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Clinical Implications and Genetic Basis of Sleep Deprivation in Children

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Abstract

Sleep is a complex biological and physiological process that allows the body to rest in addition to playing an important role in proper homeostasis in different body systems such as immune, metabolic, cardiovascular, neurological, and hormonal. It is important to preserve the quality of sleep, for adequate vitality, since the alterations that occur in any of the phases of sleep have repercussions on several systems of an organism, whether they are short or long term, such as the negative effect of sleep deprivation on the hormonal and metabolic regulation of various pathophysiological processes that will contribute to the development of obesity in pediatric patients. It has been found that sleep-related problems are common in children, being a frequent reason for medical consultations. In addition to the aforementioned, there may also be alterations at the level of the cortex, which is associated with the nonregulation of emotions in preadolescent and adolescent pediatric patients. Finally, sleep could depend on polymorphisms that become risk alleles for having short-term sleep; likewise, there are genes that have a greater expression at the time of rest, which allows a relationship to be made with diseases developed in the face of sleep depletion. This article describes the clinical implications in pediatric patients as a consequence of sleep deprivation and its genetic bases.

Keywords
- sleep deprivation
- pediatric
- genetic basis

Introduction

Sleep, beyond being a reversible behavioral state characterized by disconnection from the environment while "resting the organism," is a highly structured universal physiological process, essential for life and physical and mental health; due to its role in physiology, brain functioning, and other body systems including hormones. It is cardiovascular, metabolic, and immunological, acting as an emotional and behavioral regulator in cognitive processes of memory, learning, as well

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as in neuronal activity through synaptic efficiency and the elimination of toxic substances at the brain level.[1,2]

Healthy sleep implies regularity, adequate quality, and sufficient duration, as well as the absence of sleep disorders and/or problems.[3,4] (AASM) recommends to promote optimal health as the number of hours of sleep in 24 hours in infants aged 4 to 12 months between 12 to 16 hours, in children aged 1 to 2 years between 11 to 14 hours, in children aged 3 to 5 years between 10 and 13 hours, in children aged 6 to 12 years between 9 and 12 hours, in adolescents aged 13 to 18 years, between 8 to 10 hours of sleep are recommended.[4] The development of a sleep system from infancy to adulthood is an important point given its association and the detrimental consequences for health in a bidirectional and interrelated way existing between sleep disorders and neurological, psychiatric, metabolic disorders, and cardiovascular disorders seen in the short and long term. This is even more evident today in the face of the increasing reduction of acute and chronic nightly sleep time below the optimal recommended ranges.[5]

Chronic sleep deprivation, according to the International Classification of Sleep Disorders, Third Edition, is a disorder characterized by the presence of excessive daytime sleepiness and reduction of total sleep time necessary for proper functioning for at least 3 months and at least 3 times per week.[6] It has been linked to short- and long-term consequences, in the former a greater response to stress, somatic problems, mood disorders, cognitive deficits in memory, concentration, and performance can be observed; and in the long term, the development of hypertension, hyperlipidemia, weight gain, which lead to the development of cardiovascular and/or metabolic diseases such as type 2 diabetes mellitus.[1] This article discusses the clinical implications and genetic basis of sleep deprivation in pediatric patients.

Materials and Methods

This research article is a narrative review of the literature that addresses the clinical implications and genetic basis of sleep deprivation in the pediatric population. The research question was raised through the problem, intervention, comparison, and outcome strategy, of the clinical and genetic implications of sleep deprivation in children and adolescents worldwide as a factor in the development of chronic diseases. It was consulted in the digital research databases, PubMed and Science Direct. Inclusion criteria included review articles, clinical trials, systematic literature reviews, meta-analyses, cohort studies, and case-control studies in English and Spanish published between 2000 and March 2022, which exposed the effects of sleep deprivation on health. We excluded case reports, case series, letters to the editor, conference posters, publications prior to 2000, and studies that did not discuss the health effects of sleep disruption. The search terms were MeSH: SLEEP DEPRIVATION, SLEEP DISRUPTION CHILD SLEEP DISORDERS, HEALTH, CONSEQUENCES, RISK, OUTCOMES, EFFECTS, GENETIC. A total of 494 articles were obtained in the initial search. They were reviewed by title and abstract, from which 175 publications were chosen. When evaluated in full text by at least two reviewers, a total of 51 articles that are part of the bibliography were included (►**Fig. 1**).

