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NEUROLOGICAL IMPACT OF COVID-19 AND ITS EFFECT ON PEDIATRIC POPULATION: A COMPREHENSIVE REVIEW

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ABSTRACT

The emergence of a novel strain of ß-coronavirus in Wuhanin early December 2019, signaled what were to be the most harrowing months for humanity in recent memory. Studies relating to the epidemiology and pathophysiology of the SARS-CoV-2 virus, the causative pathogen for the present COVID-19 pandemic, revealed that the viral coat carried a spike protein specific to the angiotensin-converting enzyme 2 (ACE2)-receptors found on type II pneumocytes located within the alveoli of human lungs. Victims of the pathogen primarily demonstrated pneumonia-like symptoms and a fatal cytokine storm, the combination of which leads to acute respiratory distress syndrome (ARDS) and systemic inflammatory response syndrome (SIRS). However, as the disease began to spread, a multitude of varied symptoms was brought to the fore, one of the most significant being the effect of the disease on the brain of the patient. Besides, there is a widespread debate about the effect of the virus on the pediatric population. Hence, the purpose of the current Review is to present a consolidation of the various facts related to the neuropathophysiology of the disease, some well-established and some relatively new, along with a comprehensive detailing of the effect of the disease on the pediatric population.

Keywords. *brain, ß-coronavirus, COVID-19, novel strain, pandemic, pediatric population, SARS-CoV-2 virus*

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1. INTRODUCTORY INFORMATION ON SARS-COV-2 AND COVID-19 DISEASE

1.1 Taxonomic Classification of SARS-CoV-2

In the nomenclature of COVID-19, 'CO' stands for corona, 'VI' for virus and 'D' for the disease and was first identified in December 2019. Earlier, the pathogen of this pandemic was referred to as '2019 novel coronavirus' ('2019-nCoV'). However, The International Committee on Taxonomy of Viruses (ICTV) announced "severe acute respiratory syndrome

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coronavirus 2 (SARS-CoV-2)" as the name of this new virus on 11th February 2020 [1]. The Coronaviruses are enveloped, positive-sense RNA viruses belonging to the sub-family Coronavirinae, family Coronaviridae and order Nidovirales [2,3]. SARS-CoV-2 belongs to ß-CoV of group 2B[4].

1.2 Epidemiology of COVID-19 Disease

Epidemiologically, the outbreak of COVID-19 clearly began at the South China Wholesale Sea Food Market in Wuhan, the capital city of Hubei Province in the People's Republic of China. Since then, a number of environmental samples from around the live animal section of the market were found to be positive for SARS-CoV-2 [2]. However, whether the strain itself originated from the market is still debatable, and under the scanner.

1.3 Generalized Symptoms of COVID-19 Disease

SARS-CoV-2 targets primarily the human respiratory system. Even though the primary manifestations of the disease are pneumonia-like symptoms and a heightened immune response termed 'cytokine storm', due to the later a variety of pathophysiological effects have been found to surface. The main symptoms are severe pneumonia (with CT-SCAN revealing the presence of ground-glass opacity nodules and woolly patches in the lungs), detectable serum SARS-CoV-2 viral load (RNAaemia) and acute respiratory distress syndrome (ARDS), along with systemic inflammatory response syndrome (SIRS). Besides these primary symptoms, reports of various dermatological, neurological, and gastrointestinal manifestations have also been analyzed. One of the most worrying aspect is the effect that the disease seems to have on the human brain[5,6].High blood levels of cytokines and chemokines predominate in patients with COVID-19 infection. These include IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα and VEGFA. Critically ill patients admitted to the intensive care units(ICUs) of hospitals are usually found to display very high levels of pro-inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α and TNFα. All these together are believed to play a part in the disease symphony, complementing the more severe effects of the disease, including death[7–11].

2. IMPACT OF COVID-19 ON THE BRAIN

2.1 Sites of Infection in the Human Nervous System

As the pandemic has progressed, two of the most disturbing symptoms that have surfaced are the neurological and neuropsychiatric effects of the disease. The viral RNA has been successfully identified and isolated from the cerebrospinal fluid (CSF) [5,12]. This establishes the virus as possessing neuroinvasive properties, with the capability to infect the human central nervous system (CNS) including brain, and peripheral nervous system (PNS).

