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Brain Injury and Neuroinflammation of the Gut-Brain Axis in Subjects with Cerebral Palsy

Ana Cristina Ferreira, Marcelo Freire, Vanessa Siqueira, Carolina Ferreira and Maria Teresa Santos

Abstract

Cerebral Palsy (CP) is a limiting deficiency, characterized by a permanent neuromotor disorder which affects movements, resulting in non-progressive lesions of the immature brain during the neuro psychomotor stages. Epidemiological studies of premature births correlated with the presence of high levels of inflammation in the umbilical cord, amniotic fluid, and fetal blood, being that one of the most relevant underlying physiopathological mechanisms includes inflammation and intra-amniotic infection, with inflammatory response and damage to the developing brain. Recently attributed to the excessive production of cytokines, CP inflammation is mostly modulated through diet restriction, intestinal dysfunction, and drug intake. The high prevalence of convulsive crises in individuals with CP (77%) on its own does not bring about post inflammatory and post convulsive cytokine synthesis, treated with antiepileptic medication. In these individuals, there is high incidence of intestinal constipation (47%), besides oral dysbiosis, gingival bleeding and even greater increase in chronic inflammation. The dysbiosis causes an increase in mucous permeability (leaky-gut) of the gut-brain axis, and increase in seric endotoxin, demonstrating a persistent inflammatory state, and supporting the emergence of new side effects, which can become the object of future research.

Keywords: cerebral palsy, brain injury, neuroinflammation, inflammation, cytokines, constipation, antiepileptic drugs

1. Introduction

Cerebral Palsy (CP) covers a group of disorders in the relative development of movement and posture, causing limitation in task execution, attributed to non progressive disturbances of the central nervous system (CNS), occurring during fetal development or in the immature brain. It is the most common cause of physical incapacitation in childhood [1–3].

Motor disturbance is the fundamental alteration caused by CP and must be present. However, other multiple comorbidities are observed such as intellectual deficit, learning difficulties, communication problems (language disturbances, delay in speaking),

ophthalmic (strabismus, visual deficit), otorhinolaryngological, (hearing deficit, mouth breathing), pneumological (recurrent pneumonias), gastroenterological (oropharyngeal dysphagia, gastroesophageal reflux), nutritional (diet, deglutition), neurological (epilepsy, hydrocephalus), orthopedic (limbs, spine deformity, osteoporosis), behavioral disturbances and proprioception (disturbances in sensorial integration) and impact on the secondary musculoskeletal, constipation and epilepsy **Figure 1** [1]. Although the structural damage to the immature brain is static and permanent, the consequences vary and can of change during the child's growth and development through physical rehabilitation and assisted individualized therapy [1].

The estimated prevalence of CP varies from 2.3 to 2.9 per 1000 live births in the United States. (National Infant Health Research 2011–2013) **Figure 1** [4]. About 80% of the causes of CP are attributed to intrauterine events such as inflammations, congenital infections, reduced oxygen delivery, and encephalic strokes [5]. The remaining 20% are due to occurrences at birth, such as peripartum suffocation, low birth weight, acute maternal viral infections during pregnancy and postnatal and early childhood factors caused by accidental and non accidental traumas, hypoxia, and infections like meningitis [5–7].

Individuals with CP can be classified according to the most dominant clinical characteristic [3]:

- Dyskinetic: the lesions are located in groups of neurons at the base of the brain and present atypical movements, which are more evident when the individual makes a voluntary movement [8].
- Ataxic: caused by a dysfunction in the cerebellum, presents generalized hypotonia with a loss of muscular coordination, characterized by abnormal force, rhythm and control or precision of movement [8].

Figure 1.
Characteristics that accompany the subject's life with Cerebral Palsy. (Figures Source: Adobe stock).