Sleep Deprivation Outcomes

Obesity

Sleep has an essential function in the functioning of hormones in the human being since they are synchronized to exert their action according to the patterns of wakefulness-sleep, additionally each hormone has a specific circadian pattern in terms of its secretion and function, so altering the normal cycle in which its effect is stipulated greatly alters the functioning they have in the different tissues of the body.[7] To exemplify what has been said above, in the REM (rapid eye movement) phases, insulin, leptin, and ghrelin are secreted, but on the contrary, hormones such as thyroid hormone and cortisol disappear at the beginning of sleep, somatotropin has its peak of secretion half an hour after drowsiness and 40 minutes later prolactin is secreted; therefore, it can be said that each hormone has a programmed clock of action that could occur in the nonrapid eye movement sleep (NREM) phase (without REM) or in the REM 7 phase.

However, under normal conditions, the energy balance is maintained by a regulatory system that involves exogenous factors such as the diet from which the nutrients necessary to produce energy will come and, on the other hand, factors of the individual's energy expenditure such as thermogenesis, physical activity, and basal metabolic rate. It is not very clear how sleep deprivation might be related to obesity; however, it has been postulated that when there are not enough hours of sleep, weight gain may be due in part to the alteration of the hormones that control appetite (ghrelin) and hunger (leptin). Initially, adipocytes release leptin into the bloodstream to signal a sufficient deposit of fat, which is an appetite suppressant, and the stomach releases ghrelin when empty, which causes the feeling of hunger. However, in sleep deprivation, ghrelin levels increase and leptin levels decrease, which generates a double hit of hormones that makes the individual want to eat more since the brain is interpreting signals that the body has an energy deficit consequently increasing food intake, resulting in a higher frequency. In addition, a short duration of sleep leads to increased fatigue, tiredness, and sleepiness during the day (effects of NREM sleep deprivation) thus decreasing the motivation of individuals to engage in physical activity.[7] However, excessive food consumption is associated with reduced sleep but appears to be driven more by hedonic factors than hormonal ones, with studies consistently showing that reduced sleep increases the number of meals consumed per day and the preference for foods high in carbohydrates and fats. In particular, there is evidence to suggest that the diet of adolescents after sleep deprivation is characterized by a higher glycemic index and load, particularly sweets and desserts. Neuroimaging studies have

