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'Brain Fogging' in Special Needs Children– a Post–Covid Neurobiological Enigma

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ABSTRACT:

COVID-19 is associated with clinically significant symptoms- post-Covid syndromes, despite its immediate resolution. COVID-19 cases continue to experience the after-effects of the disease including multi-system dysfunctions, thus causing a drain-out of health resources in dealing with its aftermath. Post-COVID-19 syndrome is determined as signs and symptoms that appear during or after an infection consistent with SARS-CoV-2 disease, persist for more than 12 weeks, and are not explained by an alternative diagnosis. This review presents the most frequent neurological complaints associated with COVID-19 along with a recondite of brain fog. In the context of post-COVID-19, Pediatricians, as well as parents, should be aware of a wide spectrum of neurological COVID-19 signs and its association with impairments, commonly called ' brain fog'. Further, investigation of the molecular mechanism behind brain fog is suggested. Targeting the newly identified mechanisms may aid in finding newer molecules for treating brain fog. Though in adult Montreal cognitive tests for executive dysfunctions and Mini-mental state examination may help in suspecting it, in children, especially those with neurodevelopmental disorders it remains a challenge to differentiate it in the background of deterioration in performance. A careful history and clinical examination, especially assessing the short attention span in disorders like ADHD, clinches the diagnosis against the post-Covid brain fog. Demonstrating disruption of the blood-brain barrier and sustained inflammation in the brain by dynamic contrast-enhanced MRI may not be always feasible. Most other medical investigations are inconclusive or non-contributory. A battery of psychological tools

may help decipher the differences post-covid may help in analyzing the effects and subsequent corrective actions.

Keywords: Brain fog; Brain invasion; Cognitive impairment; COVID-19; Post-acute COVID-19 syndrome; brain fog; Long-COVID syndrome; Neurological problems; Neurodevelopmental disorders.

Introduction:

COVID-19 caused by infection with the Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) is known for its increased risk of neurological complications like encephalopathy, encephalomyelitis, ischemic stroke, intracerebral hemorrhage, anosmia, and neuromuscular disorders. Sometimes these symptoms following the infection may remain persistent [1] and were known differently as Post-Covid syndrome, permanent COVID-19, Long Covid syndrome, Brain fog, etc.; but of late they have been bought under the umbrella term- Post Acute COVID-19 Syndrome(PACS) [2,3]. This entity is defined by various studies as the continuation of acute SARS-CoV-2 infection symptoms and/or sequelae for more than 4–12 weeks following the start of initial symptoms [4,5]. A recent meta-analysis presents the global prevalence of PACS as 43%, with 54% of it occurring after hospitalization and 34% occurring in outpatients [6,7]. Brain fog was reported between 2% and 44% of children with long COVID, in a recent study [8]. A recent meta-analysis by Lopez-Leon et al. looked into 21 cohort studies covering a total population of 80,070 and found the persistence of Long COVID symptoms in 25.2% of children affected by acute COVID-19 [10]. This systematic analysis also throws light on neuropsychiatric symptoms in children, accordingly, mood swings, fatigue, sleep disorders, and cognitive dysfunctions (manifested by learning difficulty, lack of concentration, memory loss, and confusion) contribute to the pre-existing problems in children with NDD's.

Numerous neurological issues, such as encephalitis, cerebral venous embolism, micro- and macro hemorrhage, and encephalopathy, manifesting as delirium, altered levels of consciousness, and loss of various memory are reported with COVID-19 infection. This is collectively called "Cognitive Covid" [9]. Brain fog is a general nonmedical term used to describe cognitive impairment and confusion. A 6-month neurodevelopmental follow-up using the Bailey Scale of Infant Development done on high-risk new-borns who had Covid infection during the neonatal period showed significant deficits in the various developmental domains with motor domain (62.5%), cognitive domain (56.25%) and language domain (62.5%) affected [11]. Children with severe infections had more neurologic symptoms such as impaired vision, skeletal muscle impairment, and an elevated level of C-reactive protein in the plasma which may be related to macrophage activation syndrome [12]. A study done by Munblit et al. gives recommendations for selecting outcomes for assessment and quality data, based on which for the domain of cognitive functioning, outcomes to be quantified are confusion, concentration impairment, and memory impairment [13]. Unlike in adult studies that used the Montreal cognitive assessment or the MMS examination, in children, such tools have age and accuracy limitations [14]. A recent systematic review identified that post-Covid children developed concentration difficulties, indicating possible impairments in memory, and information processing speed, poor attention control, delirium, and psychiatric symptoms [15].

