stroke Study Group (IPSS), a network of institutions from 26 countries, reported eight stroke cases associated with positive SARS-CoV-2 polymerase chain reaction (PCR) results, of which one patient lacked stroke risk factors. Although the network did not detect an increase in neonatal or pediatric ischemic stroke prevalence, the survey was conducted over a relatively short time frame for a rare condition in children, and fewer than half of patients were tested for COVID-19 [29]. The Pediatric COVID Brain Imaging Group (PECOBIG) presented clinical data from 38 pediatric patients with neurologic symptoms and abnormal brain imaging within 3 months of COVID-19 diagnosis in ten countries. From this series, imaging most commonly revealed neuritis, myelitis, and/or encephalomyelitis; 18% of cases were consistent with thromboembolic or vasculitis events [33].

Hypotheses about the pathophysiology of COVID-19-associated neurologic disease are myriad, differing in part by presentation relative to the time of infection. Direct viral invasion of the central and/or peripheral nervous system is supported by biologic plausibility, but evidence supporting it as the predominant pathophysiologic process in patients is scarce [34]. Direct viral invasion requires entry into the nervous system either via the hematogenous route, most likely on blood–brain barrier disruption, or via transsynaptic routes, such as along the cranial nerves VII, IX, and X starting from nasopharyngeal, respiratory, and/or gastrointestinal entry points [34, 35]. SARS-CoV-2 cellular invasion begins with binding of the viral spike protein to a transmembrane receptor, followed by fusion of the viral membrane to the cellular membrane after activation of the spike protein by cellular proteases. SARS-CoV-2 binds to the

Table 1 Published reports of neurological manifestations of COVID-19 in children

Cohort, location, study	Acute neurologic symptoms and conditions reported	Child outcomes (entire cohort, unless specified)
35 hospitalized children, France and Switzerland, Belhadjer et al. [22]	31% meningismus	28% on ECMO, all survived, 1 inpatient
21 hospitalized children, France, Toubiana et al. [23]	29% headaches, confusion, or meningismus; 57% irritability; 5% anosmia	All discharged home
33 hospitalized children, USA, Capone et al. [24]	58% neurocognitive symptoms (e.g., headache, irritability, lethargy)	28% hospitalized, 70% discharged, 2% died (3 of 4 on ECMO, 4 of 4 with neurologic involvement)
186 hospitalized children, USA, Feldstein et al. [25]	5–11% any neurologic involvement	77% discharged, 21% hospitalized, 2 (2%) died
27 hospitalized children, UK, Abdel-Mannan et al. [26]	15% encephalopathy, headaches, brainstem and cerebellar signs, muscle weakness, and/or reduced reflexes	2 children wheelchair dependent and remained hospitalized, other children ambulating independently at hospital discharge
82 hospitalized children, Lin et al. [27]	43% neurologic manifestations (34% headache, 23% altered mental status, 11% seizures, CN VI palsy in 3 of 82)	Not reported
168 hospitalized children (65% hospitalized), Italy, Garazzino et al. [28]	2% fatigue, 2% nonfebrile seizures, 1% febrile seizures	All children had full recovery
1695 hospitalized children and adolescents, USA, LaRovere et al. [5]	21.5% neurologic involvement, 19% transient symptoms, 0.9% severe encephalopathy, 0.7% stroke, 0.5% central nervous system infection/demyelination, 0.2% Guillain–Barré syndrome/variants, 0.2% acute fulminant cerebral edema	43 (2.5%) with life-threatening neurologic involvement, 17 (1%) with new neurologic deficits at discharge, 11 (0.6%) patients died
192 children hospitalized, France, Gaborieau et al. [16]	8.9% no feeding or feeding difficulty; 5.2% anosmia, dysgeusia; 0.5% status epilepticus	24 (12.5%) hospitalized in PICU, 12 (6.3%) on invasive ventilation, 3 (1.6%) died
971 patients surveyed from 61 international sites with pediatric stroke expertise, Beslow et al. [29]	0.9% neonatal AIS, 3.6% childhood AIS, 1.9% childhood cerebral sinovenous thrombosis	3 (0.3%) of patients hospitalized in PICU
≈3700 patients in a systematic review of 26 studies/case reports, Panda et al. [18]	17% had nonspecific neurologic manifestations, such as headache, fatigue, and myalgia, and 1% presented with encephalopathy, seizures, and meningeal signs	Not reported