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It has also been noticed that the angiotensin-converting enzyme 2 (ACE2) is present on non-neuronal cells in the cerebral vasculature [13].

2.2 Neuroinvasion of SARS-CoV-2

The virus may enter the CNS by utilizing the vasculature, nerve structure, CSF or the lymphatic system [14–16]. The presence of various types of non-neuronal cells in the olfactory epithelium, as well as on the epithelial cells of the cerebral vasculature which express ACE2 receptor may act as a facilitator for the multiplication, accumulation and entry point of the SARS-CoV-2 virus [17,18]. It may be so that the virus can enter trans-neuronally via the olfactory nerve, approaching the brain across the cribriform plate [19]. This could be the pathophysiological reason behind the loss of smell reported by various patients recently. Since 'nose-to-brain' route is used for medicine delivery, this pathway could very well act as the pathway for brain infection by the virus [20,21]. Post-mortem (PM) studies have also demonstrated the presence of the virus in neural and capillary endothelial cells of the frontal lobe of the brain [22]. It also seems that co-morbidities like diabetes and hypertension enhance the expression of ACE2 in the brain and promote neurotropism [23]. The circulation of the viral particles in the blood stream, leading to their interaction with the capillary endothelium and subsequent destruction, could provide a basis for the access of the viral particles to the brain. This may be a cause for brain hemorrhage long before the lethal effects of the neuronal damage manifest [24]. These changes may be complicated by the ARDS-related hypoxic conditions. In fact, it may so happen that the condition of the patient worsens due to infection of the pneumotaxic center in the brainstem following the viral invasion [6,25].

2.3 Direct Effects of COVID-19 on the Brain

The major neurological symptoms of COVID-19 include headache, myalgia and malaise. It affects the complete neural axis, including the cerebral vasculature. The major complications implicated in this disease include meningitis, encephalopathy, meningoencephalitis, ischemic stroke, acute necrotizing encephalitis and Guillain-Barre Syndrome [25]. Reports from Wuhan and China mention various neurological symptoms including headache, vomiting, acute cerebrovascular diseases, consciousness impairment, and skeletal muscle dystrophy [8,26].

2.3.1 Headache

COVID-19 related systemic viral infection may be a cause for acute headache, resulting from primary cough-headache and tension-type headache. Headaches, centered around the 7^{th} to 9^{th} day of the illness, may be contributed to the cytokine storm [27]. Meta-analysis and systematic review have revealed the incidence of headaches to be prevalent around in 10-15% of the patients [28–31].

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2.3.2 Encephalopathy

Altered sensorium has been implicated with an increased risk of death in COVID-19 patients [32]. Hypoxia and systemic inflammation may result in delirium, with symptoms ranging from confusion to stupor to coma [33]. Psychosis with hallucination was one of the first reported instances of neurological implications of the disease. Auditory and visual hallucinations accompany persecutory delusions and Capgras delusion, with complex systematized delusional misperceptions [34].

2.3.3 Encephalitis

The first case of viral encephalitis arising as a symptom of COVID-19 along with isolation of the virus from the CSF was first reported in China [35]. Magnetic Resonance Imaging (MRI) scan of patients harboring the virus have implicated the limbic system, but otherwise normal scan of the brain [36–44]. Various studies have also revealed the presence of disseminated encephalomyelitis and immune-mediated acute hemorrhagic necrotizing encephalopathy. In the later, hemorrhagic lesions are diagnosed in the thalamus [45–47]. It has also been proposed that the respiratory distress is being precipitated by an additional or solitary medullary respiratory center dysfunction. This is based on the observation that patients lacked dyspnea, but had marked tachypnea and tachycardia [6,48].

2.3.4 Coagulopathies

The occurrence of disseminated intravascular coagulation (DIC) is well documented in severe COVID-19 infections, characterized by an increased D-dimer (a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis), prolonged prothrombin time and mild thrombocytopenia, but without hypofibrinogenemia [49,50]. Coagulopathies increase the chances of ischemic stroke and other prothrombic events in patients suffering from COVID-19 infections [51–53].