These observations were supported by other studies that reported that concentration difficulties,

attention impairment, and memory deficits were common in children with long-Covid syndrome. Further, they noted that cognitive symptoms were more common among female children, with cognitive and neurological symptoms being more common [16,17]. Deficits like attentional issues, working memory deficits, decreased processing speed, and executive dysfunctions were reported in a recent study [18]. This can have devastating effects on academic performance, more so in children with neurodevelopmental disorders. Long Covid syndrome was not found to be different in children when compared with adults, especially in the concentration and memory domains, which was proven by a recent study in which [^{18}F]-FDG PET scan showing hypo metabolism in the pons, cerebellum, and bilateral amygdala, uncus, and parahippocampal gyrus [19]. The hippocampus is an important part of memory formation. The parahippocampal cortex (PHC) is a major part of the medial temporal lobe which lies between the hippocampus and fusiform cortex. It helps in visuospatial processing and episodic memory, in addition to networking with multiple areas of the brain. PHC is been attributed to emotional processing, center-periphery organization along with the ventral visual stream, and a host of other functions including contextual associations [20]. Hence, the devastating effect COVID-19 can have on the developing brain concerning skill acquisition can be understood, especially in social and educational aspects.

Brain fog- a PACS nightmare or separate entity:

Executive functioning, memory encoding, processing speed, category fluency, recall, and post-COVID-19 course deficits are some of the cognitive impairments found during both the subacute phase and the subsequent course with both initially moderate and severe COVID-19 [21]. Fatigue and cognitive deficiencies coexist, frequently resulting in highly restricting, excessive, subjective exhaustion on a physical, cognitive, and/or psychological background [22,23]. The neuropsychological basis of "brain fog" can be explained by the slower information processing speed. Information processing speed is very much crucial for securing academic goals and overall social growth in children. A recent study on the prevalence of brain fog after the Omicron variant found that 7% of post-Covid children had brain fog and 70% had cognitive impairment at 12 months' post-infection with disturbed sleep and behavioral issues complicating it [23]. It may be noted that researchers have found that the 'cognitive covid' also varies with the strain affected. With the original virus and with every subsequent strain cognitive decline was noted when compared to controls. The greatest decline in IQ was noted with the original strain (before December 1, 2020) and the early B.1.1.7 (alpha) variant (from December 1, 2020, to April 30, 2021). A 3- 3-point loss equivalent of cognitive decline in those with mild infection and a 6-point equivalent decline in IQ was noted in those with persistent symptoms [24].

It has been observed that many neuro-divergent conditions like ADHD and Autism children experience "brain fog" even otherwise, often related to sensory overload, meltdown, and stress. Brain fogging also has been reported before with chemotherapy and other illnesses. Brain fog can also be brought on by stress, overworking, and sleep deprivation. Long-COVID (Brain fog) symptoms may mimic ADHD, but ADHD can be distinguished by a short attention span, difficulty in focusing and multitasking, and executive dysfunction. The differentiation becomes difficult in the predominantly inattentive form of ADHD as forgetfulness, difficulty in concentrating, and

following instructions are shared commonalities between the two conditions. Analysis of a few neurodevelopmental disorders revealed that ADHD had a causal relationship with 'hospitalized' COVID-19, while tuberose sclerosis conferred a causal relationship with 'critical admissions' for COVID-19, whereas Autism did not demonstrate any causal relationships [25]. Quite often, many neuropsychiatric symptoms of long COVID may be dismissed as common autism symptoms in ASD children. A recent case series reports that such presentations are common in ASD and the possible long-term activation of monocyte cytokines as a cause [26]. Whether this is a consequence of hypoxia, inflammation, or vascular damage to various connected regions of the brain or a separate entity in itself, like encephalopathy, continues to be an enigma.

Brain fog- due to direct viral invasion or consequence?

Brain fog may also be referred to as Neuro-fatigue; common in those who have had a brain injury, posttraumatic stress disorder (PTSD), or other mental or neurological problems. This fatigue or sleepiness is not the same as exhaustion caused by physical activity, insufficient sleep, or overworking. Confusion, forgetfulness, and a lack of attention and mental clarity characterize it.

Confusion, forgetfulness, loss of concentration, and mental clarity are symptoms of brain fog. Stress, sleep deprivation, and excessive internet usage among children with special needs can all contribute to this. This will manifest as poor concentration, spacing out, insomnia, confusion, thinking more slowly than usual, mood swings, fuzzy thoughts, forgetfulness, lost words, mental fatigue, etc. [27, 28]. This difference is glaring in NDD, especially in those well-behaved children with specific learning disabilities.

