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The Impact of Stress on Health in Childhood and Adolescence in the Era of the COVID-19 Pandemic

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Abstract
Background: The ongoing pandemic of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is posing many challenges to global health. Efforts from the whole scientific community have shed light on the pathogenetic mechanisms and the clinical features of SARS-CoV-2 infection as well as on potential therapeutic strategies. ***Summary:*** The consequences of stress related to social isolation and anxiety generated by the pandemic on mental and physical health are collateral effects that are yet poorly investigated.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic as well as the measures taken to contain the outbreak have deeply affected health, economics, and social life worldwide. In comparison with adults, children and adolescents have lower morbidity and mortality rates when infected with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2]. Nevertheless, children are inevitably affected, both directly and indirectly, by the stress induced by the ongoing COVID-19 pandemic [3].

Survival depends on the ability to maintain homeostasis by coping with changing and, in some cases, stressing circumstances. However, stress may induce long-term neuroendocrine and epigenetic changes that may affect health [4]. Indeed, the neuroendocrine response to stress is an excellent example of a plastic system that responds to threats to homeostasis, altering its function to meet current and expected future demands [5]. The key role played by the endocrine system in this homeostatic regulation has been known since the early studies in the 1930s, when the activation of the sympatho-adrenomedullary and hypothalamic-pituitary-adrenal (HPA) axes was shown in response to physical injury as well as perceived psychological threats [6].

The individual response to stressors is heterogeneous depending on both genetics, as elegantly shown in animal models [7], and early programming of HPA, as shown in the seminal work of Levine in 1967 [8]. The neonatal exposure to stressors (i.e., endotoxin) induces a long-term

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effect on the mechanisms generating basal pulsatile HPA activity in adult animals [9]. Herein, we review the available evidence on the potential short- and long-term consequences of being exposed to COVID-19 pandemic in childhood and adolescence.

Immediate Consequences

Probably the main indirect effect of the pandemic affecting children well-being is mediated by the impact of epidemic on parents and caregivers. The stress experienced by caregivers may undermine their ability to provide adequate nurturing care. In the present global health and socioeconomic crisis, which affects disadvantaged people more deeply, primary caregivers and parents find increasing difficulty in providing adequate health, nutrition, safety, and care of children. Therefore, this crisis may have particularly harmful effects on children already living in conditions of adversity and stress or with disabilities [10].

Another immediate effect of the pandemic-related stress is the impact on child and adolescent mental health [11]. Social isolation, combined with fear of contagion and quarantine, as well as with potential (mis)information overload, causes chronic stress and is associated with a higher risk of developing anxiety and depression. Social isolation can be defined as an impairment in the quality and/or quantity of the interactions experienced by an individual with other people. While social isolation before COVID-19 pandemic affected most commonly the older population, measures to minimize the spread of SARS-CoV-2 adopted worldwide have exposed all the age groups transversally to the effects of social isolation [12]. Pandemics and related public measures, such as quarantine, have been associated with several negative psychological outcomes, as comprehensively reviewed by Brooks and colleagues [13]. Studies exploring the effects of COVID-19 pandemic on mental health are flourishing with time, showing that the psychological impact of the pandemic deserves immediate strategies of prevention as well as early and long-term intervention [14].

Social isolation has been identified as a potent stressor in species dependent on social interactions. Increased activation of the HPA axis, enhanced glucocorticoid stress responses, and increased levels of corticosterone have been reported in rats following experimental social isolation [15–18]. Furthermore, dysregulation of brain neurotransmitters has been recognized as the mechanism responsible for the development of neuropsychological disorders associated with social isolation [19]. Recently, the impact of COVID-19 and quarantine on children's and adolescents' mental health has been reviewed by Singh and colleagues [20], reporting a significant increase in behavioral and emotional disorders in children as a consequence of school closures. Post-traumatic stress disorder has been identified in 30% of children in quarantine or isolation [21]. Age, socioeconomic/educational status, and preexisting mental health conditions influence the extent of burden on children and adolescents. Children with preexisting mental health conditions are particularly vulnerable, both for the loss of school routines, which represent fundamental coping mechanisms in these conditions, and for the lack of access to mental health services and support groups during quarantine [22].

