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Correlations between behavior, memory, sleep-wake and melatonin in Williams-Beuren syndrome

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HIGHLIGHTS

- 53% of the WBS individuals did not present a melatonin circadian rhythm variation
- WBS individuals presented auditory and visual short-term memory impairments
- 65% of WBS individuals presented an indicative of at least one sleep disorder
- Sleep disorders are correlated with melatonin content and memory in WBS

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ABSTRACT

Williams-Beuren syndrome (WBS), a neurodevelopmental disorder caused by a microdeletion on chromosomic region 7q11.23, presents with peculiar behavioral and neurocognitive phenotypes that are marked by apparently preserved social and communicative abilities, which contrasts with low overall cognitive and particularly visuo-spatial performance. In addition, parents often report complaints of sleep disorders and behavioral problems of unknown cause. Sleep is a biological phenomenon that is modulated by the plasma concentration of melatonin and with influence on behavioral aspects and memory. Thus, this study sought to investigate the behavior, memory and the presence of sleep disorders in WBS and to correlate these factors with each other and with the plasma melatonin content. We used the Child Behavior Checklist for ages 6–18 (CBCL), the digit subtest of the Wechsler scale for auditory memory, the visual sequential memory subtest of the Illinois Test of Psycholinguistic Abilities (ITPA) and the Sleep Disturbance Scale for Children (SDSC). Determination of urinary aMT6s, an indirect measure of plasma melatonin content, was held for 72 h by ELISA, and the analysis of the circadian rhythm of this content was performed by the Cosinor method. The results of the CBCL showed that 87% of the WBS group presented with a clinical score on the overall competence and total behavioral problems. Furthermore, the behavioral problems that were most frequently reported by parents were anxiety and problems of thought. All individuals with WBS presented with impairments in auditory memory and 47% with impairments in visual sequential memory; 65% of the WBS group presented with an indicative of at least one sleep disorder, where respiratory, initiation and maintenance of sleep (DIMS) and hyperhidrosis were the most frequent disorders. The night time aMT6s levels were lower in individuals with WBS when compared with controls; 53% of the WBS group did not present with circadian rhythm variations in aMT6s levels. In addition, there was a negative correlation between the scores of auditory memory and the total score of sleep disorders and between the DIMS and nocturnal aMT6s content. In conclusion, in the present study, individuals with WBS showed a high frequency of behavioral and memory problems, sleep disturbances and no rhythm variation in aMT6s levels. The low melatonin content may be related with sleep disorders in this population, which, in turn, can have an adverse effect on specific cognitive skills such as memory.

1. Introduction

Williams-Beuren syndrome (WBS) is a neurodevelopmental disorder caused by the heterozygous deletion of WBS critical region (WBSCR) 1.5 Mb–1.8 Mb on 7q11.23 in consequence to a non-allelic homologous recombination (NAHR) [9].

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With an incidence of 1:7500 in equal proportion between genders [69], WBS presents with a phenotype that includes typical facial features with flat middle third of the face, micrognatia, protruding ears, prominence and periorbital swelling, anteverted nostrils, long nasal filter and massive lips [9,48].

The intellectual disability, with average values of Intellectual Quotient (IQ) of 55, is a manifestation that is present in most cases. The behavioral phenotype includes impaired performance in both verbal and non-verbal skills [16,56,61], such as auditory and visual memory [59]. In the case of auditory memory, WBS frequently shows alterations in skills, such as background figure, auditory closure, auditory attention, separation and binaural synthesis, and auditory hypersensitivity to high frequencies [8].

Individuals with WBS apparently exhibit good social and communication skills in contrast with poor general cognitive functioning, often having difficulties in formal communication situations that require the following of rules or developing and maintaining focus in conversation [41,54,58,67]. Psychopathologic manifestations, such as fears and phobias, may also occur [10,25], as well as hyperactivity and attention deficit [26,35,52], which, when combined with intellectual disability, resulting in learning problems [23,24,31,47]. Some studies have also associated WBSCR deletions and autism spectrum disorders indicating that behaviors and neurochemical phenotypes typically associated with autism like hyperserotonemia and low melatonin production can occur in WBS patients [70,71].

Another common aspect to consider in individuals with WBS is the presence of severe disorders of the sleep-wake cycle. According to parents, sleep is not effective, as children have great resistance to going to bed, display excessive anxiety, wake up at night and remain sleepy during the day [4]. Several studies have explored the presence of sleep disorders in WBS, indicating that 36–57% of this population present with some form of sleep disorder, such as restless sleep, disorders of onset and maintenance of sleep, awakening, respiratory re-sleep and excessive daytime sleepiness [6,32,33,44,45] regardless of age [32]. The actigraphy showed that these individuals have a lower sleep efficiency, longer sleep onset latency and shorter sleep duration, so while remaining in bed for 9 h at night, the presence of sleep disorders results in excessive daytime sleepiness [32].

