Review article

Neurodevelopmental disorders due to the COVID-19 pandemic in pediatric patients

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Alteraciones en el neurodesarrollo como efecto de la pandemia por COVID-19 en pacientes pediátricos

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Abstract
The development of the central nervous system is a basic, dynamic and constant brain process that begins during the embryonic period and continues until early adulthood. Neurodevelopmental disorders involve any disruption or weakness of these processes, resulting from an interaction of genetic, environmental, and sociocultural factors. Exposure to the SARS-CoV-2 virus during the prenatal period, regardless of the trimester, produces alterations in the fine and gross motor domain; Likewise, exposure during the second and third trimester produces additional alterations in the socioemotional domain. On the other hand, prolonged quarantine, sedentary lifestyle and abuse of entertainment technologies have an impact on the areas: gross, fine motor, language, and socio-emotional, so these antecedents must be considered in well child visits in the office. Therefore, a bibliographic review was carried out including original articles, meta-analysis and review articles, with an obsolescence of five years, which studied this relationship. This study aims to determine neurodevelopmental disorders due to the COVID-19 pandemic in pediatric patients. A medical record of SARS-CoV-2 infection and having experienced the pandemic containment measures during early childhood should be considered risk factors for the development of neurodevelopmental disorders.

Keywords
Neurodevelopmental Disorders, COVID-19, Pandemics, Quarantine.

Resumen
El desarrollo del sistema nervioso central es un proceso cerebral básico, dinámico y constante que inicia durante el periodo embrionario y continúa hasta la edad adulta temprana. Los trastornos del neurodesarrollo implican cualquier disrupción o debilidad de estos procesos, resultado de una interacción de factores genéticos, ambientales y socioculturales. La exposición al virus SARS-CoV-2 durante el periodo prenatal, independientemente del trimestre, produce alteraciones en el dominio motor fino y grueso; mientras que la exposición durante el segundo y tercer trimestre produce alteraciones adicionales en el dominio socioemocional. Por otro lado, la cuarentena prolongada, el sedentarismo y abuso de tecnologías de entretenimiento repercuten en los dominios: motor grueso, fino, lenguaje y socioemocional, por lo que deben considerarse estos antecedentes al momento de realizar un control infantil en el consultorio. Se realizó una revisión bibliográfica incluyendo artículos originales, metaanálisis y artículos de revisión, publicados de 2019 a 2024, con el objetivo de determinar las alteraciones del neurodesarrollo como efecto de la pandemia por COVID-19 en pacientes pediátricos. El antecedente de infección por SARS-CoV-2 y el haber experimentado las medidas de contención por la pandemia durante la infancia temprana, deben ser considerados factores de riesgo para el desarrollo de trastornos del neurodesarrollo durante los primeros años de vida.

Palabras clave
Trastornos de Neurodesarrollo, COVID-19, Pandemias, Cuarentena.

Introduction

Neurodevelopmental disorders include a broad group of conditions characterized by early life onset, multifactorial origins, chronic course, and significant deviations in acquiring or executing functions across various areas of development. These disorders include alterations in any of the following domains: gross motor, fine motor, socio-emotional, language, and cognitive.[i] Before diagnosis, they may manifest as dissociations or deviations in one or more domains of neurodevelopment and even lead to delay or regression in some areas, which often goes unnoticed.[ii]

Dissociations are defined as a significant delay in a single domain, while the others develop normally. Deviation is defined as the appearance of milestones for an age in an unexpected order. In contrast, delay is said to occur when milestones occur in the expected order but at a later age. Regression, on the other hand, is when previously acquired skills are lost.[iii]

The risk of suffering from these disorders has been associated with infections from the SARS-CoV-2, Zika, and human immunodeficiency virus, among others. It is important to highlight neurodevelopmental conditions that may be related to SARS-CoV-2 infection and the COVID-19 pandemic, as both are external factors that can interfere with this process.[iv]

COVID-19 can manifest as acute disease, prolonged COVID-19,[v] or post-COVID-19 syndrome. In any of these clinical stages, the virus has a predilection for nervous tissue; central nervous system involvement has been found in approximately 34 % of the pediatric population, including neurodevelopmental disorders. A history of in utero exposure to the virus, due to its lodging in key brain structures, carries a 6 % risk of generating alterations in three domains: gross motor, fine motor, and socio-emotional.[vi]

