SLEEP-WAKE, ASPECTS OF MEMORY AND MELATONIN IN WILLIAMS-BEUREN SYNDROME: A REVIEW OF LITERATURE

Sono-vigília, aspectos de memória e melatonina em Síndrome de Williams-Beuren: uma revisão de literatura

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ABSTRACT

The Williams-Beuren syndrome, a genetic disorder (microdeletion in chromossome region 7q11.23) presents an apparent social skills with contrasts with the low global cognitive performance and visuo-spatial problems as receptive, structural and semantic form of communication, besides deficits in attention, hyperactivity and memory impairments in visuospatial. Another feature are disorders of the sleep-wake cycle with sleep ineffective resistance to going to bed, wake up at night and drowsiness during the day. A possibility not yet explored would be the abnormal pattern in the synthesis of melatonin, a hormone that can modulate the quality of sleep. Considering the assumption that the quality of sleep is directly influenced by the levels of melatonin and essential for the proper development of cognitive functions, sought to in this literature review which studies that investigated separately and correlated these three aspects or in Williams-Beuren syndrome: sleep-wake, memory and melatonin. To search, was used Medline/Pubmed, SciELO and Lilacs databases, with the keywords: "*Williams Beuren syndrome*, síndrome de Williams Beuren, *memory,* memória, *sleep-wake*, sono-vigília, *melatonin* e melatonina" for means of crossing and the AND connective. The literature review showed that there are no jobs that these three variables correlate with each other nor work to investigate melatonin in Williams-Beuren syndrome. The individual investigations on sleep and memory are critically discussed in this work that emphasizes the need for studies to correlate these parameters, as well as behavioral, cognitive and biochemical related to them.

KEYWORDS: Sleep; Wakefulness; Memory; Melatonin; Williams Syndrome; Developmental Disabilities

INTRODUCTION

The Williams-Beuren syndrome (WBS) is a genetic disorder caused by the hemizygous micro-deletion of a region in chromosome 7q11.23 that containing genes mainly responsible for the elastin production [1]. This syndrome presents an incidence of 1:7500 newborns cases and equal proportion between men and women [2].

The phenotype of WBS includes dysmorphic facial features like middle third of the face flattened, micrognathia, protruding ears, prominence and swelling periorbital, anteverted nostrils, long nose filter and thick lips. In addition, these individuals also have short stature, cardiovascular and connective tissue abnormalities [3].

The behavioral phenotype presents personality and a cognitive profile unique in addition to different degrees of intellectual disability. A striking feature of this syndrome is the seemingly preservation of social and language functioning called Cocktail Party Speech (CPS) for his sociability, intention to interact, report of personal experiences to unknown people, speech fluent and intelligible using stereo-typed phrases and cliches. This apparent social and communicative skills contrasts with the poor global and visuospatial cognitive performance of these individuals. In addition, more detailed studies showed problems in receptive, semantic and

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structural forms of communication that vary with the level of intellectual disability [4,5].

The attention in individuals with SWB, is usually reduced and comes associated with hyperactivity, which increase the likelihood of learning problems [6]. The problems with attention are proven the cause of most complaints from parents of these individuals and can be directly associated with failure in the academic area, since it is a basic prerequisite for memory and learning. Despite this, there is a lack of studies that evaluate this feature in this population.

Memory parameters have been studied in SWB. The first studies described this like one of its positive features with good performance in verbal and auditory short-term memory, which explains the ability of these individuals to retain auditory information, especially music [7]. However, subsequent studies have shown the great difficulty of these individuals with visuospatial memory. Now, it is believed that individuals with SWB compared to controls by mental age, present deficits in both auditory and visuospatial memory [8,9].

Another common feature, although still poorly investigated in SWB is the presence of severe disorders of the sleep-wake cycle. According to the parents, the sleep is not effective with resistance at going to bed, excessive anxiety, waking at night and daytime sleepiness [10]. Research on sleep parameters may be performed by subjective methods such as questionnaires and diaries and/or by objective methods as actigraphy and polysomnography. The polysomnography in SWB showed changes in all sleep architecture stages [11], decrease in the time and efficiency of sleep, increased eye, legs and arms movements, increased slow-wave activity and decreased alpha and sigma activity [12,13]. This condition can worsen behavioral problems present, since sleep is the time that ensures the proper performance of cognitive function in the next day [10].