- Spastic: presents hypertonia, hyperreflexia, clonus, and signs of inadequate coordination, and insufficient selective muscular control. The spasticity causes a reduction in the joint movement, secondary contractions, bone deformity, joint dislocations, and chronic pain. The conditions of spasticity must also be classified according to the anatomical distribution: unilateral (monoplegic and hemiplegic) and bilateral (diplegic, triplegic, quadri/tetraplegic and with double hemiplegia) [8].

The deambulation classification form is based on the Gross Motor Function Classification System, which is widely and internationally used, categorizing individuals with CP in one of five levels based on functional mobility or limitations in activity: Level I (walking without limitations), Level II (walking with limitations), Level III (walking using a hand-held mobility device), Level IV (self-mobility with limitations) and Level V (transported in a wheelchair) [9].

Even though CP has diverse etiology, in the center of the disease's development, the effect of the inflammation regulates CP's clinical phenotypes.

2. Inflammation early in life

Intrauterine inflammation is observed in approximately 20% of all pregnancies and a surprising 85% of premature child-birth and is associated with a series of neurodevelopment disturbances [10]. Maternal respiratory and genitourinary infections which occur during prenatal hospitalizations and at the moment of birth, emphasize the role of the maternal inflammatory medium in CP's pathogenesis, even though one should not discard an additional causal path involving hypoxemia in the scenario of respiratory infections. Intrauterine infections, extra-uterine infections, and maternal extra-amniotics diagnosed in the hospital during a pregnancy are also associated with a moderately increased risk of pathology in the child [11].

Epidemiological studies of premature births correlate the presence of high levels of inflammatories in the umbilical cord, amniotic liquid and fetal blood with white matter injury, CP and damaged development. In truth, premature babies are born in a serious state of inflammation [12–14].

When there is an association between inflammation and infection, premature delivery may be initiated with ramification of the corona amniotic membranes to the amniotic liquid, resulting in systemic fetal inflammation, which can affect several organs, including the brain. Mothers in premature labor display elevated concentrations of Interleukin (IL)-6 and IL-8 in the amniotic liquid [12]. The most commonly found cytokines were: Tumor necrosis factor alpha (TNF- α), Interferon (IFN)-gamma, IL-1, IL-6 and IL-18 and the imbalance in these cytokines in the beginning of development can have deep and long-term impact on several illnesses, such as CP. These alterations can occur starting in the intrauterine life to early infancy. The cytokines probably exert their effects, and may include modulation of other immunological mechanisms [15]. These cytokines coordinate the host's immune response and mediate normal signalling between immune and non immune cells, including in the CNS [16]. Pro-inflammatory cytokine induction in the maternal infectious process or in the beginning of life demonstrated an adverse effect on neurodevelopment [17]. While certain cytokines are considered pro or anti-inflammatory, certain types may exhibit both properties in different situations [17]. Strategies must be elaborated to inhibit the imbalance effect of cytokines as a therapeutic way of preventing or treating neurological diseases [15]. Recently, attributed to deregulated production of cytokines, CP inflammation is mainly

modulated through dietary restrictions, intestinal dysfunction, and medication intake. Convulsions alone stimulate the pro-inflammatory and pro-convulsive cytokine synthesis in epileptic individuals [18].

3. Epilepsy

Epilepsy is a chronic cerebral disease characterized by recurrent unprovoked epileptic crises [19] of diverse etiology with consequences for the neurobiological, cognitive, psychological, and social planes/plans, negatively impacting the affected individual's quality of life [20, 21].

In the history of epilepsy there are accounts that in the neolithic period (Historical Period of Polished Stone X Millennium a. C.) trepanations were performed in skulls in order to free the bad spirits. Skulls scarred from these interventions were found in Egypt, Greece, Rome, the Orient, Equatorial Africa, in Mayan, Aztec and Brazilian indians, with curative objectives. In ancient Rome people with epilepsy were avoided for fear of contagion of the illness, and in the Middle Ages, they were pursued as witches [22].