According to research, brain inflammation is the root cause of brain fog [29]. Brain fog is thought to be cellular, induced by high levels of inflammation and hormonal changes that affect mood, energy, and focus. An infection with SARS-CoV-2 can cause the body to produce immunological molecules that harm vascular endothelium, causing platelet aggregation and forming clots. Additionally, proteins seep out of the blood vessels, causing inflammation and neuronal death. When exposed to COVID, the immune hyperactivates, causing a simmering but eventually subsiding inflammation in the brain, or the virus itself directly damages the brain [30]. Though post-COVID cognitive impairment has been reported in many studies, including a few review articles, with most occurring in severe COVID-19 infection requiring ICU care, cognitive issues including decreased attention, and memory loss had been reported even in mild patients managed on an OP basis [31].

Mechanism of Brain fog:

Though a lot of studies have been done to examine the various aspects of cognitive symptoms, no single source has provided a thorough explanation of all the variables and how they interact that could contribute to the "brain fog" that patients feel. Scientists have attributed this to many aspects like hypoxia-induced damage, a surge in proinflammatory mediators, autoimmune activation leading to neuronal damage, microglial activation, and direct nerve tissue invasion [32]. Recent studies have shown that neuropilin-1, a membrane protein that is highly expressed in neurons, is one of the factors that helps SARS-CoV-2 enter nervous system cells. Researchers

also found microstructural alterations in the hippocampus and other brain regions, following Covid-19; which makes one believe that cognitive deficits might potentially be caused by these alterations [32]. However, SARS-CoV-2 RNA was not found in CSF in most published studies, and intrathecally produced SARS-CoV-2-directed IgG antibodies cannot be blamed for PCS [33]. In addition to usual mechanisms like hypoxia, and hippocampal atrophy following a vascular injury or after severe lung damage, there can be other contributors like a surge in proinflammatory mediators/ immune response or chronic inflammation. Interestingly, neurofilament, a marker of neuronal degeneration, is frequently elevated during acute infection with neurological manifestations, but not in PACS patients. This shows that an ongoing damage of neurons may not be the reason for brain fog; rather, it would result from a functional impairment of neurons. Neurons in the brain that are injured can't interact with one another. This may be one of the factors contributing to brain fog [34].

The orbitofrontal cortex controls emotion, pleasure, mood swings, depressive feelings, reasoning, and decision-making. The PHC also plays a critical role in emotion regulation, processing of spatial awareness, and memory recall [20]. An infection with COVID-19 affecting these areas can result in depression and anxiety, which can impair memory in a child- known as brain fog. Atrophy of the brain was also reported following Covid-19. They found that the virus especially in mild infection, did not affect the neurons, and produced brain fog through the mechanism with the cytokines/chemokines like CCL11. This supports the view that 'brain fog' acts through a mechanism similar to 'chemofog' a similar condition that presents in those who undergo chemotherapy for malignancy [32]. Of late a very recent study has come out with evidence for the reasons for brain fog. By doing dynamic enhanced contrast MRI, it was found that long-term blood-brain barrier disruption and sustained systemic inflammation result in Brain fog [35].

In related research on long-Covid, researchers have found that symptoms were related to lower circulating levels of serotonin through RNA virus-driven activation of type 1 interferon which decreases absorption of tryptophan (precursor of serotonin) and circulating serotonin (inside platelet) through hypercoagulability. This reduction in circulating serotonin levels by impeding the vagal stimulation impairs the hippocampal responses and memory. Considering the shreds of evidence available so far, a pictorial