Some associated factors such as hyperactivity and anxiety have been suggested as possible causes of sleep disorders in this population [11]. However , a possibility not yet explored would be an abnormal pattern in the hormone melatonin, produced by the pineal gland in the dark phase. This molecule is necessary for improve the sleep quality, since acts as a transducer of environmental photoperiodic information [14]. Abnormal patterns in the production of melatonin have been detected as a cause of sleep disorders in several developmental disorders and syndromes [14], in neurodegenerative diseases such as Alzheimer's [15], and syndromes such as Smith Magenis[16].

The pathway of melatonin synthesis involves the signaling of the environmental light-dark cicle to the pineal gland. The retina, a light sensitive organ receives photic information and synchronizes the suprachiasmatic nuclei of the hypothalamus (SCN) through retinohypothalamic tract. SCN efferent fibers reach the hypothalamic paraventricular nucleus (PVN), which in turn connects to the intermediolateral column of the spinal cord, where preganglionic fibers originated in the superior cervical sympathetic ganglion will project to the pineal gland. Thus, in the absence of light, occurs acetylation of serotonin in N-acetylserotonin (NAS) by the arylamine N- acetyltransferase (AA-NAT) enzyme. In sequence, NAS is methylated *in* N-Acetyl-5-methoxytryptamine or melatonin. The increase of melatonin production, and its release into the blood and cerebrospinal fluid mark the darkness in these two distribution compartments [17].

Various conditions such as the presence of mutations in enzymes of this pathway and the presence of molecules that signaling inflammation may be involved in the decreased production of melatonin [18]. In these cases, exogenous melatonin administration has brought satisfactory effects in improving sleep quality and consequently behavior, attention and memory in several pathologies [19]. This hormone replacement should be considered not only by its chronobiological aspect, but still by its neuroprotective, antioxidant, anticarcinogenic, anti-inflammatory and antinociceptive effects [20]. known to be an efficient and safe treatment without side effects, indications may represent a promising treatment for clinical improvement of SWB .

In conclusion, the sleep quality is essential for development of proper cognitive functions. The levels of melatonin have influence in the sleep quality and consequently in cognitive functions, besides also acts directly in memory through its neuroprotective action in the hippocampus. The aim of this review was to identify studies that specifically had investigated sleep, memory and melatonin in SWB, discussing the possible correlations between the data presented and considering the methods.

METHODS

This study was conducted in the following bibliographic databases : Medline / Pubmed, Lilacs and Scielo, with the following keywords: "*Williams Beuren syndrome*, *memory, sleep-wake* and *melatonin*", separately or using the connective "AND".

Selection Criteria

The articles selected should include the following requirements: (1) be an original research article, (2) have the SWB population, (3) have issues of sleep, memory or melatonin, (4) be published in : portuguese, english or spanish languages. Were

excluded from the sample: (1) duplicated articles, (2) articles of literature review, (3) without full version available .

The period chosen to search the topic sleep-wake was the last 20 years, for the term melatonin the last 10 years and for memory the last 5 years, the difference between the periods was determined by the demand of published articles.

Analysis of results

Following the search strategies chosen for this study, no articles were found that furnished at the same time the three themes selected, therefore the results were divided into subtopics addressing the themes separately.

116 articles were found in the Pubmed database using the keywords: sleep- wake and Williams-Beuren syndrome. These, were excluded 106 because the sleep was cited only as part of the syndrome phenotype, and one was excluded because had not been found as full text. The search in the database Scielo and Lilacs has not brought results when crossed such keywords (Figure 1).

84 articles were found when the keywords memory and Williams-Beuren syndrome were crossed in the Pubmed database. 55 were excluded because they did not contain memory analysis. 6 were excluded because were review articles and 5 had not been found as full text (Figure 2) .

Any article was found in national or international journals investigating melatonin in Williams- Beuren syndrome.