In 1494, *Malleus maleficarum*, the witch hunting manual written by dominican priests linked to the Catholic Inquisition, was published. In this treatise, epileptic crises were a characteristic of witchcraft [23, 24]. This treatise's orientation led to the the persecution, torture, and death of more than 100.000 women, being that the majority were epileptics [23, 24].

Worldwide prevalence of active epilepsy is estimated around .5% to 1.0% of the population. The prevalence of epilepsy differs among ages, sex, ethnic groups, and socioeconomic factors [25]. The incidence of epilepsy adjusted for age in North America varies between 16 in 100,000 and 51 in 100,000 people per year. The adjusted prevalence by age varies from 2.2 in 1000 to 41 in 1000, depending on the country.

Partial epilepsy may constitute up to two thirds of incident epilepsies. The incidence increases in populations of lower socioeconomic status [25]. It is estimated that near 25–30% of the recently started crises are provoked or secondary to another cause. The incidence of epilepsy is higher in younger groups and continually increases after 50. The most common cause of convulsions and epilepsy in seniors is cerebrovascular disease [25, 26].

Among epilepsy's etiological factors, those that stand out are: electrolytic (hypoglycemia, hyponatremia, hypernatremia, hypocalcemia, use of drugs like Teofilina, Aminofilina, antidepressants, Ciclosporina, Cocaine, Crack, amphetamines, Lidocaine); acute toxic effects (antidepressants, sympathomimetics, others); irregular intake of prescribed antiepileptic medicine; Sepsis, infections in the CNS; hypoxic cerebral lesions; cranial traumatism; ischemic or hemorrhagic stroke; inflammatory neoplasma (lupus cerebritis); fever and sleep deprivation [27].

Epilepsies can be classified according to the axes: topographic and etiological. On the topographic axis, generalized epilepsies occur that are manifested by epileptic seizures that start in both hemispheres simultaneously. In general, they are genetically determined and accompanied by altered consciousness; when present, motor manifestations are always bilateral. Absence seizures, myoclonic seizures and generalized tonic-clonic seizures (GTC) are its main examples [28].

In focal epilepsies, the epileptic crises begin locally in a specific area in the brain, and their clinical manifestations depend on the starting point and the speed of the spread of the epileptogenic discharge. The crises are divided into simple focals (without affecting consciousness) and complex focals (at least partially affecting consciousness during the episode). Finally, a focal crisis, be it simple or complex,

when propagated throughout the cerebral cortex, can end up in a GTC, and denominated a secondarily generalized focal crisis [29].

The symptomatic convulsions occur during the course of many clinical and neurological diseases, are generally self limited and do not persist if the subjacent disturbance is corrected. There may occur a reaction in the brain to physiological stress like sleep deprivation, fever, and abstinence from alcohol or other drugs such as sedatives. Other causes of symptomatic convulsions are hypertensive encephalopathy, renal insufficiency, sickle cell anemia, idiopathic thrombocytopenic purpura, systemic lupus, erythematosus, meningitis, encephalitis, traumatic brain injury and stroke. In these situations the cerebral function is temporarily compromised [21].

It must be pointed out, regarding characteristics of symptomatic convulsions, that fever is the most common cause of convulsions in children between six months and four years of age, with 30% chance of another convulsion, increasing the risk of subsequent epilepsy, though not associated, and do not cause intellectual deficit [21].

The objective of epilepsy treatment is to provide the best quality of life possible for the person with epilepsy, through adequate control of crises, and a minimum of adverse effects. Seventy percent of people that have epilepsy take control of the crises with the appropriate use of anticonvulsant medicine [30].

Epilepsy is one of the most common comorbidities associated with motor damage in individuals with CP, and affects close to 77% of that population [30]. Clinical treatment for epilepsy is based on long term antiepileptic drug therapy which reduces the frequency of crises, raising the threshold of motor neurons in the cortex, reducing abnormal electrical discharges of the brain and limiting the dissemination of the excitement of the abnormal foci [29].