2.3.5 Ischemic Stroke

Coagulopathies associated with COVID-19 increase the risk of ischemic stroke in patients presenting with the disease. In a particular study, it was noted that 11 out of 221 patients suffered from ischemic stroke. There were two isolated cases of cerebral hemorrhage and cerebral venous thrombosis. The patient population presenting with stroke symptoms had advanced age, and many had associated co-morbidities [54]. In a different study on 6 patients with large cerebral infarcts, high D-dimer levels (≥1000 μg/L) were noted [55]. Young (<50 or, specifically between 33-49 years of age) population also showed a predisposition to COVID-19 related strokes. The National Institute of Health stroke scale scores, on hospitalization, ranged from 13 to 19 [56,57]. A proposed mechanism for COVID-19-related strokes is vascular endothelial dysfunction and coagulopathy.

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2.4 Indirect Effects of COVID-19 on the Brain

The down regulation of the ACE2 receptors as a result of the disease hampers blood pressure regulation, increasing the chances of cerebral vascular complications [58].The development of SIRS is a prevalent syndrome linked to viral infections like COVID-19. Also, virus-mediated oxidative stress arising from acute inflammation-mediated early release of pro-inflammatory cytokines may sometimes not be compensated by the antioxidants present in the system. This may increase the systemic oxidative stress, to which the brain is susceptible as it is a metabolizer of oxygen with no antioxidant mechanism [59].It has been established that the brain-lung-brain axis is interconnected, and neurological dysfunction along with injury may be related to acute respiratory distress [60]. It is well known that SARS-CoV-2 is a potent cause for cytokine storm, and resultant apoptosis and cell death arising from a marked inflammatory and immune response [10]. SARS-CoV-2 patients have elevated levels of IL-1β, IFN-γ, IP-10, MCP-1, IL-4 and IL-10 [7,9]. An excited immune system could be the cause of enhanced vascular hyperpermeability, coagulopathies and multiorgan failure, along with neural degeneration [61]. Inflammatory damage to the Blood Brain Barrier (BBB) has been observed to be the reason behind various neurodegenerative and CNS infections. The presence of elevated levels of pro-inflammatory cytokines such as TNF-α and IL-6 is strongly correlated with neuro- inflammatory signaling [62]. Also, imbalances in the redox state pave the way for severe tissue damage and neuronal degeneration [63–65]. Hypoxia caused by the infection of the alveoli, resulting in impaired gas exchanges, increases anaerobic metabolism in the mitochondria of brain cells [66,67]. This may promote vasodilation, accompanied by the swelling of blood cells, interstitial edema, cerebral blood flow obstruction, ischemia and congestion [68].

3. IMPACT OF COVID-19 ON PEDIATRIC POPULATION

3.1 Epidemiology and Transmission

A preliminary observation and literature survey reveals the fact that neonates and children develop a milder form of COVID-19 [69–78]. The incidence of the disease in different countries are low and variable (China: 2-12.3%, Italy: 1.2%, Korea: 4.8%, USA: 5%) [69,72,79–81]. In India, age-specific COVID-19 incidence increase sharply in both settings - between the 5-17 year, and 18-29 year age groups [82]. It appears that even though children between 0-18 years of age are prone to the disease, neonates are the most vulnerable [69,83]. In the age groups, the proportion of severity of the disease dropped with increasing age. Age group <1 years had 10.5% severe case load, 1-5 years age group had 7.3%, 6-10 years had 4.2%, 11-15 years 4.1% and >16 years age group 3% [69]. Presently available literature fortunately points that there is a decreased risk of vertical (maternal-fetal) transmission. The virus has also not been isolated from amniotic fluid, umbilical cord blood and breast milk to date [74,78,84–89]. However, both symptomatic and asymptomatic carriers could transmit the virus [90–95]. The best reported cause behind transmission were infected cases as a part

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of a family cluster [76,83,96,97]. A proposed reason behind this is early imposition of lockdown conditions on schools in the current pandemic situation, and the absence of high propensity of international travel among children or travel in general [98].

A large-scale analysis of 72314 cases from China also supports this trend. Among the cases, there were 419 (0.9% of all cases) in Children 0-9 years old and 549 (1.2%) in children aged 10-19 years. There was no fatality in 0-9 year age group, while 1 individual died in the age group 10-19 [99].

3.2 Increased Rate of RT-PCR False Negative Tests in Children

Increasing evidence is pouring in from various studies of an innate immune response very strong in pediatric population against SARS-CoV-2 to show that the viral replication is shut down even before it can replicate enough to reach the threshold level for a positive result in a RT-PCR test for COVID-19.