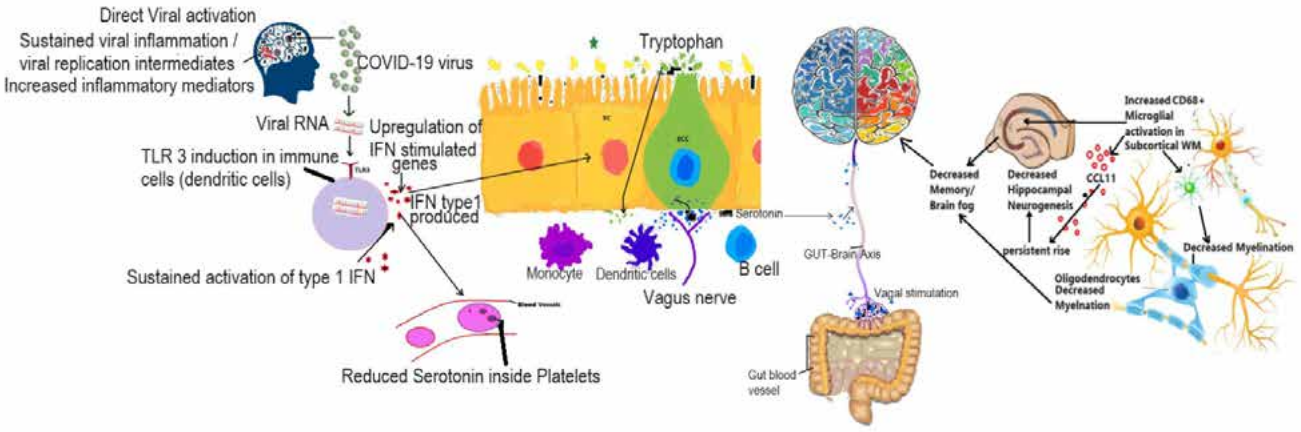

Figure:1 Pathophysiology behind Brain fog- neurochemicals, & role of Gut-brain axis

expression of the possible mechanism leading to this new issue affecting humans is proposed as in Figure 1.

Thus brain fog has been explained with a combination of various neurobiological processes, but a conclusive opinion remains elusive making it a continuing enigma.

Management:

Managing brain fog can be quite challenging, but there are no specific medications designed solely for treating it. However, addressing underlying factors and maintaining overall well-being can help alleviate brain fog. A multi-pronged approach for the evaluation of cognition, neuro-inflammatory markers, psychological factors, and sleep disorders should be used in the treatment of brain fog [36]. If sleep problems are present, assess disorders such as insomnia, obstructive sleep apnea, or restless legs syndrome in addition to late screen exposure.

Investigations:

Usual Brain MRI, awake and sleep EEG, and cardiological evaluation may be ordered, but are usually non-contributory to the issue at hand. Managing this challenge requires considerable effort on the part of a Developmental Pediatrician/ Pediatrician, as often they have to collaborate with a psychologist/psychiatrist. Parent especially the mother's concern for the child's health may be measured formally using some tools like the "thoughts" subscale of the "Health anxiety scale by proxy scale" or similar tools available. This is a 26-item Likert scale that addresses the intensity of thoughts, feelings, and behaviors of parental concern for the child's health [37]. Similarly, the child's mental health also may need to be assessed using the "*Strength and Difficult Questionnaire"* and Maternal perceptions of child health anxiety can be measured by "Health Anxiety Symptoms," a subscale of the *Soma Assessment Interview*. It is a parental interview assessing children's functional symptoms [38]. Memory may be checked by calculating age-appropriate digit span and clinical judgment. A formal cognitive battery testing may be useful as it often brings out deficits in memory, reasoning, and executive functioning in Brain fog children. Agata et al., have validated a Brain fog scale (BFS) with mental fatigue, impaired cognitive acuity, and confusion which has six items loading on the mental fatigue factor, nine items loading on the impaired cognitive acuity factor, and eight items loading on the confusion factor [39]. Deterioration of the autistic symptoms and the effect of interventions can be reliably quantified using the T-score of CARS-2 rather than the raw score-based severity ratings. ADHD often has severe manifestation due to the inherent nature of the disorder with 'brain fog', even otherwise part of it. Brown ADD scale may become handier in assessing school-going children affected by COVID-19 brain fog than the Vanderbilt ADHD rating scale. Its components viz, activation (organizing and activating to work), attention (sustaining attention& concentration), effort (sustaining energy& effort), affect (managing affective interference), and memory (using working memory and accessing recall) help in quick assessment of the functional impact on the child. PTSD and depression assessment may be considered especially in children admitted to ICUs for a long duration and may be quantified using relevant tools for the same.

Treatment:

The few possibilities available for treatment tried in adults are antiviral, Ensitrelvir, which was found to reduce the risk of long COVID-19

when started in the acute phase of COVID-19, and Metformin, when started within 7 days of COVID-19 infection, was shown to reduce the risk of long COVID in an RCT [40].

Brain fog is often accompanied by symptoms of fatigue which makes it difficult especially in activity-based learning attempted in children with special needs. This becomes more troublesome in hypoactive children with genetic autism or clumsy children as in developmental coordination disorder (DCD). Hence while attempting therapy sessions or assessing the deterioration this factor should be in the back of the mind of the paediatrician.