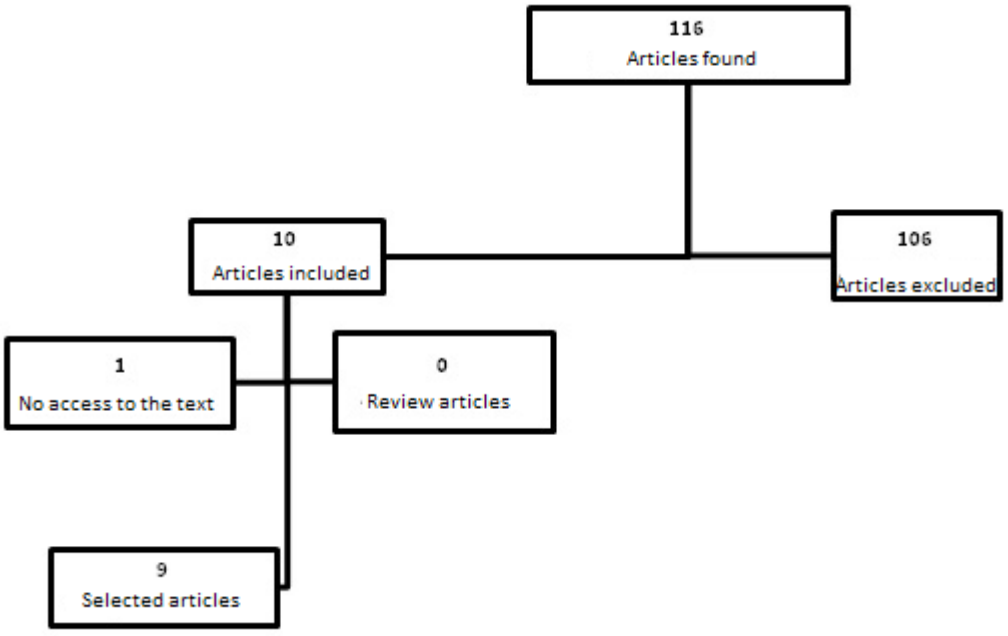

Figure 1 – Flowchart of the articles used in this review with the search strategy sleep-awake (sono-vigília) and Williams-Beuren syndrome (síndrome de Williams-Beuren)

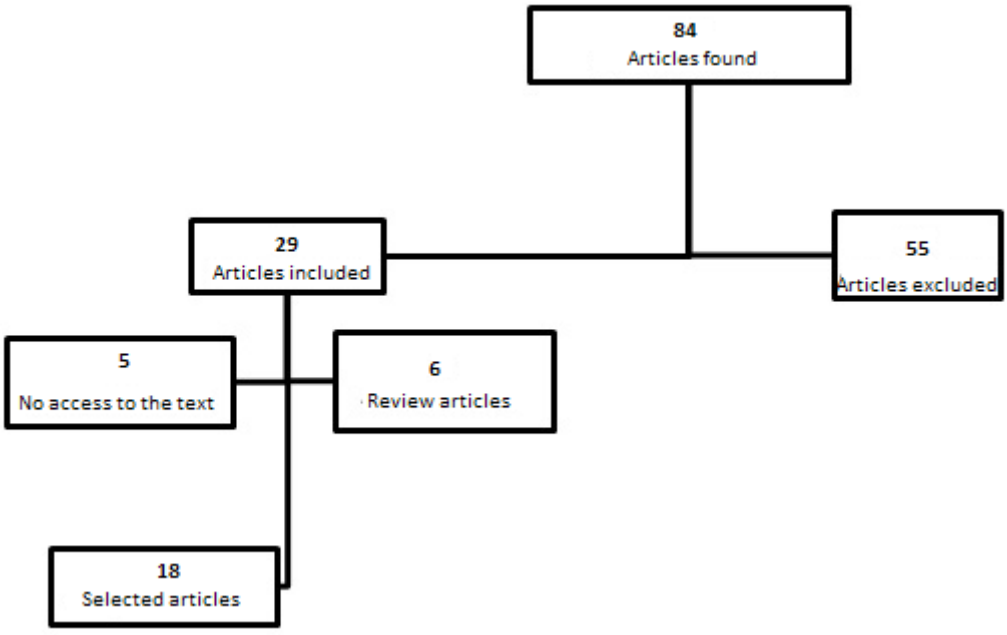

Figure 2- Flowchart of the articles used in this review with the search strategy memory (memória) and Williams-Beuren syndrome (síndrome de Williams-Beuren)

LITERATURE REVIEW

Sleep-wake and Williams-Beuren syndrome

Early studies of WBS dating from the second half of the last century, however only about 50 years later started the investigations on aspects of sleep in this population. These articles described the behavior of individuals with WBS and often brought complaints of the parents regarding sleep habits [21]. The first investigation of sleep disorders was performed in 28 families, which 16 had complaint with excessive movements during the sleep and reduced time of sleep compared to controls. Thus the study had concluded that there was sleep disorders in this population and this could be related to the great agitation at night [22].