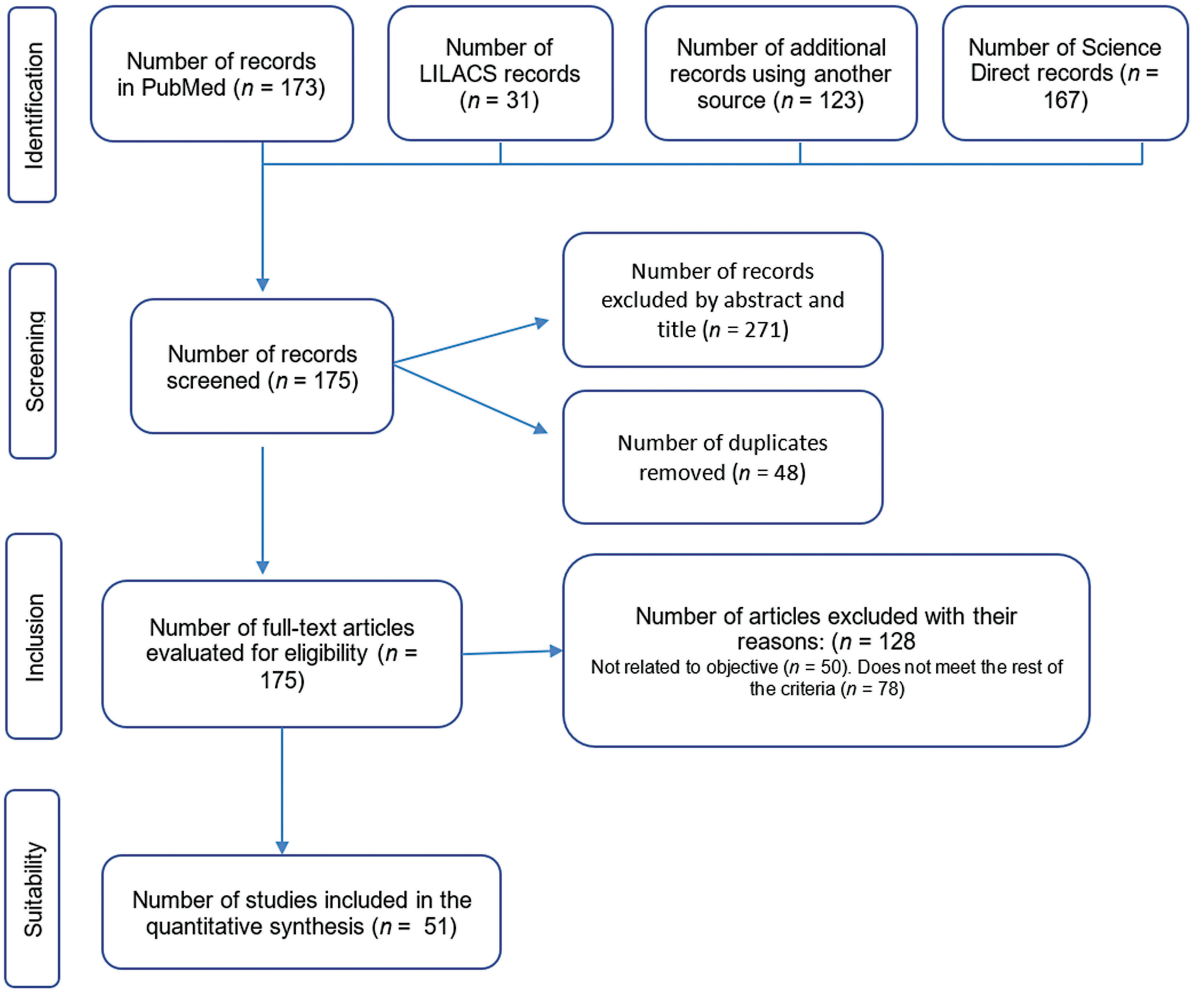

Fig. 1 Search strategy.

described evidence in particular of the insular cortex and areas thought to be involved in hedonic functions, such as the orbitofrontal cortex and dorsolateral prefrontal cortex, where greater activation is shown in response to unhealthy foods compared with healthy food stimuli after sleep restriction. On the other hand, Spiegel et al restricted the sleep of a group of young people to a total of 4 hours/night for six consecutive nights and showed a decrease in glucose tolerance in 40% of them, which also showed as a consequence a lower response of acute insulin to glucose and an additional increase in plasma concentration of glucose and insulin-like growth factor 1. This shows the greater susceptibility of children and adolescents to metabolic diseases such as diabetes mellitus and, of course, obesity.[8]

Depression and Anxiety

Sleep is a vital necessity since it allows, in the case of emotions, to improve the functioning of the structures that are responsible for modulating human behavior as well as cognitive and emotional actions, if the sleep period is insufficient, ability to regulate both emotions and our behavior declines, causing anxiety, impulsivity, and negativity in those children who do not sleep for the right number of hours.

This study involved 11,067 children between the ages of 9 and 11 years in the United States.[9] It allowed us to investigate the relationship between sleep duration and future psychiatric problems, results obtained showed that those people who slept less had a higher risk of developing psychiatric pathologies, in addition to this children who presented sleep deprivation and in turn depressive symptoms had a greater risk. Also, the authors reported that the children with short sleep had reduced cortical areas and volumes in the lateral and medial orbitofrontal cortex, the superior and middle frontal gyri, the medial superior frontal gyrus, the inferior and middle temporal gyri, and some motor cortical areas. Specifically depression has been related to the little area that is in the orbitofrontal cortex which is composed of a medial part that is activated when having rewarding and pleasant stimuli, however, its connectivity and area is decreased in depression, and by the lateral part that is stimulated with unpleasant stimuli and those that do not provide rewards and usually have greater connectivity in states of depression.[10] Of 199 adolescents with whom a study was performed at 9, 10, or 11 years of age and later at 18 years of age to verify the association between sleep problems in childhood and the development of psychiatric pathologies in