AIS arterial ischemic stroke, *CN VI*, cranial nerve VI, *COVID-19* coronavirus disease 2019, *ECMO* extracorporeal membrane oxygenation, *PICU* pediatric intensive care unit

angiotensin-converting enzyme receptor 2 (ACE2), a protein coexpressed with the protease transmembrane serine protease 2 in endothelial cells throughout the body that is particularly abundant in the small intestine, kidneys, lungs, and heart [36]. ACE2 is present in human adult and fetal brain, with highest expression in the pons and medulla oblongata in the brainstem [37]. In mice, brain ACE2 levels are higher in the early postnatal period than in the adult, whereas ACE2 activity is similar across the lifespan [38]. ACE2 is also expressed in pericytes, cells that play key roles in the cerebral microvasculature [39, 40]. SARS-Co-V2 may bind instead, or also, to the neuronal adhesion molecule neuropilin 1 (NRP1) and undergo activation by furin, an ubiquitous protease, to allow entry into the host cell [41]. NRP1, a glycoprotein essential for normal nervous and cardiovascular system formation and function in vertebrates, is expressed in immune (i.e., macrophages, microglia) and nonimmune cells (i.e., endothelia, neurons) [42, 43]. NRP1 plays essential roles in axon guidance, dendrite formation, and cerebral vasculogenesis, among others. Indeed, mouse brain NRP1 expression is two to three times higher in embryonic than adult tissues [44, 45].

In summary, SARS-CoV-2 entry and replication within the human nervous system at any developmental stage is plausible. However, clinical encephalitis, meningitis, and intracranial ischemia/hemorrhage reported thus far are, almost without exception, marked by negative PCR tests results in cerebrospinal fluid [26, 34]. Autopsy studies suggest that greater time after infection is associated with more inflammation and decreasing viral load [46]. Although PCR positivity in brain slices was noted in some studies, pathological evidence of viral-specific injury is lacking. Most commonly, autopsy studies report cellular effects of hypoxia and/or show microvascular plugging by neutrophils on histopathologic examination [46, 47].

Other pathophysiologic hypotheses about COVID-19-associated neurologic disease do not preclude viral invasion of the nervous system as an initiating event. A feature that appears to distinguish neurologic disease associated with COVID-19 from that seen in most other respiratory viruses is the markedly prothrombotic state and increased risk of stroke, particularly ischemic, noted in patients with COVID-19 who are critically ill [34]. Thrombotic and thromboembolic stroke, as well as endotheliitis and plugging of the cerebral microvasculature most likely caused by COVID-19, have been reported in patients ranging in age from elderly to middle age to as young as 7 years [46, 48]. In a recent systematic review, ischemic and hemorrhagic stroke occurred in up to 4.9% and 0.9%, respectively, of published cases, of which many were likely multifactorial [49]. In a retrospective review of 4400 patients with COVID-19 in New York, stroke occurred in 1.9% of cases [50]. Factors common to the elderly and critically ill, such as comorbid conditions, are often present. Nevertheless, in selected cases, SARS-CoV-2 appears to play a major role in cerebral macrocirculatory and microcirculatory occlusion or insufficiency in young adults and children [48, 51–53]. Two case reports, one of a 12-year-old boy with focal cerebral arteriopathy and ischemic stroke without antecedent or concomitant respiratory symptoms and another of two patients with large-vessel ischemic stroke within weeks of mild respiratory disease, are examples of primarily cerebrovascular presentations of COVID-19 [31, 32]. The recent 42-center survey published by the IPSS reported eight pediatric stroke cases associated with COVID-19, but they did not detect an overall increase in neonatal or pediatric ischemic stroke prevalence [29].

Seizures, delirium, and encephalopathy observed in critically ill patients with COVID-19 are likely related at least in large part to multiorgan failure, medications, hypoxia, and hypotension. The pooled estimates of seizure and encephalopathy frequency in children with severe COVID-19 are 3.1% and 12.6% of cases, respectively [18]. COVID-19-specific factors postulated to play a role include a dysregulated immune response, impaired ACE2 activity, and microcirculatory insufficiency. In adults, severe COVID-19 is associated with elevated cytokine levels, reflecting a dysregulated innate immune response [54]. ACE2 overexpression is protective against cerebral ischemia in vitro and in vivo [55]. Conversely, loss of ACE2, as occurs in cells infected with SARS-CoV-2, increases the likelihood of vasoconstriction, procoagulation, and inflammation from unopposed angiotensin II [40]. Indeed, high serum angiotensin II levels in patients with severe COVID-19 appear to correlate with viral load and severity of lung injury [56]. Other pathways downstream of ACE2 could play a role in COVID-19 pathophysiology. For example, ACE2 loss leading to unopposed bradykinin, neurotensin, and dynorphin levels could help explain increased vascular permeability, delirium, and high sedative requirements [57]. Finally, microcirculatory insufficiency in the brain is thought to occur secondary to SARS-CoV-2-induced endotheliopathy [58].