The antiepileptic pharmaceuticals act through different mechanisms which may or may not be favorable for the treatment [31]. The antiepileptic pharmaceuticals act through one or several mechanisms such as increasing gabaergic inhibition, blocking sodium channels, blocking calcium channels or connecting to protein SV2A of the synaptic vesicle [32].

Regarding gamma-aminobutyric acid, (GABA) it was possible to identify specific benzodiazepine receptors in the CNS structures, principally in the limbic system, allowing the comprehension of the action mechanism of these medications. By connecting to these receptors, the benzodiazepines facilitate GABA's action, which is the primary inhibitory neurotransmitter of the CNS. The specific activation of GABA receptors induces the opening of chloride channels in the neuron membrane, amplifying the influx of this anion into the cell, which results in decreased excitability and the spread of excitatory impulses. Among the effects observed for these drugs are described the reduction of salivary flow, the vomiting reflex and the relaxation of skeletal muscles [33].

Voltage-dependent Na^+ is one of the principal channels responsible for the rapid depolarization of the widely and disorganized presence and neuronal membrane in the epileptic processes [34]. These channels represent the important site of connection for several antiepileptic drugs such as hydantoin, carbamazepine, valproic acid, lamotrigine, among others [33].

The first evidence of the possible participation of channels Ca^{2+} dependent on voltage in epilepsies came from the verification that the accentuated reductions in extracellular concentration of this ion can create epileptic activity in cerebral tissue such as the dentate gyrus and other hippocampal structures. It is known that the acute increase in Ca^{2+} influx is important to maintain the reflex hyperexcitability, which occurs in convulsive processes. In this context, the Ca^{2+} channels dependent on voltage have an important role in the functional processes of the nervous system. For example, the presynaptic Ca^{2+} entry is associated with the liberation

of these neurotransmitters and to their postsynaptic entry with sustained neuron depolarization. Blocking the Ca^{2+} channels can produce several effects on the neuronal functioning: (a) blocking Type T channels (associated to absence crisis treatment); (b) blocking type L channels (associated with partial crisis treatment); (c) blocking Ca^{2+} channels can prevent the liberation of excitatory neurotransmitters such as glutamate and (d) blocking these channels reduces the concentration of Ca^{2+} ions in the neuronal cytoplasm, reducing the possibility of excitotoxic cellular damage [33].

The first study, which evaluated the association between intestinal constipation, use of antiepileptic drugs (AEDs), and gingivitis in subjects with spastic CP, was published by our work group (**Figure 2**) [35]. It was clearly demonstrated an association between intestinal constipation and the use of GABA antiepileptic drugs (phenobarbital, primidone, benzodiazepines including diazepam, lorazepam, and clonazepam; topiramate, felbamate, ezogabine); GABA transporter tiagabine; GABA transaminase (vigabatrin); synaptic release machinery SV2A (levetiracetam, brivaracetam $\alpha 2\delta$ gabapentin, gabapentin enacarbil, pregabalin).

Figure 2. Gingival bleeding and medication type: bleeding is measured by the percentage of teeth which bled after periodontal probing. Each kernel density estimation plot shows clustering by the type of medication taken by subjects. (A) Green figure show constipated subjects; (B) blue figure show non-constipated subjects; (C) Green-to-Blue figure show the full population.

It was described that the use of AEDs should be considered as a causal factor of constipation in CP subjects. A wide range of AEDs has been used either in the form of monotherapy or polytherapy for seizure control. Monotherapy has the advantage of lowering the potency of toxicity and side effects. Nevertheless, polytherapy may be recommended for the most neurologically compromised, despite its greater side effects and toxicity to the users of this treatment modality. GABA is localized in the gastrointestinal tract and is present in enteric nerves [35].

Regarding those people with epilepsy, it is necessary to emphasize the caution needed in the occurrence of a GTC in an odontological office. It characteristically occurs in two phases: Initially there is loss of consciousness followed by muscular convulsions. The steps to be taken are to immediately stop the odontological procedure, position the patient in lateral decubitus, and activate the medical emergency system.