adolescence, it was possible to demonstrate that sleep–wake inconveniences in childhood do generate a significant positive association with a p-value < 0.01 in externalizing behaviors, adolescent anxiety and depression.[11] Likewise, according to a longitudinal study, it was concluded that sleep problems in preschool age influenced the development of anxiety and depression 2 years later; in addition to this, girls tend to develop either direct or indirect depressive symptoms and poor emotional regulation due to sleep depletion, while in boys sleep deprivation is not an important factor in developing depression as it is great social competition that occurs as they grow up.[12]

With all of the above, it is important to emphasize that sleep depletion affects emotions in those children who are going through preadolescence and adolescence,[13] at which time they are more susceptible to alterations in their mood, with a greater tendency to express their emotions in a negative and impulsive way, additionally, with little control over their behavior, which leads to isolation from other peers of their age.[14]

Memory and Learning

Memory is defined as the ability of an individual to acquire, retain, and use knowledge or information[15]; On the other hand, learning is defined as a process related to the changes that occur in an individual at neuronal, cognitive, and behavioral levels as a result of experiences, allowing adaptation to the environment.[16,17] Children's sleep health, as indicated by the duration, timing, and different aspects of children's lifestyle, and environment can influence the functioning of higher mental abilities by altering their ability to respond and process any type of stimulus and new situations that arise in their day-to-day lives, contributing to the establishment and development of cognitive abilities for their survival as an independent individual, which includes the ability to acquire new information, process it, store it in the long term (consolidation and stabilization), understand, and assimilate (integration), thus acquiring the ability to retrieve it effectively if necessary.[18]

It is common for a night of sleep deprivation to generate a significant deficit in hippocampal activity during the encoding of episodic memory, resulting in a lower capacity for subsequent retention. During sleep, the ability to remember spoken language, motor skills, and factual information would be improved. In the literature, different studies have been described that seek to measure the changes in the processes described above, which are essential especially for learning and memorizing; three forms of intervention have been proposed for their study: the first is long-term total sleep deprivation ($>$ 45 hours), second, short-term total sleep deprivation (45 hours), and partial sleep deprivation (sleeping less than 7 hours/24 hours).[18] As a result, all forms of sleep deprivation have been found to result in an increase in negative physical states, such as feelings of fatigue, loss of vigor, drowsiness, and confusion.[18] Similarly, feelings of irritability, anxiety, and depression have been generated as a result of inadequate sleep frequently in the subjects studied, regardless of other environmental conditions or their environment.

It is important to note that much of the study on sleep deprivation has focused on declarative memory, which involves memories that are consciously accessible and that involve autobiographical memory of actual events in the past (episodic memory) or memories of facts and general knowledge (semantic memory).[19] The consolidation and integration of these types of memories depend on the hippocampus to a large extent, but additionally, the structures of the medial temporal lobe are related during the encoding of information; in addition to this, functional neuroimaging taken in experimental studies to evaluate the performance of memory-related tasks has shown that sleep deprivation not only negatively affects regions of the temporal lobe but also other areas of the brain such as the prefrontal and parietal cortices that try to compensate for deficits and thus maintain performance.[20]

On the other hand, temporal memory is responsible for the ability to remember when a particular event occurred; sleep deprivation has been shown to significantly affect the encoding and retention of positive and neutral stimuli, but memory of negative stimuli appears to be relatively impervious to sleep loss, which could have implications for the development of pathological moods such as depression.[20]

Neurodegenerative Diseases

In the study of the main neurodegenerative diseases: Alzheimer's, Parkinson's, and Huntington's, several hypotheses have been proposed related to sleep habits, highlighting sleep deprivation as a contributing cause to the development and worsening of the course of diseases, since it is considered a risk factor (noxa) that, added to specific genetic bases, leads to a chronic imbalance at the brain level that activates harmful cellular processes and increases neuronal damage.[21]