Moreover, the restriction of physical activity, especially outdoor and in group, represents a further burden on mental health of children and adolescents [23]. Whether these consequences of pandemic on mental health may have an impact on the behavior and particularly on suicide risk in childhood and adolescence is object of investigation [24–26].

The change of life style induced by the pandemic has inevitably led to an increased risk of overweight and obesity in children and adolescents [27, 28]. There is a close interplay between stress and eating behavior, which often interact each other, leading to a vicious circle worsening both stress and adiposity [29]. Adipose tissue is an active endocrine gland and secretes a wide variety of hormones and regulatory factors. These factors reflect the metabolic status of the adipocytes and exert effects on the brain as well as other organs to control energy intake and expenditure [30]. A known stressing condition such as sleep deprivation is associated with increased appetite and insulin resistance [31]. An impairment in sleep quality has been reported by several authors across the world in connection with stress generated by COVID-19-related containment measures [32–34]. Despite these data refer to adult subjects, it is reasonable to speculate that sleep disturbances could also affect children. Chronic exposure to high cortisol levels in turn stimulates mesolimbic reward pathways within the brain, leading to increased intake of palatable food such as sucrose solutions [30]. Therefore, it is not difficult to foresee a further increase of obesity epidemic in the coming years [35].

Finally, a significant increase of cases of central precocious puberty and a faster pubertal progression in girls has been reported since the beginning of COVID-19 pandemic [36, 37]. This might be related to multiple environmental triggers, including the increase in fat mass, the

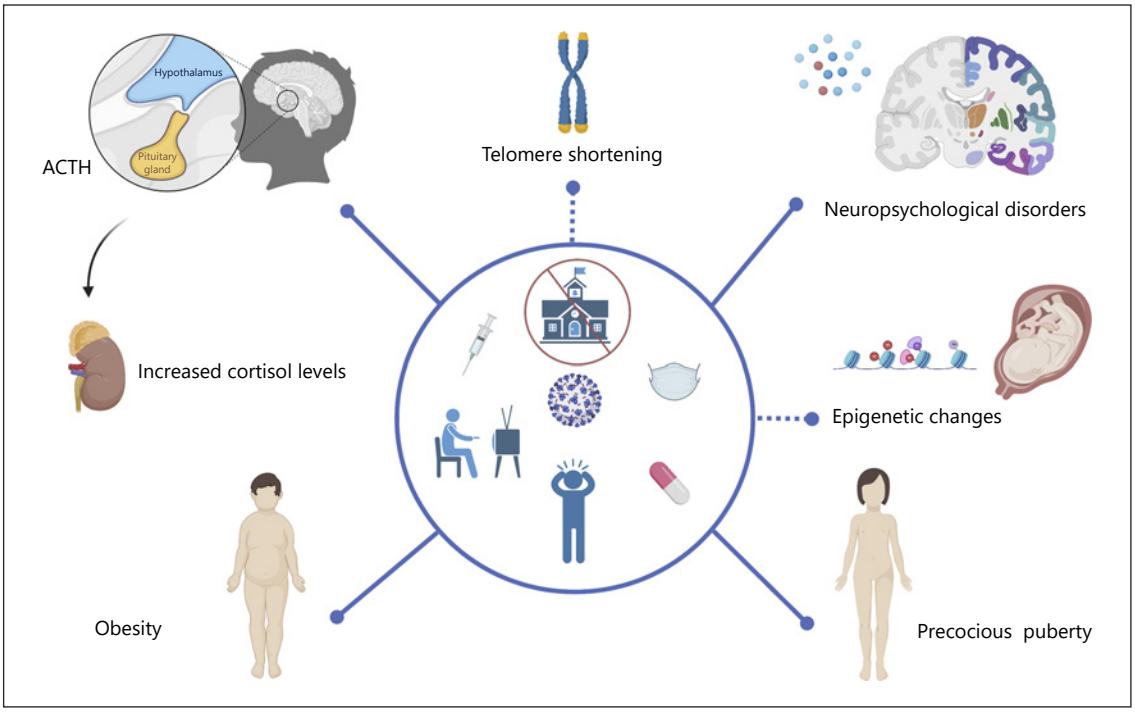

Fig. 1. Schematic representation of the consequences on mental and physical health associated with COVID-19 pandemic. COVID-19, coronavirus disease 2019.

prolonged exposure to electronic devices, as well as the psychological stress itself [36], whose role in acceleration of puberty timing proposed in past studies [38] remains to be demonstrated.