Some neurologic manifestations of COVID-19 in adults and children may be triggered by autoimmunity. Postinfectious neurologic diseases, including Guillain–Barré syndrome, encephalomyelitis, and necrotizing autoimmune myositis, have followed nonneurologic, neurologic, and asymptomatic COVID-19 infection [59]. Prevalence of neurologic manifestations in pediatric patients with MIS-C, a disorder that typically presents weeks after SARS-CoV-2 infection, ranges from 12 to 22% [60, 61].

Immune profiling suggests that autoantibodies in these pediatric patients may play a role in the end-organ effects of MIS-C [60, 62]. Shared sequence similarity between SARS-CoV-2 and sialic acid residues on neural tissue, as well as the observation that patients with neurologic manifestations often have positive COVID-19 serology results but negative PCR testing results, supports the role of autoimmune mechanisms in adults and children alike after resolution of the acute infection [26]. Serum and cerebrospinal fluid from a series of adult patients with severe COVID-19 infection contained high-affinity SARS-CoV-2-neutralizing antibodies that cross-reacted with mammalian self-antigens, including self-antigens found in the central nervous system [63]. Although causal links are largely lacking, there have been limited reports of Guillain–Barré syndrome and acute disseminated encephalomyelitis following COVID-19 in adults and children [18, 59, 64, 65]. LaRovere et al. [5] reported eight cases of acute disseminated encephalomyelitis in their series of 1695 pediatric patients.

Pediatric cases, especially those with neurologic manifestations, raise alarm for the potential for health sequelae to affect child and family functioning over many life-years. Adult survivors of COVID-19 report worse quality of life (up to 44% of cases) and a high prevalence of impaired memory, difficulty with concentration, and fatigue [66]. COVID-19 symptoms, including neurocognitive dysfunction and mental health impairments, may persist beyond 3 weeks after acute illness in 10–35% of adults, the so-called long-haulers [66, 67]. Emerging data about neurologic manifestations in children raise further concern about acute and chronic sequelae of pediatric SARS-CoV-2 infection. Ludvigsson [68] reported that five pediatric patients had persistent cognitive dysfunction 6–8 months after clinically diagnosed COVID-19 and that none had fully returned to school. Survivors of COVID-19 are at significant risk for post-intensive-care syndrome and posthospital syndrome, characterized by physical, cognitive, and emotional health sequelae after discharge [69]. Post-COVID-19 dysexecutive function and neuropsychiatric sequelae are increasingly reported even in patients who did not require intensive care [70, 71]. The relatively small sample sizes and short periods to follow-up in these studies limit definitive outcome assessment. In summary, prevalence of persistent neurocognitive dysfunction after pediatric infection with SARS-CoV-2 is unknown. In addition, pediatric-specific sequelae of COVID-19 may exist. Transgenic studies demonstrating that a lack of the macrophage growth factor colony-stimulating factor 1 impairs normal brain development, particularly of the olfactory system, raises questions about the effects of even transient anosmia on the developing brain [72].

An effective response to this pandemic requires multidisciplinary collaboration among clinicians, basic scientists, and patients and families. The relatively low prevalence and heterogeneity of infected children at any one center requires prospective multicenter studies of children with COVID-19 or MIS-C that collect detailed data on acute neurological manifestations, as well as on child- and family-centered outcomes after discharge. Indeed, in March 2021, the National Institutes of Health solicited applications to study postacute sequelae of SARS-CoV-2 infection under the Research Opportunity Announcement OTA-21-015B, targeting data on at least 500 cases of postacute sequelae of SARS-CoV-2 infection in children [73]. We applaud the collaborative efforts of the World Health Organization, IPSS, and PECOBIG to help fill this gap. However, data are urgently needed to gain knowledge about long-term neurologic effects of COVID-19 in children and to generate pathophysiologic hypotheses for future mechanism-based treatments. In addition, therapeutic interventions in children with COVID-19 or MIS-C are empiric and/or derived from adult trials in the absence of controlled studies in pediatrics. Evidence-based therapy for COVID-19 nervous system involvement is also lacking in patients of all ages. A coordinated, international approach is needed to collect granular data on neurologic signs, symptoms, and treatments used in children with acute COVID-19 and to follow long-term neurobehavioral outcomes. Results of such an effort will guide the provision of comprehensive recovery care and the advocacy for resources needed to mitigate disparities in outcomes and generate hypotheses regarding the impact of empiric therapies on long-term neurologic outcomes.