That is why immunity, cellular processes, hormones, enzymes, and the role of the biological clock, and circadian rhythm play an important role in the course of these diseases. From the beginning, there is an immune dysregulation since generally, during sleep, processes of elimination of metabolic waste products are performed and when there is a chronic activation at the brain level, there will be a decrease in these processes that leads to neuroinflammation and neuronal damage in which some proinflammatory mediators participate: TNF-a (tumor necrosis factor α), IL-1B (interleukin 1β), and COx-2 (prostaglandin-endoperoxide synthase 2).[22] In addition to the increase in enzymes that regulate brain proteins and, therefore, an increase in irregular proteins and the inability to break them down, which generates abnormalities in functioning and begins to degenerate, this is what explains some neurodegenerative disorders pathologically. In turn, cells such as astrocytes and microglia are activated in specific regions of the brain; piriform cortex and hippocampus allow normal brain functions; however, their abnormal activation affects such functionality and leads to deficits in memory, learning, anxiety, and damage to the blood–brain barrier.[23] Increased oxidative stress affecting cellular organelles such as mitochondria and endoplasmic reticulum is also described, leading to cell death, apoptosis, and dysregulation of neuronal autophagy,

altering homeostasis.[24] Melatonin, a neuroendocrine hormone synthesized by the pineal gland, plays a role in sleep control, regulation of the circadian rhythm, and has certain antioxidant antiaging and antitumor effects, and decreasing its levels has a negative impact on the neuroprotective role with the decrease of neurotrophins, which predisposes to neurodegenerative findings.[25]

When awake, the biological clock is interrupted and generates circadian dysfunction that chronically explains the characteristics of neurodegenerative symptoms; normally, the circadian rhythm works independently in the cells and adapts to the time span of 24 hours by posttranslational regulation by means of the transcriptional factor RNNTL (nuclear receptor translocator of aryl hydrocarbons) that when heterodimerized with CLOCK or NPAS2 (protein 2 of the neuronal PAS domain) allows the binding to the E-box sequence located in promoter regions of gene[26] and that, together with the participation of the central nervous system through structures of the eye such as the retina, receives light inputs that allow synchronization of a series of neurons that will make synapses and thus translate the information into nuclei of the hypothalamus. However, when there is damage, there is a loss of circadian rhythms, of normal neuronal activity, and it favors asynchronous functioning,[27] promoted by orexin, a neuropeptide that participates in the regulation of the sleep-wake cycle as well as increasing the production and aggregation of proteins such as β-amyloid (Aβ) protein,[27] found in Alzheimer's disease and abnormal levels of syncline α, found in Parkinson's disease.

Immune System

It has been identified that sleep is closely related to the immune system and the response to stress; this occurs because during the hours of sleep various physiological processes are induced, including the maintenance of the immune system through the stimulation of the innate and adaptive response that contributes to the elimination of free radicals, cellular and neuroimmunoendocrine regulation and increased levels of cytokines, markers of inflammation, and immune response cells.[28]

Poor sleep in pediatric patients will increase biomarkers of physiological stress (neuroendocrine, immune, metabolic, cardiovascular) as the body reacts to the few hours of sleep and responds to environmental changes to optimize the individual's adaptation.[29] Total leukocyte count, memory T cell count, naive and regulatory T cell count, and proliferative function have all been shown to peak at night. Pro-inflammatory cytokines such as IL-1β, IL-2, TNFα, interferon-γ, and IL-6 are elevated during the night and generally promote sleep, while anti-inflammatory cytokines such as IL-4 and IL-10 are induced after awakening and could inhibit sleep; studies claim that a close relationship has been found between the increase of such anti-inflammatory cytokines and children who have alterations in sleep pattern.[28]

On the other hand, in terms of the immune response to lipopolysaccharide stimulation, vaccination and susceptibility to infection also vary and can be altered with sleep loss, as sleep deprivation could result in a change in the balance of the Th1/Th2-mediated immune response and could alter the functional rhythm of regulatory T cells. Recent discoveries show that sleep is vitally important in the homeostasis of the immune system. The National Institutes of Health (NIH) sponsored an interdisciplinary workshop in which they linked sleep and circadian biology to immune function, stating that short-term sleep disruption can affect circadian regulation in peripheral tissues such as the blood, brain, and lungs.[30]

