

Chapter

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].
Brain Injury and Neuroinflammation of the Gut-Brain Axis in Subjects with Cerebral Palsy
DOI: http://dx.doi.org/10.5772/intechopen.95763

- 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 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; Sepse, 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 thrombocyto-
penic 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
cri ses 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 medica-
tions. 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 mem-
brane 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 depen-
dent 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 α2δ 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
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 Mucinophilia 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 Lactobacilliaceae 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-1β, 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-1β [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) TNFα, (B) IL1β, (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 hipoxemia, 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-1β, IL-1Ra, IL-7, IL-8, IL-9, IL-10, basic FGF G CSF, GMCSF, IFNγ, 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 TNFα 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

| Abbreviation | Description |
|--------------|-------------|
| CP           | Cerebral Palsy |
| CNS          | Central nervous system |
| IL           | Interleukin |
| TNF-α        | Tumor necrosis fator 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           | Gengival 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 |
Brain Injury and Neuroinflammation of the Gut-Brain Axis in Subjects with Cerebral Palsy
DOI: http://dx.doi.org/10.5772/intechopen.95763

Author details

Ana Cristina Ferreira1*, Marcelo Freire2,3, Vanessa Siqueira1, Carolina Ferreira1 and Maria Teresa Santos1

1 Department of Individuals with Special Needs, Postgraduate Program in Dentistry, Cruzeiro do Sul University, São Paulo, Brazil

2 Department of Genomic Medicine and Infectious Diseases, J. Craig Venter Institute, 4120 Capricorn Lane, La Jolla, California, USA

3 Department of Infectious Diseases School of Medicine, University of California San Diego, La Jolla, California, USA

*Address all correspondence to: anacristina.ferreira@gmail.com

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
References

[1] Bax M, Goldstein M, Rosenbaum P, Leviton A, Paneth N, Dan B, et al. Proposed definition and classification of cerebral palsy, April 2005 [Internet]. Vol. 47, Developmental Medicine & Child Neurology. 2005. p. 571-6. Available from: http://dx.doi.org/10.1017/s001216220500112x

[2] O’shea TM. Diagnosis, Treatment, and Prevention of Cerebral Palsy [Internet]. Vol. 51, Clinical Obstetrics and Gynecology. 2008. p. 816-28. Available from: http://dx.doi.org/10.1097/grf.0b013e31870ba7

[3] Cans C, Dolk H, Platt MJ, Colver A, Prasauskene A, Rägeloh-Mann IK. Recommendations from the SCPE collaborative group for defining and classifying cerebral palsy. Developmental Medicine & Child Neurology [Internet]. 2007 Feb;49:35-38. Available from: http://doi.wiley.com/10.1111/j.1469-8749.2007.tb12626.x

[4] Maenner MJ, Blumberg SJ, Kogan MD, Christensen D, Yeargin-Allsopp M, Schieve LA. Prevalence of cerebral palsy and intellectual disability among children identified in two U.S. National Surveys, 2011-2013. Ann Epidemiol [Internet]. 2016 Mar;26(3):222-6. Available from: http://dx.doi.org/10.1016/j.annepidem.2016.01.001

[5] Tollanes MC, Wilcox AJ, Lie RT, Moster D. Familial risk of cerebral palsy: population based cohort study [Internet]. Vol. 349, BMJ. 2014. p. g4294–g4294. Available from: http://dx.doi.org/10.1136/bmj.g4294

[6] Johnson A. Prevalence and characteristics of children with cerebral palsy in Europe [Internet]. Vol. 44, Developmental Medicine & Child Neurology. 2002. Available from: http://dx.doi.org/10.1017/s0012162201002675

[7] Schendel D. Executive summary: neonatal encephalopathy and neurologic outcome, Report of the American College of Obstetricians and Gynecologists’ task force on neonatal encephalopathy. Obstet Gynecol. 2014;123(4):896-901.