In addition, quarantine and factors associated with confinement measures led to the impairment of four domains: gross motor, fine motor, socio-emotional, and language. Children exposed to these conditions have a 7 % risk of neurodevelopmental disorders[vii] due to the limitation of different types of play at various chronological moments in infancy. For example, sedentary lifestyles and technology-based entertainment limit imitative play, which occurs in one-year-old infants and is based on emulating the actions of other children. Likewise, in preschoolers over two years of age, observed play—where the child analyzes how others play—and parallel play, where children play together but do not interact among them.[viii]

Consequently, early detection of neurodevelopmental disorders allows for interventions during critical windows, which are the ages when children must have developed certain skills or be in the process of acquiring them, allowing for timely intervention so that children can recover skills that may be affected, such as adaptive skills, social communication, language, and behavior, improving their quality of life.[ix]

This literature review included original articles, meta-analyses, and review articles no more than five years old, published between 2019 and 2024, in the PubMed, HINARI, Google Scholar, and Elsevier databases, in Spanish and English. The Boolean operator "AND" was used to link "Neurodevelopment" with the following MeSH terms: "COVID-19.""Pandemic,""Motor Skills," "Language Skills," "Pediatrics," and "Milestones." The purpose of this review is to determine the neurodevelopmental alterations resulting from the COVID-19 pandemic in pediatric patients.

Discussion

Stages of neurodevelopment in the pediatric population

The development of the central nervous system is a basic, dynamic, and constant brain process that begins during the embryonic period, in the third week of gestation, with the development of the neural tube, and continues into early adulthood, approximately until the age of 25.[x] During the fetal period, this process is characterized by neurogenesis, gliogenesis, and cell migration. Neurodevelopment can be assessed through tests that determine motor and sympathetic nervous system development. The results of these tests indicate the integrity of brain development in utero.[xi]

After birth, neurodevelopment can be assessed directly through milestones expected for a particular age, which reflect internal processes in the central nervous system, such as differentiation, cell migration, and myelination.[xii] Neurodevelopmental milestones allow for objective standardization of assessment in five domains: gross motor, fine motor, socioemotional, language, and cognitive.[xiii]

First, the gross motor domain requires optimal development of the motor cortex, which is located in the precentral gyrus, and the extrapyramidal system, composed of the substantia nigra, red nucleus, basal ganglia, and cerebellum.[xiv] This domain is assessed by the appearance of muscle tone, changes in position, coordination, and walking.[xv]

Fine motor skills depend on the joint action of the primary motor pathway, the extrapyramidal system (cerebellum, basal ganglia, thalamus, among others), and efferents from the extraocular muscles, innervated by cranial nerves III, IV, and VI.[xvi]

This domain is assessed by performing precise movements through eye-hand coordination, such as pincer movements, following objects with the eyes, and drawing geometric shapes.[xvii]

On the other hand, socio-emotional mastery depends on the development of the amygdala, hippocampus, and frontal lobe; it is also influenced by interaction with parents and other children, and learning is consolidated through imitation.[xix] Another important element is the development of attachment, that is, the interaction that the infant establishes with his or her mother in stressful situations culminates in the development of empathy, self-regulation, and social skills.[xx]

Language development depends on Wernicke's area, Broca's area, and the motor cortex, especially in the dominant cerebral hemisphere. This domain is assessed through the ability to understand and formulate language.[xxi] The last domain is cognitive development, which depends on the frontal lobe, measures reasoning and problem-solving skills, and is assessed from the age of three, when the child can follow instructions, imitate household tasks, and understand abstract concepts.[xxii]

Therefore, both anatomical and functional neurodevelopment depend on genetic factors, as well as external environmental factors, which can either promote the proper development of skills or hinder the process, causing deviations or delays.[xxiii]

Among the important environmental factors include neurotropic viruses, defined as those with a high affinity for nervous tissue. A direct cause- and-effect relationship has been established with viruses of the TORCH complex (rubella, cytomegalovirus, herpes), Zika, rabies, and poliomyelitis, which are RNA viruses capable of causing chronic manifestations, such as microcephaly, due to their lodging in important areas of the brain that impact neurodevelopment, such as the corpus callosum and basal ganglia, among others.[xxiv]