Analysis of antibody raised in 3 children of under 10, whose parents contracted the disease, demonstrated the presence of antibodies specific for SARS-CoV-2. However, even after repeating RT-PCR tests 11 times over 28 days none of the children tested positive despite being in close contact with their parents [100].

The same result was observed even in children who developed the rare, but severe complications of multisystem inflammatory syndrome in response to SARS-CoV-2 infections. The rate of positive RT-PCR tests ranged from 29% to 50% [101–103].

A possible reason behind this may be hidden in the type of antibodies which are raised in children, as compared to adults. A study encompassing 32 adults and 47 children under the age of 18 revealed that antibodies in children were primarily aimed against SARS-CoV-2 spike glycoprotein (S). In adults, along with this antibody, there are antibodies against SARS-CoV-2 nucleocapsid proteins which are essential for viral replication. The presence of such antibodies is indicative of widespread viraemia. Hence, the lack of nucleocapsid-specific antibodies suggest the absence of widespread virus infections in children [104].

3.3 Possible Reasons Behind Low Transmission of Infections in Pediatric Population

Even though no straightforward answer is available yet, but one may survey literature and come to on an evidence-based conclusion of what might be the possible reasons why children in general fair better when infected by the SARS-CoV-2 virus.

One such identifiable cause is the down regulated expression of ACE2 receptors in their noses, thus reducing the probable host cell entry points. In a study statistically analyzing the expression of the said receptor distribution in population, based on age grouping, it was observed that ACE2 gene expression was the lowest (mean log2 counts per million, 2.40;

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95% CI, 2.07-2.72) in younger children. The study analyzed 305 individuals between ages 4 and 60, of which 45 belonged to this category. The values of expression increased with age, with mean log2 counts per million of 2.77 (95% CI, 2.64-2.90) for older children (n = 185), 3.02 (95% CI, 2.78-3.26) for young adults (n = 46), and 3.09 (95% CI, 2.83-3.35) for adults (n = 29). However, in order to establish this as a determined trend, more diverse and population-wide studies are required [105].

An assay for SARS-CoV-2 S-reactive antibodies demonstrated the presence of such antibodies in SARS-CoV-2 uninfected individuals. These were particularly abundant in children and adolescents. These antibodies were primarily targeted against S2 subunit of the Spike protein. The uninfected donor sera carried specific neutralizing activity against SARS-CoV-2 and its pseudo types. The marked absence of IgM and IgA antibodies was suggestive of cross-reactive immunological memory [106].

In a study to examine the presence of such antibodies, 48 young uninfected healthy donors (sampled between 2011 and 2018; aged 1-16 years) were identified. 21 individuals had detectable SARS-CoV-2 S-reactive IgG antibodies. In contrast, out of 43 young adults (aged 17-25), only one individual had it. The presence of SARS-CoV-2 S-reactive IgG antibodies attained a value of 62% between the age of 6 and 16. This correlated well with an increase in the HCoV (Human Coronavirus, non-SERS and MERS types) seroconversion in this age group. The value was significantly higher than in adults ($P<0.00001$, Fisher's exact test) [106–109].

The presence of antibodies often does not impede pathogenesis. However, an assay of the neutralizing capacity of the majority of sera from SARS-CoV-2 uninfected donors containing flow-cytometry-detectable cross-reactive antibodies did demonstrate neutralization of authentic SARS-CoV-2 infection of Vero-E6 cells [106].

Therefore, prior HCoV infection may be a putative reason for the age distribution of susceptibility to COVID-19, which has so far demonstrated an inability to cause widespread disease in children. However, such antibodies are widespread in adults, which indicate some additional requirement such as random B cell receptor repertoire or focusing on frequency of HCoV infection rather than the time since last infection. The frequency of HCoV infection is biased towards children and adolescents [108–111] .

An aspect which requires further analysis as a factor affecting pathogenesis of SARS-CoV-2 in pediatric population is the nature of T cells involved. It has been suggested that relative naivety of T-cells in pediatric population might make them more efficient in their response to the virus. This topic is severely debated with multiple studies proposing otherwise and has not found footing as a major determinant of pathogenesis in the pediatric population [112,113].