[8] Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl [Internet]. 2007 Feb;109:8-14. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17370477

[9] Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol [Internet]. 1997 Apr;39(4):214-223. Available from: http://dx.doi.org/10.1111/j.1469-8749.1997.tb07414.x

[10] Elovitz MA, Brown AG, Breen K, Anton L, Maubert M, Burd I. Intrauterine inflammation, insufficient to induce parturition, still evokes fetal and neonatal brain injury [Internet]. Vol. 29, International Journal of Developmental Neuroscience. 2011. p. 663-71. Available from: http://dx.doi.org/10.1016/j.ijdevneu.2011.02.011

[11] Bear JJ, Wu YW. Maternal Infections During Pregnancy and Cerebral Palsy in the Child. Pediatr Neurol [Internet]. 2016 Apr;57:74-79. Available from: http://dx.doi.org/10.1016/j.pediatrneurol.2015.12.018

[12] Dammann O, O’Shea TM. Cytokines and perinatal brain damage. Clin Perinatol [Internet]. 2008 Dec;35(4):643-663, v. Available from: http://dx.doi.org/10.1016/j.clp.2008.07.011
[13] Malaeb S, Dammann O. Fetal inflammatory response and brain injury in the preterm newborn. J Child Neurol [Internet]. 2009 Sep;24(9):1119-1126. Available from: http://dx.doi.org/10.1177/088307380938066

[14] Carlo WA, McDonald SA, Tyson JE, Stoll BJ, Ehrenkranz RA, Shankaran S, et al. Cytokines and neurodevelopmental outcomes in extremely low birth weight infants. J Pediatr [Internet]. 2011 Dec;159(6):919-25.e3. Available from: http://dx.doi.org/10.1016/j.jpeds.2011.05.042

[15] Kuban KCK, Joseph RM, O'Shea TM, Heeren T, Fichorova RN, Douglass L, et al. Circulating Inflammatory-Associated Proteins in the First Month of Life and Cognitive Impairment at Age 10 Years in Children Born Extremely Preterm. J Pediatr [Internet]. 2017 Jan;180:116-23.e1. Available from: http://dx.doi.org/10.1016/j.jpeds.2016.09.054

[16] Estes ML, McAllister AK. Maternal immune activation: Implications for neuropsychiatric disorders. Science [Internet]. 2016; Available from: https://science.sciencemag.org/content/353/6301/772.abstract

[17] Goeden N, Velasquez J, Arnold KA, Chan Y, Lund BT, Anderson GM, et al. Maternal Inflammation Disrupts Fetal Neurodevelopment via Increased Placental Output of Serotonin to the Fetal Brain. J Neurosci [Internet]. 2016 Jun 1;36(22):6041-6049. Available from: http://dx.doi.org/10.1523/JNEUROSCI.2534-15.2016

[18] Młodzikowska-Albrecht J, Steinborn B, Zarowski M. Cytokines, epilepsy and epileptic drugs--is there a mutual influence? PharmacoL Rep [Internet]. 2007 Mar;59(2):129-38. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17556791

[19] Epilepsy: A Comprehensive Textbook. JAMA [Internet]. 2008 Jul 23 [cited 2020 Dec 10];300(4):442-6. Available from: https://jamanetwork.com/journals/jama/article-abstract/182267

[20] Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia [Internet]. 2005 Apr;46(4):470-472. Available from: http://dx.doi.org/10.1111/j.0013-9580.2005.66104.x

[21] Huff JS, Murr N. Seizure. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28613516

[22] Gomes M da M. História da epilepsia: um ponto de vista epistemológico. J epilepsy clin neurophysiol [Internet]. 2006 [cited 2020 Dec 10];12(3):161-7. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1676-26492006000500009&lng=pt&tlng=pt

[23] Riggs AJ, Riggs JE. Epilepsy’s Role in the Historical Differentiation of Religion, Magic, and Science [Internet]. Vol. 46, Epilepsia. 2005. p. 452-3. Available from: http://dx.doi.org/10.1111/j.0013-9580.2005.55405.x

[24] Masia SL, Devinsky O. Epilepsy and behavior: a brief history. Epilepsy Behav [Internet]. 2000 Feb;1(1):27-36. Available from: http://dx.doi.org/10.1006/ebeh.1999.0021

[25] Banerjee PN, Filippi D, Allen Hauser W. The descriptive epidemiology of epilepsy-a review. Epilepsy Res [Internet]. 2009 Jul;85(1):31-45. Available from: http://dx.doi.org/10.1016/j.eplepsyres.2009.03.003

[26] Sen A, Jette N, Husain M, Sander JW. Epilepsy in older people
Advancement and New Understanding in Brain Injury

[27] Lowenstein DH, Alldredge BK. Status epilepticus at an urban public hospital in the 1980s [Internet]. Vol. 43, Neurology. 1993. p. 483-483. Available from: http://dx.doi.org/10.1212/wnl.43.3_part_1.483