Currently, another RNA virus that has gained relevance is SARS-CoV-2, not only because it is the causative agent of the COVID-19 pandemic, but also because of its demonstrated neurotropism, as it has an affinity for key areas in the neurodevelopmental process, mainly fine and gross motor skills.[xxv] In addition to its neurotropism, the mandatory lockdown measures imposed due to the pandemic hindered the proper development of socio-emotional, language, and motor skills because of poor social interaction, limited coexistence, and play with peers. Not attending school in person limited language development and influenced cognitive ability due to the deprivation of activities developed through imitation, such as memorizing songs or repeating words.[xxvi] Therefore, the COVID-19 pandemic cannot be ignored as a presumed risk factor for neurodevelopmental disorders.

Main neurological manifestations of COVID-19 in the pediatric population

SARS-CoV-2 is a single-stranded RNA virus that binds via its (S) protein to target cells that have the angiotensin-converting enzyme 2 (ACE2) receptor, present in the respiratory and digestive epithelium, endothelium, and central nervous system.[xxvii] This virus can enter the cell, where its RNA polymerase produces more copies of its genetic material, which are subsequently translated by ribosomes in the infected cells into proteins, which assemble virions within the cell and are then released.[xxviii]

The ACE2 receptor is expressed to a greater extent in cells of the olfactory bulb, hippocampus, red nucleus, substantia nigra, and ventral tegmental area,[xxix] the latter three, are important for fine and gross motor skills, socio-emotional function, and cognition. The virus is also capable of binding to the neuropilin-1 receptor present in the olfactory epithelium.[xxx]

Consequently, the main acute neurological manifestation of the virus is anosmia, due to its binding to the aforementioned receptors located in the olfactory bulb.[xxxi] Smell is key in infants due to their reduced visual acuity, which is limited to the perception of odors to recognize their mother, thus initiating the attachment process, which is included in the socio-emotional domain and culminates in the development of empathy.[xxxii]

Another acute neurological manifestation is encephalopathy secondary to COVID-19.[xxxiii] Its onset is directly related to a hyperreactive immune system, which produces the massive release of proinflammatory cytokines within the central nervous system; these are capable of causing neuroinflammation and deterioration of the blood-brain barrier.

Therefore, viral encephalitis hinders the growth, proliferation, and differentiation of immature neurons, leading to the onset of neurodevelopmental disorders.[xxxiv]

On the other hand, difficulty concentrating and memory problems are neurological manifestations that are grouped within the spectrum of post-COVID-19 syndrome.[xxxv] This is due to the virus binding to ACE2 receptors in cells of the hippocampus, an area prominent in memory consolidation and language production through feed-

back. It has been shown that infection in this area causes morphological changes in microglia and leads to a reduction in the astrocyte population.[xxxvi]

SARS-CoV-2 is also capable of producing chronic motor neurological manifestations such as tics, which are always included in post-COVID-19 syndrome. These have been associated with abnormalities because the virus binds to ACE2 receptors present in dopaminergic neurons, which are located in the mesencephalic substantia nigra. This region is part of the extrapyramidal system and helps regulate the muscle tone necessary for gross and fine motor development.[xxxvii]

In addition, the virus affects the oculomotor nerve due to its path through the red nucleus and medial to the substantia nigra, areas that are sites of SARS-CoV-2 accommodation.[xxxviii] This cranial nerve innervates the extraocular muscles, which are key to the consolidation of eye-hand coordination. Recent studies have revealed negative implications in gross and fine motor domains in pediatric patients exposed to the virus in utero.[xxxix]

In relation to the above, patients born during the pandemic whose mothers had COVID-19 during pregnancy have been studied, and significant impairments in gross and fine motor skills were found compared to infants whose mothers were not infected, regardless of the gestational age at the time of infection. Additionally, infants exposed during the second and third trimesters also showed repercussions in the socio-emotional area, due to the connections between the structures that make up the social brain and its myelination occur around week 30, transition period between the second and third trimesters.[xl]

Therefore, SARS-CoV-2 infection, combined with the deprivation of interaction and poor stimulation typical of the pandemic, was a risk factor for the onset of neurodevelopmental disorders.