Another situation to be observed is the possibility of leukopenia and thrombocytopenia induced by antiepileptic drugs such as phenytoin, carbamazepine, and valproic acid, requiring the request for additional tests (blood count).

Another prevalent condition refers to drug-induced gingival overgrowth, also referred to as drug-induced gingival enlargement, and previously known as drug-induced gingival hyperplasia, is a side-effect of certain drugs where the gingival tissue is not the intended target organ. The key offending drug classes are anticonvulsants, immunosuppressants, and calcium channel blockers [36]. Gingival overgrowth impedes proper dental hygiene and, apart from the cosmetic damage, causes painful chewing and eating. Therefore, patient education and information about the condition and its management are essential.

4. Gut-brain axis

The gut-brain axis is an information exchange platform which allows bidirectional communication between the host's intestine and nervous system. The information can be exchanged through a neural network, hormones, and immunological system [37].

The enteric nervous system consists of approximately 200 million neurons which control the entire digestive tract. It is composed of a web of intrinsic nerve fibres and ganglia, the myenteric and the submucous plexus. The myenteric plexus mainly controls motility of the digestive tract (peristalsis) and is located deep between the longitudinal and the circular layers of the entire digestive tract. It is mainly composed by a network of ganglia connected by unmyelinated fibres which are connected to the vagus nerve and to sympathetic ganglia. The submucous plexus (Meissner plexus) is located more superficially and closer to the intestinal lumen. It is mainly composed by nerve fibres and ganglia which control the mucous secretions, vascular flow and absorption [38]. The vagus nerve allows the direct connection between the intestine and the brain. By controlling motility and intestinal secretion, the vagus nerve can alter the intestinal environment and the response to the enteric immunological system with direct consequence to the intestinal microbiota. On the other hand, the intestinal bacteria produce metabolites which can influence the CNS and enteric and affect the production of neurotransmitters, such as GABA, acetylcholine, and the serotonin precursor, tryptophan [39].

Intestinal microbiota composition is regulated by extrinsic factors, such as lifestyle, precocious exposure to microbiota and diet, and intrinsic factors, such as metabolism, genetic history and the host's immunological and hormonal systems activity [40]. Intestinal dysbiosis can have an infinite amount of consequences for

the CNS. Microbes can stimulate the liberation of small molecules, like cytokines, and produce metabolites which work as neuromodulators, such as short-chain fatty acids (SCFAs), GABA and serotonin precursors [41–43].

One of the most studied extrinsic factors is diet, since it can alter the intestinal microbiota. Epidemiological studies show a positive correlation between the increase in risk of cognitive decline and high ingestion of animal protein, refined sugar and foods with high content of saturated fats [44]. Patients with refractory epilepsy can benefit from a ketogenic diet, since it can influence the intestinal microbiota [39]. The commensal bacteria in the intestine degrade the dietary fibre and lead to the production of SCFA, which are beneficial to the brain [44].

SCFAs are important bacterial metabolites which can reduce the inflammatory response, promote CNS plasticity, and increase the hematoencephalic permeability [45]. An exacerbated inflammatory response in the hippocampus is associated with a diet rich in fructose, and can be a consequence of alterations in intestinal bacteria [46].