[28] Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia [Internet]. 1981 Aug;22(4):489-501. Available from: http://dx.doi.org/10.1111/j.1528-1157.1981.tb06159.x

[29] Elger CE, Schmidt D. Corrigendum to “Modern management of epilepsy: A practical approach” [Epilepsy Behav 12 (2008) 501-539] [Internet]. Vol. 13, Epilepsy & Behavior. 2008. p. 575. Available from: http://dx.doi.org/10.1016/j.jyebeh.2008.06.018

[30] Bearden DR, Monokwane B, Khurana E, Baier J, Baranov E, Westmoreland K, et al. Pediatric Cerebral Palsy in Botswana: Etiology, Outcomes, and Comorbidities. Pediatr Neurol [Internet]. 2016 Jun;59:23-29. Available from: http://dx.doi.org/10.1016/j.pediatrneurol.2016.03.002

[31] Perucca E. An Introduction to Antiepileptic Drugs [Internet]. Vol. 46, Epilepsia. 2005. p. 31-7. Available from: http://dx.doi.org/10.1111/j.1528-1167.2005.463007.x

[32] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies [Internet]. Vol. 51, Epilepsia. 2009. p. 1069-77. Available from: http://dx.doi.org/10.1111/j.1528-1167.2009.02397.x

[33] Moloney PB, Costello DJ. Unanticipated improvement in seizure control in drug-resistant epilepsy- real world observations. Seizure [Internet]. 2020 Nov 21;84:60-5. Available from: http://dx.doi.org/10.1016/j.seizure.2020.11.005

[34] Kwan P, Sills GJ, Brodie MJ. The mechanisms of action of commonly used antiepileptic drugs. Pharmacol Ther [Internet]. 2001 Apr;90(1):21-34. Available from: http://dx.doi.org/10.1016/s0140-6736(19)33064-8

[35] Ferreira ACFM, Mayer MPA, Kawamoto D, Santos MTBR. Constipation, antiepileptic drugs, and gingivitis in children and adolescents with cerebral palsy. Int J Paediatr Dent [Internet]. 2019 Sep;29(5):635-641. Available from: http://dx.doi.org/10.1111/ipd.12488

[36] Marshall RI, Bartold PM. Medication induced gingival overgrowth. Oral Dis [Internet]. 1998 Jun;4(2):130-151. Available from: http://dx.doi.org/10.1111/j.1601-0825.1998.tb00269.x

[37] Collins SM, Surette M, Bercik P. The interplay between the intestinal microbiota and the brain. Nat Rev Microbiol [Internet]. 2012 Nov;10(11):735-742. Available from: http://dx.doi.org/10.1038/nrmicro2876

[38] Furness JB, Callaghan BP, Rivera LR, Cho H-J. The Enteric Nervous System and Gastrointestinal Innervation: Integrated Local and Central Control [Internet]. Advances in Experimental Medicine and Biology. 2014. p. 39-71. Available from: http://dx.doi.org/10.1007/978-1-4939-0897-4_3

[39] Olson CA, Vuong HE, Yano JM, Liang QY, Nusbaum DJ, Hsiao EY. The Gut Microbiota Mediates the Anti-Seizure Effects of the Ketogenic Diet. Cell [Internet]. 2018 Jul 12;174(2):497.
Available from: http://dx.doi.org/10.1016/j.cell.2018.06.051

[40] Zhu S, Jiang Y, Xu K, Cui M, Ye W, Zhao G, et al. The progress of gut microbiome research related to brain disorders. J Neuroinflammation [Internet]. 2020 Jan 17;17(1):25. Available from: http://dx.doi.org/10.1186/s12974-020-1705-z

[41] Wang H-X, Wang Y-P. Gut Microbiota-brain Axis [Internet]. Vol. 129, Chinese Medical Journal. 2016. p. 2373-80. Available from: http://dx.doi.org/10.4103/0366-6999.190667

[42] Bauer KC, Huus KE, Brett Finlay B. Microbes and the mind: emerging hallmarks of the gut microbiota-brain axis [Internet]. Vol. 18, Cellular Microbiology. 2016. p. 632-44. Available from: http://dx.doi.org/10.1111/cmi.12585

[43] Oleskin AV, Shenderov BA. Neuromodulatory effects and targets of the SCFAs and gasotransmitters produced by the human symbiotic microbiota. Microb Ecol Health Dis [Internet]. 2016 Jul 5;27:30971. Available from: http://dx.doi.org/10.3402/mehd.v27.30971