Cancer

Sleep deprivation has been shown to alter the inflammatory response by multiple mechanisms that could lead to increased susceptibility to chronic inflammatory diseases. Multiple controlled studies[31] have shown an increase in leukocytes, monocytes, B lymphocytes, TCD4 cells, and a decrease in the number and cytotoxic activity of circulating NK (natural killers); in addition to this, it is seen that after sleep deprivation, the phagocytic activity of the neutrophil decreased and the adhesion of lymphocytes to expression molecules was altered. Along with this, the production of IL2, IL12, IL1, IL6, and TNF-a are reduced. Studies have also shown that when sleep is not disturbed, there is a predominant TH1 response, but when sleep is disturbed, the TH2 response becomes predominant (increasing the expression of IL4, IL5, IL10, and IL13).[31] In animal model, it has been shown that sleep deprivation increases the proliferation and invasion of tumor cells through proinflammatory TLR4 and exosome signaling.[32,33] In controlled experiments used mice ($n = 48$), where half of them were chronically deprived of sleep and the other group were not, and half from both the groups were inoculated with human adenocarcinoma tumor cells and it was observed that after 3 weeks, the group in which there was chronic sleep deprivation developed larger, heavier, and much more invasive tumors compared with the non sleep deprived group.[33] In addition, this is closely related to exosomes that have been studied in recent years, especially among patients with obstructive sleep apnea, where it is possible to show that exosomes are a type of intercellular communication that can target multiple genes, approximately 132 genes that can alter normal cell function and favor tumor growth. These pro-inflammatory changes favor tumor growth, stromal activation, and promotion of angiogenesis, it can be extrapolated in humans since an experiment in which cells of a lung adenocarcinoma were used in which they were incubated in a medium with all the necessary requirements for their survival and proliferation, they applied the exosomes that were found in the peripheral blood of 10 different patients with a diagnosis obstructive sleep apnea and it was observed that in these samples there was an increase in cell proliferation.[32] Multiple studies corroborate that chronic sleep disturbance could be considered an important factor for the development and/or poor prognosis of cancer, where the genetic bases involved in this pathology are broad, but not yet very clear, and therefore an object of study today and for the coming years.[33]

Genetic Basis

Sleep regulation is of multifactorial etiology, where genetic, environmental, and sociocultural factors play an important role; however, from a genetic approach, polymorphisms have been proposed and found that induce alleles considered to be at risk, as well as epigenetic changes that, although they do not induce a nucleotide change in DNA (deoxyribonucleic acid), do modify gene expression.[34,35]

Regarding the relationship between sleep and epigenetics, it is necessary to highlight the increase in ROS (reactive oxygen species) generated by daily activities and their subsequent reduction at the time of rest, that is, sleep works as an antioxidant.[36] Lack of sleep leads to an increase in metabolic expenditure to maintain neuronal electrical potentials that are already depleted, which means a greater requirement for both oxygen and ATP (adenosine triphosphate). This significantly increases the production of ROS. It has been detected that due to lack of sleep, the levels of GSH (glutathione) in the plasma are decreased. Glutathione is an important antioxidant, and therefore in turn, there is an increase in oxidative stress, cysteine which is a precursor of GSH by 50%; ATP which is needed for the synthesis of GSH and homocysteine from the transsulfuration pathway allow the obtaining of cysteine. These changes lead to epigenetic alterations such as DNA methylation (addition of a methyl group to a cytosine-guanine dinucleotide [CpG]), which can trigger gene silencing and alterations in genomic imprinting.[37] These epigenetic changes increase the risk of future neurodegenerative diseases.[38] A study conducted by Koopman–Verhoeff[39] analyzed regions of mDNA (methylated DNA) in peripheral blood samples from 465, 10-year-old children. Based on the results, gene coexpression was identified through a network analysis that allows evidence of nodules or regions of mDNA comethylated in sleep-deprived individuals. The results showed 64 modules with 30 to 65,804 methylated CpG sites, and of these, one region was found to be associated with decreased sleep intake. This region contains nine genes located on chromosome 17 and includes the *MAPT* (microtubule-associated protein tau) gene which is a regulator of Tau 39 proteins. It has an important association with the pathogenesis of neurodegenerative diseases; in these cases, it induces the formation of microtubules (MAP) in neurons, if it is methylated or silenced in the human brain, its activity is depressed, and in this state, it polymerizes forming abnormal neurofibrillary networks such as those found in Alzheimer's disease.[40] For context, sleep depletion can cause an increase in ROS and a decrease in antioxidants such as glutathione, leading to DNA hypomethylation and aberrant gene expression. This alteration in gene regulation does not allow the brain to function properly. Therefore, the implementation of antioxidants in the diet of children who frequently experience sleep loss could prevent all damage from oxidative stress.