Although negative consequences of the pandemic deserve attention in order to tailor early and long-term intervention strategies, it is noteworthy that positive effects of COVID-19 pandemic on mental health in children are also existing. In particular, increased proximity with parents and close relatives in appropriate and healthy familiar environment can be of benefit for children. Furthermore, we recently reported an improved glucometabolic control in very young children with type 1 diabetes as an effect of the increased time spent with parents during quarantine [39].

Long-Term Consequences

The long-term impact of COVID-19 epidemic-related stress on health of children and adolescents is still unknown. According to the concept of the Developmental Origins of Health and Disease (DOHaD), early exposure (during fetal and early postnatal life) to a suboptimal environment may predispose the individual to develop certain diseases in later life [40, 41]. According to the DOHaD concept, parental environmental factors, including diet, body composition, metabolism, and stress, affect the health and chronic disease risk of the offspring throughout their lives. In this context, the period around conception is considered crucial for the long-term parental influences on the health of the next generation. In particular, the exposure to an adverse environment can influence long-term risks of offspring cardiovascular, metabolic, immune, and neurological morbidities [42, 43].

Psychological stress itself is an environmental stressor that can affect DOHaD with a variety of long-term consequences. Maternal stress and suboptimal intrauterine environment may program fetal development by inducing epigenetic changes, ultimately leading to rearrangement of offspring metabolic status [44, 45]. For instance, epigenetic changes involving methylation of genes playing a key role in adiposity regulation account for the observed relationship between intrafamilial childhood adversity and the risk of obesity in young adulthood [46]. A recent systematic review has shown that maternal stress exposes the offspring to a higher risk of obesity, hyperglycemia, insulin resistance, diabetes mellitus, metabolic

syndrome, cardiovascular disease, hypertension, restricted fetal growth, as well as reduced birth, adrenal, and pancreas weights [47]. Furthermore, maternal stress has been associated with increase in incidence of infections and in noninfectious illnesses as well as the risk of asthma in the offspring [48, 49].

As with other stressors, such as environmental chemicals or nutritional imbalance, the effects depend on the type of stress, as well as the strength, timing, and duration of the exposure. A recent meta-analysis explored anxiety and depression in pregnant women during COVID-19 pandemic, identifying a significant increase in the risk of these disorders during pandemic compared to non-pandemic times [50].

Follow-up studies are needed to verify the long-term effects of fetal exposure to maternal stress related to the COVID-19 pandemic. Interestingly, accelerated shortening of telomeres has been identified as a potential biomarker of stress environments, including social stress, and social disadvantage has been linked to accelerated telomere shortening in children [51].

Conclusions

Living in the time of COVID-19 pandemic exposes children and adolescents to stress in both a direct and an indirect way (Fig. 1). Pediatricians and pediatric endocrinologists should be informed about the potential consequences of the exposure to the stress related to the pandemic in order to provide a more careful monitoring of children health in the coming years. Media should be involved in an awareness campaign to inform parents and caregivers, in a communication tailored to meet children needs, and in a global educational strategy aimed at mitigating the short- and long-term impact of stress on health of children and adolescents.

Key Messages

In this minireview, we report the available evidence on the potential short- and long-term consequences of being exposed to COVID-19 pandemic in childhood and adolescence.

Conflict of Interest Statement

S.C. is the Editor-in-Chief of *Hormone Research in Paediatrics*. V.P. has no conflicts of interest to declare.

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Author Contributions

Both S.C and V.P. participated in the conception, design, and writing of the manuscript.

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