[44] Tremlett H, Bauer KC, Appel-Cresswell S, Finlay BB, Waubant E. The gut microbiome in human neurological disease: A review [Internet]. Vol. 81, Annals of Neurology. 2017. p. 369-82. Available from: http://dx.doi.org/10.1002/ana.24901

[45] Welcome MO. Gut Microbiota Disorder, Gut Epithelial and Blood–Brain Barrier Dysfunctions in Etiopathogenesis of Dementia: Molecular Mechanisms and Signaling Pathways [Internet]. Vol. 21, NeuroMolecular Medicine. 2019. p. 205-26. Available from: http://dx.doi.org/10.1007/s12017-019-08547-5

[46] Li J-M, Yu R, Zhang L-P, Wen S-Y, Wang S-J, Zhang X-Y, et al. Dietary fructose-induced gut dysbiosis promotes mouse hippocampal neuroinflammation: a benefit of short-chain fatty acids [Internet]. Vol. 7, Microbiome. 2019. Available from: http://dx.doi.org/10.1186/s40168-019-0713-7

[47] Galland L. The Gut Microbiome and the Brain [Internet]. Vol. 17, Journal of Medicinal Food. 2014. p. 1261-72. Available from: http://dx.doi.org/10.1089/jmf.2014.7000

[48] McDonald TJW, Henry-Barron BJ, Felton EA, Gutierrez EG, Barnett J, Fisher R, et al. Improving compliance in adults with epilepsy on a modified Atkins diet: A randomized trial. Seizure [Internet]. 2018 Aug;60:132-8. Available from: http://dx.doi.org/10.1016/j.seizure.2018.06.019

[49] Hasegawa S, Goto S, Tsuji H, Okuno T, Asahara T, Nomoto K, et al. Intestinal Dysbiosis and Lowered Serum Lipopolysaccharide-Binding Protein in Parkinson's Disease [Internet]. Vol. 10, PLOS ONE. 2015. p. e0142164. Available from: http://dx.doi.org/10.1371/journal.pone.0142164

[50] Xie G, Zhou Q, Qiu C-Z, Dai W-K, Wang H-P, Li Y-H, et al. Ketogenic diet poses a significant effect on imbalanced gut microbiota in infants with refractory epilepsy. World J Gastroenterol [Internet]. 2017 Sep 7;23(33):6164-71. Available from: http://dx.doi.org/10.3748/wjg.v23.i33.6164

[51] Huang C, Li Y, Feng X, Li D, Li X, Ouyang Q, et al. Distinct Gut Microbiota Composition and Functional Category in Children With Cerebral Palsy and Epilepsy [Internet]. Vol. 7, Frontiers in Pediatrics. 2019. Available from: http://dx.doi.org/10.3389/fped.2019.00394

[52] Joseph J, Depp C, Shih P-AB, Cadenhead KS, Schmid-Schönbein G. Modified Mediterranean Diet for...
Enrichment of Short Chain Fatty Acids: Potential Adjunctive Therapeutic to Target Immune and Metabolic Dysfunction in Schizophrenia? [Internet]. Vol. 11, Frontiers in Neuroscience. 2017. Available from: http://dx.doi.org/10.3389/fnins.2017.00155

[53] Yamawaki Y, Yoshioka N, Nozaki K, Ito H, Oda K, Harada K, et al. Sodium butyrate abolishes lipopolysaccharide-induced depression-like behaviors and hippocampal microglial activation in mice. Brain Res [Internet]. 2018 Feb 1;1680:13-38. Available from: http://dx.doi.org/10.1016/j.brainres.2017.12.004

[54] Perry RJ, Peng L, Barry NA, Cline GW, Zhang D, Cardone RL, et al. Acetate mediates a microbiome-brain-β-cell axis to promote metabolic syndrome [Internet]. Vol. 534, Nature. 2016. p. 213-7. Available from: http://dx.doi.org/10.1038/nature18309

[55] Paouri E, Georgopoulos S. Systemic and CNS Inflammation Crosstalk: Implications for Alzheimer’s Disease. Curr Alzheimer Res [Internet]. 2019;16(6):559-574. Available from: http://dx.doi.org/10.2174/1567205016666190321154618