Polysomnography shows changes in several stages of sleep: increased activity of slow wave and decreased alpha and sigma activities, reduced sleep time and decreased sleep efficiency, increased eye movements and movement of arms and legs [33,44].

The relationship between sleep and behavioral aspects has been demonstrated in several neurodevelopmental disorders [18,27,68,75,76] and was already hypothesized in WBS [45].

As causes of sleep disorders in this population, nocturia and periodic limb movements in sleep have been considered due to their association with arousals and awakenings [6,17]. Hyperactivity and anxiety are also mentioned as possible candidates [44]. One possibility that has been poorly explored in this population is the abnormal pattern in the synthesis of the hormone melatonin, produced by the pineal gland in the dark phase; melatonin modulates sleep quality because it transduces environmental photoperiodic information [36,50]. In several conditions, melatonin has been linked to improved quality of sleep, behavior, attention and memory [7,15,21,65,72].

Recently, it has been shown that there is no significant difference between the afternoon and bedtime melatonin salivary levels in children with WBS, which indicates a possible blockage in nocturnal melatonin synthesis. This study did not investigate the rhythmicity in this content for continuous days [66].

The present study is the first one that sought to investigate, in the same group of individuals with WBS, the relationship between behavior, memory, sleep disturbances and possible changes in the melatonin rhythm. Our hypothesis is that sleep disorders associated with deficit in melatonin production may be correlated with behavioral changes and memory in WBS.

2. Methods

2.1. Participants

This cross-sectional clinical study was conducted in accordance with regulatory standards of research involving human subjects, approved by the local ethics committee (Process 0548/2012). The study gathered 15 individuals from the Williams Syndrome Brazilian Association with clinical and molecular cytogenetic WBS diagnostics (FISH positive to elastin gene deletion at 7q11.23). The parents of 25 children with WBS were contacted, and all agreed to take part in the study. In this study, 60% of the children were male and 40% were females, aged 6–17 years (mean = 12.1 ± 3.7 months). The control group consisted by 20 individuals with typical development (67% male and 33% female; 11.2 ± 3.9 years-old).

Socioeconomic levels were determined according to the Brazilian Association of Research Companies [1]. The socio-demographic profile of the WBS group showed that 20% of the investigated population was in classification A2, 35% of the population in classification B2, 20% in the C1 class, 20% in the C2 class, and 5% in classification D.

The Full Scale Intelligence Quotient (FSIQ) estimated that subjects with WBS ranged from 44 to 68 points. The Verbal Intelligence Quotient ranged between 46 and 71 points, and the Performance Intelligence Quotient ranged between 52 and 70 points. The estimated values of Intelligence Quotient were established from two verbal subtests (Vocabulary, Similarities) and two execution subtest (Object Assembly and cubes) from the Brazilian version [30] of the "Wechsler Intelligence Scale for Children" (WISC-III) for children ages 6–16 years [74], and the Brazilian version [49] of the "Wechsler adult Intelligence Scale" WAIS-III, for adults ages 16–89 years [73].

For exclusion criteria, individuals who had co-morbidities, were medicated by melatonin or drugs that influence melatonin synthesis, such as β_1-adrenergic antagonists or some flavonoids [15,64], had conditions that could affect sleep such as epilepsy, had problems with tonsils/adenoids or demonstrated hearing or visual impairments were excluded from this study.

2.2. Procedures

2.2.1. Child behavior inventory

The behavioral profiles of individuals with WBS were obtained from the Brazilian version of the "*Child Behavior Checklist for ages four–18*" (CBCL/6–18) as normed by Bordin et al. [13].

This questionnaire is given as a direct interview with parents and consists of 113 items that are related to behavior problems; the informant classifies the behavior as not true or absent (score = zero), partially or sometimes true (score = one), or very true or often true (score = two) over the last six months. The sum of scores allows the evaluator to draw a behavioral profile of the child or adolescent (internalizing problems or externalizing problems) that is derived from an analysis of eight groupings of items: anxious/depressed, attention problems, delinquent behavior, social problems, thought problems, withdrawn, somatic complaints and aggressive behavior.