SNPs (single nucleotide variants) have been associated with susceptibility to various conditions.[41] An association of SNPs with short sleep has been identified using the GWAS (Genome-Wide Association Study). For example, a study that included 91,105 genomes of participants in the UK Biobank found an association between short sleep and gene SNPs (►**Table 1**.) PAX8 (paired box 8) located on chromosome 2q14.1 associated with thyroid development and organogenesis, was found as SNP rs7556815-G that causes the short sleep phenotype, MEIS1 (Homeobox Meis1) located on chromosome 2P14 loci 20 which is a home box gene related to restless legs syndrome, was found as SNP rs113851554-G related to short sleep cycles was reported, and MAPK8IP1P2 (mitogen-activated protein kinase 8 interacting with protein 1 pseudogene 2) located on chromosome 17q21.31 which produces a mitogen-activated protein kinase 8 interaction protein 1 pseudogene 2, was found as SNP rs7502280-T [REMOVED HYPERLINK FIELD] associated with short sleep.[42]

In a meta-analysis that analyzed 446,118 participants of European ancestry, 202 risk loci associated with insomnia and short sleep were found, among them was (►**Table 1**) a new MEIS1 found on chromosome 2P14 loci 20 which is a home box gene, *FOXP2*, located on chromosome 7q31.1 that encodes a CNS transcriptional repressor factor. The SNP rs2863957-C associated with short sleep was found in SLC39A8 (solute carrier family 39 member 8), located on chromosome 4q24, which encodes a transcription factor necessary in organogenesis, a SNP rs13107325-T related to

Table 1 Single nucleotide genes and variants associated with short sleep

Nearby gene	Location	Related variant	Allele	Function
MEIS1	2p14	rs113851554-G	G/A/T	Gen Home box
PAX-8	2Q14.1	rs7556815-G	G/A/C	Transcription factors essential for the development of the thyroid, urogenital tract, placenta, and inner ear
MAPK8IP1P2	17Q21.31	rs7502280-T	T/G	Encodes mitogen-activated protein kinase 8 interaction protein 1 pseudogene 2
FOXP2	7q31.1	rs1229762-T	C/G/T	It encodes for a regulatory factor that functions as a transcriptional repressor in the central nervous system.
SLC39A8	4Q24	rs13107325-T	C/A/T	Codes for ZIP8 zinc transporter which is a cationic importer/bicarbonate protein
TCF4	18Q21.2	rs12963463-C	C/G/T	Encodes for the actor Transcript immunoglobulin 2

short sleep was reported), TCF4 (transcription factor 8) located on chromosome 18q21.2 that encodes immunoglobulin transcription factor 2, A SNP rs12963463-C was found that is also related to short sleep cycles) and among 18 other genes that present polymorphisms found among those that become risk alleles for short-duration sleep.[43]

In the same way, just as there are polymorphisms associated with short sleep, there are also those of prolonged sleep; in this case, a GWAS meta-analysis and SNP heritability estimates of sleep duration were performed in 10,554 children of European ancestry, with this it was possible to identify a significant variant related to a long sleep cycle on chromosome 11q13.4 that covers several SNPs. Without significant heterogeneity, the minor allele of the upper SNP within this locus found was rs74506765, this polymorphism is located in an intronic region of the *ARAP1* gene, a phosphatidylinositol 3,4,5-triphosphate-dependent GTPase activator gene that is also associated with ARF-GAP activity (ADP ribosylation factor), which mediates changes in the Golgi apparatus and filopodia formation.[44,45]