[56] Lum GR, Olson CA, Hsiao EY. Emerging roles for the intestinal microbiome in epilepsy. Neurobiol Dis [Internet]. 2020 Feb;135:104576. Available from: http://dx.doi.org/10.1016/j.nbd.2019.104576

[57] Javdan B, Lopez JG, Chankhamjon P, Lee Y-CJ, Hull R, Wu Q, et al. Personalized Mapping of Drug Metabolism by the Human Gut Microbiome [Internet]. Vol. 181, Cell. 2020. p. 1661-79.e22. Available from: http://dx.doi.org/10.1016/j.cell.2020.05.001

[58] Holmes M, Flaminio Z, Vardhan M, Xu F, Li X, Devinsky O, et al. Cross talk between drug-resistant epilepsy and the gut microbiome [Internet]. Vol. 61, Epilepsia. 2020. p. 2619-28. Available from: http://dx.doi.org/10.1111/epi.16744

[59] Santos MTBR, Maria Teresa Botti, Diniz MB, Guare RO, Ferreira MCD, Gutierrez GM, et al. Inflammatory markers in saliva as indicators of gingival inflammation in cerebral palsy children with and without cervical motor control [Internet]. Vol. 27, International Journal of Paediatric Dentistry. 2017. p. 364-71. Available from: http://dx.doi.org/10.1111/ipd.12270

[60] Ming X, Chen N, Ray C, Brewer G, Kornitzer J, Steer RA. A Gut Feeling: A Hypothesis of the Role of the Microbiome in Attention-Deficit/Hyperactivity Disorders. Child Neurol Open [Internet]. 2018 Jul 11;5:2329048X18786799. Available from: http://dx.doi.org/10.1177/2329048X18786799

[61] Ertugrul AS, Sahin H, Dikilitas A, Alpaslan N, Bozoglan A. Comparison of CCL28, interleukin-8, interleukin-1β and tumor necrosis factor-alpha in subjects with gingivitis, chronic periodontitis and generalized aggressive periodontitis [Internet]. Vol. 48, Journal of Periodontal Research. 2013. p. 44-51. Available from: http://dx.doi.org/10.1111/j.1600-0765.2012.01500.x

[62] Gamonal J, Acevedo A, Bascones A, Jorge O, Silva A. Characterization of cellular infiltrate, detection of chemokine receptor CCR5 and interleukin-8 and RANTES chemokines in adult periodontitis [Internet]. Vol. 36, Journal of Periodontal Research. 2001. p. 194-203. Available from: http://dx.doi.org/10.1034/j.1600-0765.2001.360309.x

[63] Finoti LS, Nepomuceno R, Pigossi SC, Corbi SC, Secolin R, Scarel-Caminaga RM. Association between interleukin-8 levels and
chronic periodontal disease: A PRISMA-compliant systematic review and meta-analysis. Medicine [Internet]. 2017 Jun;96(22):e6932. Available from: http://dx.doi.org/10.1097/MD.0000000000006932

[64] Batool H, Nadeem A, Kashif M, Shahzad F, Tahir R, Afzal N. Salivary Levels of IL-6 and IL-17 Could Be an Indicator of Disease Severity in Patients with Calculus Associated Chronic Periodontitis. Biomed Res Int [Internet]. 2018 Feb 18 [cited 2019 Sep 7];2018. Available from: https://www.hindawi.com/journals/bmri/2018/8531961/abs/

[65] Naito Y, Uchiyama K, Takagi T. A next-generation beneficial microbe: Akkermansia muciniphila. J Clin Biochem Nutr [Internet]. 2018 Jul;63(1):33-35. Available from: http://dx.doi.org/10.3164/jcbn.18-57

[66] Millman AJ, Finelli L, Bramley AM, Peacock G, Williams DJ, Arnold SR, et al. Community-acquired pneumonia hospitalization among children with neurologic disorders. J Pediatr [Internet]. 2016;173:188-95. Available from: https://www.sciencedirect.com/science/article/pii/S0022347616002717

[67] Heymann DL, Shindo N. COVID-19: what is next for public health? Lancet [Internet]. 2020; Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30043-7/fulltext?hss_channel=tw-27013292

[68] Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical characteristics of 2019 novel coronavirus infection in China. MedRxiv [Internet]. 2020; Available from: https://www.medrxiv.org/content/10.1101/2020.02.06.20020974v1.abstract

[69] Liu H, Wang L-L, Zhao S-J, Kwak-Kim J, Mor G, Liao A-H. Why are pregnant women susceptible to viral infection: an immunological viewpoint? J Reprod Immunol [Internet]. 2020;103122. Available from: https://www.sciencedirect.com/science/article/pii/S0165037820300437

[70] Organization WH, Others. WHO Director-General's opening remarks at the media briefing on COVID-19—11 March 2020. Geneva, Switzerland: World Health Organization; 2020.