To help address this need, we partnered with clinicians, patients, families, and research societies to create the GCS-NeuroCOVID-Pediatrics [74, 75]. Numbering more than 104 registered pediatric centers in 26 countries, we created harmonized data collection instruments and definitions to prospectively obtain data on hospitalized children with or without neurological manifestations of COVID-19 infection and/or MIS-C. We will test the hypothesis that children with neurological manifestations of COVID-19 and/or MIS-C are at greater risk (1) for adverse neurological outcomes at hospital discharge and/or (2) after discharge compared with children without neurologic manifestations (Fig. 1). Centers with regulatory approval have begun collecting focused data, including neurologic symptoms and examination findings, results of laboratory and neurologic testing obtained as part of clinical care, COVID-19-directed and/or MIS-C-directed therapies, and in-hospital functional outcomes. Preliminary findings for this effort are expected in the first half of 2021. Next steps are to launch

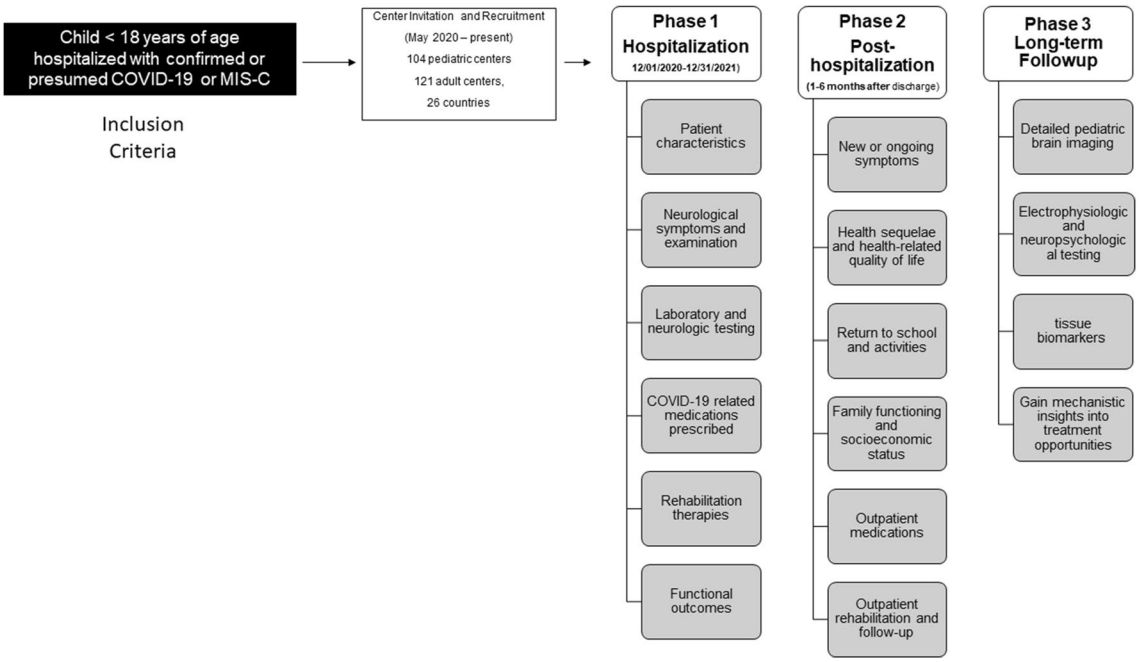

Fig. 1 GCS-NeuroCOVID-pediatrics. The hypothesis of this study is that children with neurological manifestations of COVID-19 and/or MIS-C are at greater risk for adverse neurological outcomes (1) at hospital discharge and/or (2) after discharge when compared with children with COVID-19 and/or MIS-C without neurologic manifestations at hospitalization. COVID-19 coronavirus disease 2019, GCS-NeuroCOVID Global Consortium Study of Neurologic Dysfunction in COVID-19, MIS-C multisystem inflammatory syndrome in children

a post-hospital-discharge child- and family-centered outcomes study [76, 77]. A cohort of families of children from the hospital-based study will report on new or ongoing late symptoms, health sequelae and health-related quality of life, participation in school and other activities, family functioning, and outpatient medications and rehabilitative therapies. Importantly, investigators have reported that the COVID-19 infection rate in children varies by race, ethnicity, and socioeconomic status, as it does in adults [78]. Our group collects data on race, ethnicity, and socioeconomic variables as well as comorbid conditions. Our long-term objective is to use results from this study to investigate detailed pediatric brain imaging, electrophysiologic and neuropsychological testing, and tissue biomarkers to gain mechanistic insights into treatment opportunities that inform clinical trials.

In conclusion, COVID-19-related disease, already associated with important neurological manifestations in children, is expected to adversely impact child psychiatric and neurologic outcomes, including child and family health, for years to come. We add our voices to the call for vigilance as to the possibility of past COVID-19 infection in children who present with new, unexplained neurologic disease of the central and/or peripheral nervous system. Collaborative research by our consortium and others is a unique opportunity to bring together the coordinated efforts of scientists and clinicians across the world to focus on developing mechanism-based treatments for the acute and long-term neurologic complications of an infectious disease. The products of this initiative are likely to benefit other neurologic disorders in the future and enable society to face future pandemic challenges.

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