Colonization with *Akkermansia Mucinophila* e *Parabacteroides* bacterias offers protection against convulsions, altering the level of cerebral neurotransmitters in the hippocampus, including GABA and glutamate. Intestinal microbiome dysbiosis can alter GABA, which is the main inhibitory neurotransmitter in the brain, and the reduced levels have been known to exacerbate convulsions [47–49]. But the reduction of *Prevotellaceae* and increase of *Lactobacillaceae* are related to neuroinflammation and were discovered in neurodegenerative diseases such as Parkinson's Disease [49]. An increase in *Proteobacteria* and *Cronbacteria* was found in patients with epilepsy [50]. Individuals with epileptic CP (CPE) exhibited lower proportions of *Anaerostipes*, *Faecalibacterium* e *Bacteroides* [51] which can produce butyrate with acetate [52] since butyrate can stimulate the differentiation of regulatory T cells (Treg) and relieve the neuroinflammation charge [53]. Nevertheless, great quantities of acetate would accumulate in these individuals, which could activate the parasympathetic nervous system [54] and unchain a convulsion. Besides that, the reduction of *Bacteroids* would also reduce butyrate secretion and attenuate its neuroprotector effect in patients with CPE [53]. On the other hand, a greater abundance of *Enterococcus*, *Bifidobacterium*, *Clostridium* IV and *Akkermansia* were discovered in patients with CPE [51]. A deeper analysis of the microbial functions revealed an increased systemic immunological and neurodegenerative diseases in patients with CPE [51], and that neuroinflammation probably carried out a fundamental role in CPE pathology [55].

Dysbiosis and frequency of epileptic events are frequently correlated, suggesting that the drugs can interact directly with the intestinal microbiota, modifying their metabolism and, therefore, affecting the efficacy and toxicity of the drugs [56]. Drugs are transformed into bioactive metabolites, inactive or toxic through direct microbial action or host-microbial co-metabolism. These metabolites are responsible for therapeutic effects or collateral effects induced by these medications [57]. Alteration in the microbiome can affect absorption and medicine metabolism, influencing their efficacy and resistance to the drug [58].

The antiepileptic medication is normally used in long-term clinical treatment, and for this reason can cause serious collateral effects in the childhood development of patients with CP and epilepsy, such as: gastrointestinal complications including oral dysbiosis, gingival bleeding (GB) and increase in systemic inflammation [35, 59].

CP's inaccessibility and vulnerability to oral care and consequently the development of caries and gingival diseases can also phenotypically affect the intestine

through the microbiome’s oral-intestine axis. These facts do not alone indicate alterations in the microbiome, but indicate that the gingival bleeding index suggests dysbiosis in the host-microbial interactions in the oral mucosa interface which then can influence an individual’s systemic inflammatory profile.

Current literature indicates that intestinal disturbances play a prominent role in inflammatory responses and neurological conditions [60]. This line of evidence is fundamental in identifying the effects of dysbiosis in mucosa inflammation in the entire digestive tract. Significantly higher levels of IL-1 β , IL-6, IL-8 and IL-10 were found in constipated individuals with GB (**Figure 3**), besides this, presence of chemokine IL-8 induces the secretion of lymphocytes, monocytes, epithelial cells, fibroblasts, tumor cells, bone reabsorption and IL-1 β [61, 62], indicating a continuous inflammatory process and progression of the periodontal disease [61–64]. The use of this medication caused individuals with CP to present reduced salivary flow, increase in the salivary osmolarity, dry mouth and gingivitis, which is represented by elevated levels of inflammatory cytokines in tetraplegics [59].

There is an elevated risk of immunological system diseases in these vulnerable individuals, and oral and intestinal dysbiosis is attributed to an exacerbated increase of Akkermansia in patients with CPE [51]. The excessive increase in Akkermansia would degrade the mucin in the mucous layers and would increase the mucous permeability [65], which allows for more bacterial antigens to be exposed to the host’s immunological system, unchaining systemic immune reactions in individuals with CPE.

Figure 3. Constipation actions on Inflammatory Cytokine Levels. Distributions of each measured cytokine—(A) TNF α , (B) IL1 β , (C) IL6, (D) IL8, and (E) IL10—in constipated subjects (blue) and non-constipated subjects (green) are mapped using a violin plot. White dots mark the means, bars show the inner quartiles, and whiskers mark the 5% confidence interval.