[71] Kuiken T, Fouchier RAM, Schutten M, Rimmelzwaan GF, van Amerongen G, van Riel D, et al. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. Lancet [Internet]. 2003 Jul 26;362(9380):263-270. Available from: http://dx.doi.org/10.1016/S0140-6736(03)13967-0

[72] Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. Lancet [Internet]. 2015 Sep 5;386(9997):995-1007. Available from: http://dx.doi.org/10.1016/S0140-6736(15)60454-8

[73] Society of Pediatrics, Chinese Medical Association, Editorial Board, Chinese Journal of Pediatrics. [Recommendations for the diagnosis, prevention and control of the 2019 novel coronavirus infection in children (first interim edition)]. Zhonghua Er Ke Za Zhi [Internet]. 2020 Feb 9;58(0):E004. Available from: http://dx.doi.org/10.3760/cma.j.issn.0578-1310.2020.0004

[74] Smith JA, Judd J. COVID-19: Vulnerability and the power of privilege in a pandemic. Health Promot J Austr [Internet]. 2020 Apr;31(2):158-160. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/hpja.333

[75] Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 Among Children in China. Pediatrics [Internet]. 2020 Mar 16; Available from: http://dx.doi.org/10.1542/peds.2020-0702
Advancement and New Understanding in Brain Injury

[76] Rosenthal DM, Ucci M, Heys M, Hayward A, Lakhanpaul M. Impacts of COVID-19 on vulnerable children in temporary accommodation in the UK. Lancet Public Health [Internet]. 2020 Mar 31; Available from: http://dx.doi.org/10.1016/S2468-2667(20)30080-3

[77] Arpaia N, Barton GM. Toll-like receptors: key players in antiviral immunity. Curr Opin Virol [Internet]. 2011 Dec;1(6):447-454. Available from: http://dx.doi.org/10.1016/j.co(viro.2011.10.006

[78] Bonjardim CA. Interferons (IFNs) are key cytokines in both innate and adaptive antiviral immune responses—and viruses counteract IFN action. Microbes Infect [Internet]. 2005 Mar 1;7(3):569-578. Available from: http://www.sciencedirect.com/science/article/pii/S1286457905000328

[79] Totura AL, Baric RS. SARS coronavirus pathogenesis: host innate immune responses and viral antagonism of interferon. Curr Opin Virol [Internet]. 2012 Jun;2(3):264-275. Available from: http://dx.doi.org/10.1016/j.co(viro.2012.04.004

[80] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [Internet]. Vol. 395, The Lancet. 2020. p. 497-506. Available from: http://dx.doi.org/10.1016/s0140-6736(20)30183-5

[81] Mäkinen TM, Juvonen R, Jokelainen J, Harju TH, Peitso A, Bloigu A, et al. Cold temperature and low humidity are associated with increased occurrence of respiratory tract infections. Respir Med [Internet]. 2009 Mar;103(3):456-462. Available from: http://dx.doi.org/10.1016/j.rmed.2008.09.011

[82] Foxman EF, Storer JA, Fitzgerald ME, Wasik BR, Hou L, Zhao H, et al. Temperature-dependent innate defense against the common cold virus limits viral replication at warm temperature in mouse airway cells. Proc Natl Acad Sci U S A [Internet]. 2015 Jan 20;112(3):827-832. Available from: http://dx.doi.org/10.1073/pnas.1411030112

[83] Saghazadeh A, Rezaei N. Immune-epidemiological parameters of the novel coronavirus – a perspective [Internet]. Expert Review of Clinical Immunology. 2020. p. 1-6. Available from: http://dx.doi.org/10.1080/1744666x.2020.1750954

[84] Saghazadeh A, Rezaei N. The Physical Burden of Immunoperception. In: Rezaei N, Saghazadeh A, editors. Biophysics and Neurophysiology of the Sixth Sense [Internet]. Cham: Springer International Publishing; 2019. p. 137-54. Available from: https://doi.org/10.1007/978-3-030-10620-1_10