After this, a study report was published about one and a half year old child with obstructive sleep apnea and otitis media, whereupon the difficulty of sleeping was proven by the presence of high rates of sleep-disordered breathing in polysomnography with low oxygen saturation [23].

Besides sleep disturbance in children of SWB, was investigated the persistence of this problem until adulthood and what were their characteristics. When the sleep period of 23 subjects with SWB was analyzed through questionnaires and actigraphy, was found, as well as in children, reduced sleep time, agitation and excessive legs and arms movements, in adition to fragmented sleep and excessive daytime sleepiness. The authors stated that these characteristics are common in other disorders of development but the reasons was not clear [24].

In 2011 there was a significant increase in research in research about SWB sleep features, showing that deficit in sleep efficiency, increased percentage of slow-wave sleep, deficit in REM (Rapid Eye Movement) stage, increased movement of legs, compose the changed architecture of sleep in this population. The polysomnography enable to analyze which sleep stages were changed and thereby evaluate their impact in other functions, such as learning difficulties suggesting future studies correlating these aspects [13].

Thus, assuming that sleep architecture was changed in SWB, studies have investigated the impact that this generate in the functionality of individuals. One hypothesis was that agitation and changes in sleep could influence the cognitive functions and behaviors of these individuals as hypersociability, cocktail party speech (CPS), anxiety and difficulty of attention [10].

Polysomnography study with 35 individuals with WBS showed similar results to previous studies, but the frequent arousals were associated with sleep-disordered breathing [11]. It is suggested that oscillations in the thalamus would be a possibility for the alteration observed in the pattern of NREM (Non Rapid Eye Movement or “Movimento não rápido de olhos”) in WBS [25]. The behavior of WBS were comparable with individuals with Attention Deficit and Hyperactivity Disorder (ADHD), however in respect of sleep, individuals with WBS had the worst

aspects. This factor supports the hypothesis of the authors that despite the unrest is closely related to sleep, there is a genetic influence that can change these defaults [11] .

There are around 28 microdeletion in genes in WBS and some of them are candidates for regulators of changes in sleep stages. The investigation of genetics has grown in aspects related to sleep, so in 2013 the WBS aspects of sleep were compared with those with Down Syndrome [26]. The WBS had problems in initiating sleep, extreme agitation and nocturnal enuresis. When compared to controls both syndromes had lower sleep quality [26]. According to the authors the sleep disorders should be reported as a typical feature of WBS.

Memory and Williams-Beuren syndrome (WBS)

Memory is a subject that has been taken into consideration in the study of SWB phenotype due to the apparent good performance in memorizing sentences, words and songs.

Interesting are the causes that lead children with SWB retain some information and discard others essential for activities, such as writing. As well as hypersociability brought the erroneous idea that these individuals had perfect language in its condition for communicative acts, there was difficulty in understanding the memory capacity in SWB. The problem in the design of memory and hypersociability were due largely to the unique aspects of their language, so the challenge was focused on discern how much these factors are a consequence of one another. Investigations of the peculiarities of language revealed an apparent facility in retaining phonological information and recover it immediately, but with difficulty in understand its meaning, use them properly and keep them for a long period.

Memory researchs on SWB would bring important information for the treatment of disorders with influence in aspects of executive function. Findings such as the dissociation of visual and auditory memory were the inicial point for the increasingly address about this subject in the posterior studies.

In the last five years the number of articles that focus on memory in SWB almost doubled due to the increase in the number of cases, probably due to the precise diagnosis, assessment instruments and the interest from professionals and family to assist in the aspects that influence cognition.

Study published in 2009 proposed the analysis of visuospatial memory in children with SWB, and confirmed that these individuals had deficits in visuospatial tasks [27]. However, no explication to the superior ability of object recognition and the difficulty of spatial organization of the same were found. The study was not able to answer what the neurofunctional disorder that causes the deficit in visuospatial memory, but was hypothesized that it could be due to a hypoplasia of the areas in the parietal cortex or changes in subcortical structures such as basal ganglia and cerebellum (processing deficit) [27]. Evidence for recognition and localization of objects, showed clear superiority of visual recognition and difficulty in locating objects in space. In a study of recognition of visual stimuli in fast and slow modes it was found that: the longer the waiting time for rescue information, worse will be the performance of this population [28]. This feature can be directly related to the problems in the long-term memory.