Neurodevelopmental disorders in pediatric patients exposed to the COVID-19 pandemic and their implications

At the beginning of the pandemic, because SARS-CoV-2 had a high mortality rate and there were no curative treatments or vaccines developed, extreme measures were taken.[xli] For example, the implementation of prolonged quarantines, the strict use of masks, the closure of airports and schools, the latter being forced to adopt virtual modalities so as not to interrupt the learning process.[xlii]

The effects of prolonged quarantines and social isolation, combined with the neurotropism of the SARS-CoV-2 virus described above, have led to an increase in neurodevelopmental disorders. For their evaluation, two key groups have emerged, namely those patients who were born during the pandemic and those who were born before it but who were similarly exposed to the lockdown measures imposed due to the pandemic.[xliii]

Regarding the first group, the cohorts studied of those born during the pandemic are more likely to present developmental milestone disorders in the socio-emotional, gross motor, and fine motor domains compared to historical cohorts.[xliv] Due to the lack of knowledge about the disease at the beginning of the pandemic, infected mothers faced prolonged hospitalizations to protect their newborns, which meant mother-infant separation, interruption of skin-to-skin contact, and breastfeeding, concluding that the above is related to delays in gross motor skills, evidenced by lower scores on the ASQ-3 (Age and Stage Questionnaire) for three months of age.[xlv] On the other hand, the confinement of the pandemic led to a lack of stimulation typical of face-to-face activities with other children. This was mainly due to the absence of imitative, observed, and parallel play, which may have contributed to delays in the development of socio-emotional, gross motor, and fine motor skills. Additionally, this group was under partial physical activity restrictions, which exacerbated the aforementioned alterations.[xlvi] Regarding the effect of sedentary lifestyles secondary to prolonged quarantines, cohorts of active children scored better than the sedentary group in the areas of gross motor and fine motor skills.[xlvii] The restrictions established during the pandemic increased the use of tablets, computers, cell phones, and televisions for entertainment and communication, further discouraging physical activity and failing to stimulate muscle development balance, and social interaction.[xlviii]

Regarding the second group of children, those born before the pandemic, delays in language and socio-emotional development (children aged 30-36 months) were evident compared to historical cohorts of children who did not experience childhood during the pandemic.[xlix] Similarly, pediatric patients under one year of age at the start of the pandemic showed alterations in fine motor skills and language. This is always consistent with the absence of types of play vital for socio-emotional development, coupled

with the importance of play in the proper development of language.[I]

Consequently, these alterations, resulting from reduced social interaction and exposure to the virus, have repercussions at the school level. For example, children with language impairments, particularly in constructing phrases and sentences (syntax), have a lower capacity for calculation, as shown when performing addition exercises and comparing them with children who do not have such language impairments.[Ii]

Gross and fine motor skills are important for psychosocial development during early childhood. Therefore, it has been shown that children with deficiencies in these areas at age three have a significant association with peer victimization, as the lack of skills necessary for play leads them to be marginalized and, at later ages, to experience negative actions from their peers repeatedly.[Iii] Additionally, fine and gross motor difficulties are related to poor psychosocial adaptation, which culminates in behavioral problems as they encounter situations where they are not included in work or play teams.[Iiii]

It is important to consider a history of COVID-19 infection, in combination with the social restrictions of the pandemic, as possible risk factors in further research. Currently, the severity of the condition is unknown, and the degree of reversibility is not mentioned, so further studies are required to explore this issue in greater depth.

Conclusion

SARS-CoV-2 is a neurotropic virus, which is located in key structures for normal neurological development. Conditions occur in the fine and gross motor domains in children exposed in utero, regardless of the gestational age at which the infection occurs. However, infection during the second and third trimesters may impact the socio-emotional domain, as the social brain develops during this period due to the virus invading important structures such as the hippocampus and amygdala. On the other hand, the consequences of prolonged quarantines, sedentary lifestyles, the use of technology for entertainment, and the absence of in-person school activities led to a lack of stimulation from playful activities with other children. This contributed to the onset of neurodevelopmental disorders. Therefore, a history of SARS-CoV-2 infection, as well as having experienced pandemic containment measures during early childhood, can be considered risk factors for the development of neurodevelopmental disorders during the first years of life. For this reason, periodic assessment of neurodevelopmental disorders, with an emphasis on these children, during pediatric consultations is important for early detection of problems, timely treatment, and mitigation of damage.

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