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3.4 Symptoms

It has been observed that the median time of incubation of the virus in children is longer than in adults. Clinical manifestations of the disease in children include fever and respiratory symptoms like cough, sore throat, pharyngeal erythema, nasal congestion, tachypnea/dyspnea, and tachycardia [114–116]. Gastrointestinal symptoms are also common, and include abdominal cramps, nausea, vomiting and diarrhea [72,85,90,117,118]. Neurological manifestations are luckily rare [116,118–121]. Analysis of 66 children spanning 12 different studies revealed that the patients maintained normal leucocyte count, but has elevated C-reactive proteins (CRPs) and procalcitonin by 13.6% and 10.6% respectively [122–124]. The prevalence of hyperinflammatory state, with features similar to atypical Kawasaki disease, was also reported [125,126]. New evidences indicate complications leading to Multisystem Inflammatory Syndrome in children (MIS-C), as well as Kawasaki's Disease [127]. Radiological findings are variable in the pediatric population, with several presenting with interstitial pneumonia and CT-Scan showing opacities of high density [72]. Ground glass opacities which are common in adults are fortunately reported lesser in children [72]. Time lapse between hospitalization and the onset of clinical symptomsis found to be 2 days, while recovery time is between 1-2 weeks [90–95].

Data relating to importance of comorbidity as a precipitating factor for increased severity of COVID-19 disease presentation is sparse. However studies do exist, and reveal that there is a high probability of experiencing severe symptoms when COVID-19 is conjugated with co-morbidities in children. Obesity has been identified as one of the most important factors in this case. In 42 different studies encompassing 275661 children without co-morbidities and 9353 with co-morbidities, severe COVID-19 was present in 481 (5.1%) children with co-morbidities and 579 (0.2%) children without co-morbidities. A relative risk ratio was obtained on the basis of random-effects analysis which was 1.79 (95% CI 1.27 – 2.51; $I2$ = 94%). Children with obesity has a relative risk ratio of 2.87 (95% CI 1.16 – 7.07; $I2$ = 36%). In this analysis of children presenting with severe COVID-19, 64 children were obese, 58 presented with chronic respiratory disease, 45 had cardiovascular disease, 33 had neurological conditions, 26 had immune disorders, 19 had metabolic diseases and additionally 12 had hematological disorders. These were the primary identified co-morbidities, along with 11 cases of cancer [128].

However, good news is that most identified cases in the pediatric population carry mild clinical manifestation. Most cases carry a good prognosis and recover within 1-2 weeks of disease onset [76].

4. CONCLUSION

It is thus quite evident from published literature that the viral disease COVID-19 has profound neurological effects which are independent of disease severity. Multiple symptoms

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manifest and are hidden from primary analysis. It is only now, when the world is slowly reviving itself, that these symptoms and their long-term effects are becoming more apparent.

These symptoms themselves are not to be taken lightly, and careful analyses have identified unique neurological manifestations of the disease. The apparent direct impact might overshadow the indirect effects of the disease on the brain. However, in a disease well characterized by a cytokine storm, the brain cannot go amiss, and various studies have verified this through analyses of the physical manifestations of the effects on the brain. However, more research and statistical analyses of large populations are required to correctly establish the true scale and impact of the neurological symptoms of this viral disease.

The extent of the disease in the pediatric population was initially assumed to be mild, and that view continues to be supported by varies population-based studies. The reasons behind such a bias are yet to be scientifically analyzed and identified. The logical reasoning of facts and data has already indicated possible explanations of this. Future research prospects lie in the analyses of the importance of the innate immune response in children against SARS-CoV-2. The established fact of the lack of expression of ACE2 receptors on nasal epithelium also needs to be revisited through diverse population-wide studies. It would be only logical to assume the importance of prior HCoV infections in raising cross-reactive antibodies which offer possible immunity against COVID-19. However, the assumption that this is a result of higher frequency of HCoV infections in children needs to be carefully studied to ascertain the exclusive truth. It may be so that some mechanisms that are still hidden from scientific glance might be responsible for the same.

The decreased efficiency of transmission in children due to social distancing, absence of physical interaction in educational institutions and absence of mobility might also have helped in containing transmission among children, and the spread of the disease in the pediatric population. More data and further research is required to ascertain the effect of such precautions that might have helped in dampening the effect of the crisis in the pediatric population.

So, as we head further into the changed world in this new-normal era, it is only advisable to take proper precautions against this disease and the ‘invisible’ virus, about which we still do not know much.

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