Cognitive deficits are extremely important when it comes from executive functions, which rely on full intellectual functioning. The memory aspects in individuals with intellectual deficits, must necessarily be explored. Due to the difficulty in finding a population that could be paired chronologically and mentally with children with WBS, several studies used the Down syndrome, that present similar cognitive and executive characteristics. An interesting study investigated the ability to recognize faces between this two populations, and a third group composed of high-functioning autistic children. The results indicated that children with WBS were able to recognize familiar faces, but showed a different strategy to accomplish this task: splitting the whole into parts [10]. This strategy demonstrate the difficulty in understand global visual stimulus, create concepts and engram them. This process is very similar to that necessary for the formation of long-term memory. Another study investigated the influence of behavior and cognition in aspects of memory in the population of WBS and Down syndrome, and showed deficits in aspects of auditory and visual memory in both populations [29]. The difference lies in the fact that WBS have shown positive correlation of these findings with cognitive disabilities, and Down syndrome have in turn presented a positive correlation between visual memory and behavioral aspects.

The cognitive profile of WBS can not be considered homogeneous due to degrees of intellectual disability within the same population, but there is a proportionality between cognition and memory. Disagreeing with the fact that only the cognitive profile would be associated with the mnemonic capacity, recent research has indicated that executive function would be the main cause of memory impairment, and should be evaluated with the same attention, especially if taken into account the hypothesis of the relation between behavior and changes in the frontal lobe [30]. Among all executive functions, memory is the aspect that go along with the levels of IQ, as well as variations of IQ [31].

Since 2010, investigations of neural structures began to be realized looking for anatomical bases of the memory difficulties. One of the first investigations of this nature suggested that changes in the size and function of the hippocampus in the left hemisphere would be present in individuals with WBS, and be correlated with memory disorders [32]. So could be suggested that hippocampal and parietal lobe changes, present in this population, in addition to the genotype, would result in difficulty in refocusing and rescue visual information. Structural changes could be generalized to issues such as body orientation, justifying motor problems in WBS, such as the lack of coordination from the visual memory [33].

Based on pattern of normality in recognition of visual stimuli, and abnormalities of visuospatial memory [8], is suggested that these issues should be examined with behavioral tests and exams of neuroimaging. Changes in the cerebellum have also been implicated in the causes of memory deficits in the WBS, because of its role in the planning and information recover processes. Through neuroelectrophysiological tests it was observed that children with dystonia in the cerebellar region showed ability to memorize words (lexicon), but they were unable to rescue these words after a time and also to use appropriately these words in their speeches (syntax) [34]. This showed the superiority of short-term auditory memory when comparing to long-term auditory memory.

The discussion between the structural causes of memory changes remains around the difficulty in understanding if the unusual pattern of performance shown would be result of a general immaturity or due structural abnormalities from the brain in WBS. One study investigated the ability of preschoolers with SWB in memorizing a static object, and also to follow it in the space, this population showed performance close to adequate to the task of static memory, but had exacerbated difficulties looking for the visual stimulation in different points of the space [35]. According to the authors, this fact could be justified for some parietal alterations, since static memory would use another cortical area. The possible deficit in the blood flow of dorsal cerebral artery found in this population, could also decrease memory, especially the visual modality, because of its direct influence on the central function [36].

Behavior analysis in studies of WBS showed that factors such as hyperactivity, hypersociability, misconduct and emotional alterations can be directly related to the levels of attention and consequently memory [5,8]. Cognitive deficits and hypersociability could be related to social inhibitory responses in turn these responses could be a definitive factor for difficulty in adapting and memorizing [37]. Behavioral issues are consistently related to executive functions and consequently with working memory, both factors altered in the WBS. The processing of information received from hearing or visually is impaired in this population and when added to the behavior alterations, becomes even more difficult the performance on recover the stimulus [38].