5. Correlation between covid-19, brain injury and neuroinflammation

Vulnerable children are those with neurological diseases and lung problems, requiring respiratory care [66]. This situation is currently a priority with the advent of the new coronavirus disease of 2019 (COVID-19). This is a zoonotic virus, an enveloped RNA, which can be transmitted from a sick person to another by close contact through touch, handshake, droplets of saliva, sneeze, cough, phlegm and contaminated objects or surfaces [67, 68].

It was first detected in December 2019 and became an epidemic in Wuhan, Hubei province, China and quickly spread to several countries on six continents [69]. On March 11, 2020, the World Health Organization announced that COVID-19 was characterized as a pandemic, threatening global public health and creating a record economic burden. Coronaviruses are a large family of viruses that cause diseases such as the common cold to more serious diseases, such as Severe Acute Respiratory Syndrome (SARS). A new coronavirus is typically a new strain of infectious disease that has not been previously identified in humans [70].

The new 2019 coronavirus, coronavirus 2 of the severe acute respiratory syndrome (SARS-CoV-2) appeared after six other human coronaviruses. Four common human coronaviruses which cause light to moderate illness of the superior respiratory tract, including 229E (coronavirus alpha), NL63 (alpha coronavirus), OC43 (beta coronavirus) and HKU1 (beta coronavirus), were registered for the first time in the 60's [71]. Two other human coronaviruses are SARS-CoV and MERS-CoV, which cause grave infections to pulmonary lesions, known as Severe Acute Respiratory Sickness (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV), respectively. The MERS-CoV outbreak occurred in 2012, starting in Saudi Arabia and spreading to other countries with a mortality rate of 37% [71, 72].

These are the diagnostic criteria [73]:

1. Asymptomatic Infection: without symptoms and clinical signs and normal thorax image, while the 2019 nCoV nucleic acid test is in a positive period.
2. Light: Acute symptoms of infection of the superior respiratory tract, including fever, fatigue, myalgia, cough, sore throat, coryza and sneezing. The physical exam shows pharyngeal congestion and absence of auscultatory abnormalities. Some cases may not have fever or only present digestive symptoms such as nausea, vomit, abdominal pain and diarrhea.
3. Moderate: with pneumonia, fever and frequent coughs, especially dry cough, followed by productive cough, some may have a chest wheezing, but no obvious hypoxemia, with lack of air or dry wheezing and or wet wheezing. Some cases may not have signs or clinical symptoms but the Computerized Tomography of the thorax shows subclinical pulmonary lesions.
4. Serious: precocious respiratory symptoms, such as fever and cough, can be followed by gastrointestinal symptoms, such as diarrhea. The disease generally progresses for about one week and dyspnoea occurs, with central cyanosis. Oxygen saturation is inferior to 92%, with other manifestations of hypoxia
5. Critical: Children can rapidly progress to acute respiratory distress symptom or respiratory insufficiency and can also present shock, encephalopathy, myocardial or cardiac injury, coagulation dysfunction, and acute renal lesion. The organic dysfunction can be fatal.

The majority of discussions based on evidence demonstrate the power of privilege during a pandemic, where it is indicated that the most vulnerable, such as seniors, people with deficiencies and aborigenes, will be the most impacted [74].

Children of all ages are sensitive to Covid-19, and there is no significant difference between the sexes. The clinical manifestations of cases of children with Covid-19 were less serious than those of adult patients. Nevertheless, small children, especially babies, are also vulnerable to infection by Covid-19 [75]. Many families have to live in just one room with shared bathrooms and kitchen, causing overcrowding and making self isolation impossible in confined spaces. Many times, the children have inadequate space to crawl or play, and no access to fresh air. The duration of the outbreak is not clear and these children are more vulnerable both to the primary as well as the secondary effects, it is absolutely vital that they are no longer marginalized [76].

Antiviral immunity includes innate and adaptive immune responses. There are different innate immune receptors, the Toll like receptors (TLRs) are more intimately related to adaptive immune responses, therefore the TLRs are important antiviral immunity elements [77]. After a virus is recognized, the TLR signaling positively regulates the expression of pro-inflammatory cytokines and co-stimulatory molecules, through the accumulation of interferons (IFNs). Consequently, the adaptive antimicrobial immunity is processed by co-stimulatory molecules [78].