It has also been found that some genes may have increased expression with sleep deprivation. A study conducted in a mouse model, where gene expression was evaluated by microarray after the induction of sleep of 8 hours each day for 1 week showed that some genes such as *P-CREB* (cAMP response element binding protein), *Arc* (cytoskeleton-associated protein regulated by activity), *BDNF* (brain-derived neurotrophic factor), and others that are part of the induction of neuronal plastic changes had greater expression in the brain at the time of awakening compared with when they were sleeping.[46] With this, it can be concluded that sleep is not necessary for the expression of genes that allow the development of neuronal plasticity since its greatest activity occurs in the waking state, so why is sleep a physiological process of vital importance? According to[47] the sleep period serves to avoid the synaptic overload that occurred while the person was awake, this re-calibration then allows the brain to be energetically efficient day by day when performing various activities; therefore, sleep becomes a necessary and vital homeostatic process.

However, other more recent studies suggest that there are genes that do have a higher expression at the time of sleep deprivation, among them we find some genes such as:

- Homer1a: It is a protein encoded by the early *HOMER1* gene located on chromosome 5q14.1, a fairly important component that allows the expression of proteins that serve as scaffolds in the postsynapse.[48] Homer1a is a protein of paramount importance in synaptic remodeling during sleep and in intracellular calcium signaling, according to the study, mice that lacks it cannot be maintained in a waking state.[49]

On the other hand, in a study with male mice that were deprived of sleep for an hour or 3 hours and then allowed to perform compensatory sleep for another 3 hours to make a comparison, analysis was done by means of images extracted from brain tissue (dissection of five regions of the brain, the cloister, the piriform cortex, the lateral hypothalamus, the tuberomammillary nucleus, and the locus coeruleus) and an in situ hybridization was performed in addition to immunostaining to establish in which places there is a greater expression of the genes, as a result, it was obtained that the expression of Homer1 increased in the brain before the loss of sleep, being higher in the claustrum and to a lesser extent also important at the level of the pyriform crust. Similarly, once mice were allowed to rest, protein expression levels decreased in claustrum.[48]

- c-Fos: Coming from an immediate encoded early proto-oncogene called fos located on chromosome 14 q24.3, c-Fos is a protein that regulates cell proliferation and is part of an intracellular biochemical cascade that activates gene transcription. [50] It was studied in the brain of a mouse, in which lack of sleep induced a dysregulation of its expression in various tissues such as the amygdala, the somatosensory cortex, the cerebellum, and among others.[51]

In the study of male mice that were deprived of sleep for 1 hour or 3 hours, it was necessary to perform immunostaining on brain slices, in which results were obtained that showed a high expression of c-Fos in the deprivation of 3 hours of sleep in the locus coeruleus, lateral hypothalamus, and tuberomammillary nucleus, places where there was no high expression of Homer1a, meaning that there are significant regional differences in the expression of these two genes. On the other hand, in this case, c-Fos levels during sleep recovery remained even higher.[48]

Conclusion

Sleep is a complex biological and biological process that involves the body's reversible restful behavioral state and is essential for physical, mental, and emotional health. This process is of vital importance for individuals at any stage of life, given the multiple functions it fulfills, and that in the early stages of life, it is an activity in which more hours of a day are invested since it is a determinant of the health and optimal development of the child. This is why alterations in sleep patterns or poor sleep are directly related to various outcomes that negatively affect pediatric patients; it is said that these outcomes are related to a greater predisposition to the development of autoimmune diseases, cancer, and neurodegenerative diseases in addition to the accumulation of adipose tissue and memory and learning problems that, if persistent, will manifest themselves in adulthood. Sleep depletion is due to a multifactorial etiology where environmental, socioeconomic, cultural, and genetic factors take on importance. The latter has been related not to mutation in a specific gene but to polymorphisms that induce the existence of risk alleles for short-term sleep. On the other hand, within the physiological functions and processes it fulfills, such as the elimination of neurotoxic substances and the product of oxidative stress that the body faces, a reduction of it will have a negative impact on the increase in oxidative stress, which in turn increases DNA methylation leading to genetic mutations involved in the pathophysiology of multiple chronic diseases that affect the health of human beings

and the pediatric population with deleterious effects on growth and development. This highlights the importance of recognizing and establishing the importance of healthy sleep habits from childhood to avoid the negative effects that come with sleep deprivation in both the long and short term.

Conflict of Interest

None declared.

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