Neuropsychological evaluations are designed to detect cognitive impairments compared to an individual's peer group. They can also serve as a measurable outcome to address the impact of interventions in the treatment of brain fog post-COVID-19. Cognitive rehabilitation used for traumatic brain injury is often recommended for individuals with cognitive complaints. This includes patient education or "psychoeducation" along with training of cognitive skills which were deemed to be a weakness for that individual. This concept may be used by clinicians in the treatment of brain fog in adolescents and may be included as an educational component to provide an overview of brain fog. Such psychoeducation can detail the definition of brain fog, possible etiology, and general factors impacting the recovery process. When this psychoeducation is supported with group intervention with the patient's peers, the validation, reassurance, and access to qualified healthcare providers can facilitate recovery [41]. Using visual representation to make the learning disabled or NDD child understand will help in the process of counseling.

A brief cognitive-behavioral therapy (CBT) may be considered for older children with primarily cognitive complaints without a clinically significant mental health condition, to support adjustment to illness or disability. Such a brief CBT may include the applying skills required to manage cognitive complaints. Also, mildly symptomatic borderline IQ adolescents disinterested in individual psychotherapy may be offered support through formal or informal groups of other people experiencing persistent COVID-19 symptoms. While a formal evidence-based group treatment can alleviate symptoms, peer-led support groups offer connection and help to decrease feelings of isolation [42].

Other options and lifestyle modifications that could assist in overcoming brain fog include lowering brain inflammation through an anti-inflammatory diet (whole grains, lean meat, and plant-based foods) may help with symptoms of brain fog. Getting regular exercise -150 minutes of physical activity each week is recommended by the Centers for Disease Control and Prevention. Sleep deprivation can either increase or cause brain fog. Though the requirement of sleep for younger children is higher, a typical adolescent may require seven to eight hours of sleep every night to maintain their physical and mental health. Tech-savvy children and adolescents may benefit from strategic online chess. mindful breathing meditation, learning a new language. Guided imagery exercises can reduce stress and reduce brain fog by changing the focus of the mind to peaceful and positive images.

In a recent study on understanding the basis of Brain-fog due to Long Covid syndrome, it was found by single-nucleus RNA sequencing (snRNA-seq) analysis that COVID-19triggered the immune reactions in both microglia and astrocytes, and exacerbated oxidative stress in

oligodendrocytes, oligodendrocyte progenitors, and neurons. It was found to inhibit mitochondrial oxidative phosphorylation and suppress the expression of some mitochondrial complex genes. They suggested a holistic approach to protecting mitochondrial complex function, rather than targeting a single molecule, as an effective therapeutic strategy to prevent and treat the long-term consequences of "long COVID" [42]. It is in this context that the information on benefits and fast recovery following intake of some food supplements is to be considered. Fish oil containing long-chain Omega-3 fatty acid-DHA may help in recovery from inflammation [43]. Choline Bitartrate is chemically connected to the vitamin B group. Cell membranes and the synthesis of the neurotransmitter acetylcholine, which is involved in memory and muscular function, both depend on choline. γ-oryzanol was demonstrated to increase the central nervous system's neurotransmitter levels. Additionally, it encourages peaceful sleep and emotional relaxation. Ginkgo Biloba extract with its potent anti-inflammatory, antioxidant, platelet-forming, and circulation-boosting properties has been suggested to enhance mood, bring higher energy, and better memory, enhance cognitive function, and decrease symptoms associated with certain chronic illnesses [44]. Vitamin A, and B complexes not only help in better immune functions, but they also help in healthy cell development and proliferation. Its antioxidant properties shield cells from harm caused by free radicals, which is a further essential role. However, how far these theoretical benefits help in actual management is not conclusively proven.

Conclusion:

Even mild COVID-19 infection can result in a sustained inflammatory response resulting in sustained cytokine/chemokine elevations and disruption of the blood-brain barrier leading to brain fog in children. The effect of serotonin on the hippocampus also adds to the effect resulting in brain fog. The changes in memory, concentration, and confusion seen in children post covid has to be distinguished from the "brain fog" seen in some of the NDDs like ADHD or ASD. In the absence of an effective tool to measure it in children, identifying it clinically may be an option for differentiating it, especially in ADHD and ASD children. Currently, the options are mainly supportive and cognitive rehabilitation with psychological support.

Conflict of interest statement:

We hereby declare that there is no conflict of interest.

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