Patients with serious SARS-CoV infection show an aberration of the innate immune system. Particularly, the induction of proinflammatory cytokines, IFNs type I and genes stimulated by interferon (ISG) would suffer oscillations clearly favorable to SARS-CoV. The liberation of cytokines and pro-inflammatory chemokines occurs on the first day of infection. High levels of proinflammatory cytokines in patients with SARS-CoV are correlated to symptoms of respiratory discomfort in old animals. The IFNs can help to control the replication of SARS-CoV. Therefore, it is possible to suppose that other innate immunological mechanisms will have an essential role in immunity against SARS-CoV [79].

A certain subgroup of the population of T cells develops a cytokine storm during initial stages of the SARS-CoV-2, involving cytokines and chemokines from the beginning until the other phases of the illness. In its initiation phase, SARS-CoV-2 would increase the plasma concentration of different cytokines, including IL-1 β , IL-1R α , IL-7, IL-8, IL-9, IL-10, basic FGF G CSF, GMCSF, IFN γ , IP10, MCP1, MIP1A, MIP1B, PDGF, TNF- α and endothelial vascular growth factor. Critical patients interned in intensive care units (ICUs) presented higher levels of IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A and TNF α compared to those who did not need to be in the ICU. In SARS-CoV-2, there appears to be an interaction between different subsets of the population of T-helper cells (Th), for example, Th1, Th2 and Treg [80].

Both winter and low humidity act as stressors for the immune system. Evidence shows an association between cold temperatures and low humidity with respiratory tract infections whereby the lower the temperature/humidity, the greater the infections in the respiratory tracts of the population [81].

Precocious induction of interferon-gamma (IFN- γ) in viral infections, indicates a battle between innate immunity and the virus, so the immune system would start with a fever, to allow the expression of TLR4, and would unchain a series of antiviral immune responses characterized by the production of cytokines. In almost 99% of cases, the most common initial symptom of SARS-CoV-2 is fever [82].

Evidence points to the effect of this new coronavirus in inhibiting antiviral immune responses and, therefore, its powerful capacity to replicate in the host cells. On the other hand, SARS-CoV-2 demonstrated a greater rate of incidence of

mortality in the senior population and in people with certain comorbidities which are known since they have differences in their immune profile [83].

Comorbidity is present in more than 30% of cases of infection with SARS-CoV-2 [80]. Organized by related mortality rates, the chronic conditions in victims with the virus include cardiovascular diseases, diabetes, chronic respiratory diseases, hypertension and cancer. All of these conditions, in the long run, tend to make the immune system imperfect, both in innate and adaptive terms in the immune functions [84].

Brain injury caused by hypoxia increases the risk of developing epilepsy that is difficult to control. In the presence of infection by SARS-CoV-2, there is greater susceptibility to the occurrence of convulsions, increasing their vulnerability.

6. Conclusion

Dysbiosis causes an increase in mucous permeability (leaky-gut) of the gut-brain axis, and increase in serum endotoxin, demonstrating a persistent inflammatory state, and supporting the emergence of new side effects, which can become the object of future research.

Abbreviations

CP	Cerebral Palsy
CNS	Central nervous system
IL	Interleukin
TNF- α	Tumor necrosis factor alpha
IFN	Interferon
GABA	Gamma-aminobutyric acid
AEDs	Antiepileptic drugs
SCFAs	Short-chain fatty acids
CPE	Cerebral Palsy epileptic
GTC	generalized tonic-clonic seizures
GB	Gingival Bleeding
COVID-19	Coronavirus disease 2019
SARS	Severe Acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
MERS	Middle East Respiratory Syndrome
TLR	Toll like receptor
ICU	intensive care unit
Th	T-helper cells

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