The ability to remember melodies and the facility in learning and handling musical instruments are striking feature in the WBS. Based in this information, the auditory memory was tested with verbal or verbal sung stimuli. Results showed that children attending music lessons showed superior performance in the singing task as well as in auditory memory [39]. It is not known in what extent the musical ability of aids in auditory memory performance of individuals with WBS, but it is true that the melodic training provides effectively in the temporal processing and neuroplasticity. Perhaps, in this population, such characteristic is an attempt to compensate the malfunction of some other brain structure, such as the hippocampus.

Recent neuroimaging studies have confirmed the existence of strong correlation between enlargement of the posterior cerebellar vermis and changes in executive functions, especially verbal short-term memory [36]. The type of reported brain changes has also been related to some features of the phenotype of WBS as hypersociability and emotional lability, important aspects of the deviations of behavior exhibited.

There is evidence of changes in long-term memory in WBS, however research that explores this aspect are rare. A recent study evaluated the ability of children with WBS to retain information and be able to rescue them appropriately after a long period [40]. The results indicated a dissociation between long-term memory and familiarity with the given stimulus, reinforcing the idea that to preserve the information would be a complicated task in these cases, however, the main difficulty is related to the ability to manipulate this information. The improved performance on tasks with familiar stimuli to these children brings important information, that regardless of the difficulty of memory training is able to increase the expectation of learning.

Recent study reported difficulty in delineating the development of memory in the population of WBS [29]. The results indicated alterations in both visual and spatial, memory in distinct degrees, independent of the age. Despite the decreased performance for age, there is an evolution in the process of mnemonic capacity in accordance with the advancement of age, this raises the hypothesis that aspects of memory in this population have the

capacity to improve slowly. This statement brings to light the need to differentiate between what is really an alteration and what is a delay in the memory development.

CONCLUSION

Problems of long and short-term of visual and auditory memories, and sleep disturbances are part of the phenotype in Williams-Beuren syndrome. Despite the importance of these aspects in cognitive and behavioral impairment, there are still few studies of correlation between them. Moreover, biochemical studies about the causes of sleep disorders are lacking in the literature. Based on the fact that aspects of sleep has been considered in performance levels of attention and memory in the population in general, we can suggest that studies are needed to investigate and correlate sleep and memory, as well as behavioral, cognitive and biochemical factors related to them in the WBS. These studies could contribute to the therapeutic and clinical direction for improvement in executive functions of this population.

RESUMO

A Síndrome de Williams-Beuren, distúrbio genético (microdeleção na região cromossômica 7q11.23), apresenta como fenótipo aparente habilidade social que contrasta com o mau funcionamento cognitivo global e visuo-espacial, problemas na forma receptiva, estrutural e semântica da comunicação, além de déficits na atenção, hiperatividade e na memória visuoespacial. Outra caracteristica são desordens no ciclo sono-vigília, com sono ineficaz, resistência em ir para a cama, acordares durante a noite e sonolência durante o dia. Uma possibilidade ainda não explorada nesta síndrome seria o padrão anormal na síntese de melatonina, hormônio capaz de modular a qualidade do sono. Considerando que a qualidade do sono é diretamente influenciada pelos níveis de melatonina e que tanto a melatonina quanto o sono são essenciais para o desenvolvimento adequado das funções cognitivas, buscou-se nesta revisão de literatura quais estudos investigaram separadamente e ou correlacionaram estes três aspectos (melatonina, sono-vigília e memória) na síndrome de Williams-Beuren. Para busca, foram utilizadas as bases de dados Medline/Pubmed, SciELO e Lilacs, com os seguintes descritores: "*Williams Beuren syndrome*, síndrome de Williams Beuren, *memory,* memória, *sleep-wake*, sono-vigília, *melatonin* e melatonina", por meio de cruzamento e com o conectivo AND. O levantamento bibliográfico mostrou que não existem na literatura trabalhos que correlacionaram estas três variáveis entre si nem tampouco trabalhos que investigaram a melatonina na síndrome de Williams-Beuren. As investigações sobre sono assim como as investigações sobre memória são criticamente discutidas neste trabalho que ressalta a necessidade de estudos que correlacionem estes parâmetros, bem como outros fatores comportamentais, cognitivos e bioquímicos a eles relacionados.

DESCRITORES: Sono; Vigília; Memória; Melatonina; Síndrome de Williams; Deficiências do Desenvolvimento

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