The raw scores on each factor were transformed into T scores at three levels, representing unaffected to the most severely affected individuals with symptoms ranging from non-clinical to clinical, respectively. The score for the non-clinical category is <67; the score for the borderline category is 67–70, inclusive; the score for the clinical category is >70. For internalizing and externalizing problems, this ratio should be <60 for the non-clinical category, from 60 to 63 for the neighboring category and >63 for the clinical category.

2.2.2. Auditory and visual memory

Auditory and visual sequential memory were investigated consecutively from the subtests "Digits" of the Brazilian version of the Wechsler Intelligence Scale (WISC-III, [30] and WAIS-III, [49]) and the subtest

Table 1
Percentual (%) of individuals with WBS that showed Clinical range or Borderline clinical range in the "*Child Behavior Checklist for ages four–18*" (CBCL/4-18) parameters.

	Activities	Social	School	Total competence	Anxious/ depressed	Withdrawn/ depressed	Somatic complaints	Social problems	Thought problems	Attention problems	Rule-breaking behavior
% clinical range	67	47	73	87	40	27	27	54	87	53	40
% borderline clinical range	6	13	20	6	20	27	0	13	7	34	20

	Aggressive behavior	Internalizing problems	Externalizing problems	Total problems	Affective problems	Anxiety problems	Somatic problems	ADH problems	Oppositional defiant problems	Conduct problems
% clinical range	34	87	60	87	73	73	13	60	27	40
% borderline clinical range	33	7	20	13	14	14	7	33	7	13

"Sequential Memory Visual" of the Brazilian version of Psycholinguistic Illinois Test of Abilities (ITPA; [12,62]). The digits subtest is an additional task of the Wechsler scale and consists of an oral presentation with instant replay of a sequence of eight series of numbers in direct order and a sequence of seven series of numbers in reverse order. The visual sequential memory subtest is a task that consists of the visual tasks ITPA and 25 sequences of meaningless figures ranging from 1 to 8 elements and evaluating the ability to reproduce the sequence of these figures immediately after presentation.

The scores obtained in the auditory and visual sequential memory tasks were compared with the scores provided by the respective instruments according to the chronological age of each participant to determine whether the performance was as expected.

2.2.3. Sleep Disturbance Scale for Children (SDSC)

To identify individuals with WBS who had sleep problems according to their parents, we used the SDSC [29], which contains 26 items, for the assessment of sleep in children and adolescents aged three to 18 years. Each item is scored from one (never) to five (always) according to its frequency in the last six weeks. Thus, higher numeric values reflect a greater severity of clinical symptoms.

The SDSC contains six subscales: *disorders of initiating and maintaining sleep-DIMS* (including sleep duration, sleep latency, going to bed without being sleepy, difficulty sleeping, sleep without anxiety, nocturnal awakenings and difficulty sleeping), *sleep-breathing disorders-SBD* (including breathing difficulties, sleep apnea and snoring), *disorders of arousal-DA* (including sleepwalking, sleep terrors, and nightmares), *sleep–wake transition disorders-SWTD* (including hypnic jerks, rhythmic movement disorders, hypnagogic hallucinations, nocturnal hyperkinesias, and bruxism), *disorders of excessive somnolence-DES* (including difficulty waking up, waking up tired, sleep paralysis and daytime sleepiness) and *sleep hyperhidrosis-SHY* (including sweating during sleep and perspiring during the night). The sum of the scores provides an overall score of sleep disturbance. The questionnaires were completed by parents of patients with WBS.

2.3. Laboratory methods

It has been established that the urinary levels of 6-sulfatoxymelatonin (aMT6s) closely parallels those found in the corresponding melatonin blood samples [34,63]. The parents received labeled sterile flasks for use in a continuous 72-hour urine collection during the day and nighttime, whether it was during wakefulness or spontaneous arousals during sleep. Sampling at nighttime was performed under low-intensity red light that did not disturb melatonin pineal synthesis [14]. The samples were kept at 4 °C until the end of the sampling when flasks containing urine were transferred to the lab where the samples were centrifuged (3900 rpm, 15 min) and divided according to the time of micturition as follows: 6:00 to 11:59 AM (excepted the first micturition of the day), 12:00 to 5:59 PM, 6:00 to 11:59 PM and 12:00 to 5:59 AM (including the first micturition of the day) for each 24 h and aliquoted in 1 mL final volume stored at −20 °C. The aMT6 levels were evaluated in duplicate by a competitive enzyme linked immunosorbent assay (ELISA) kit according to manufacturer's instruction (IBL, Hamburg, Germany). The samples from 6:00 to 11:59 AM, 12:00 to 5:59 PM and 6:00 to 11:59 PM were considered as containing aMT6s, thereby representing the light period. On the other hand, the samples from 12:00 PM to 5:59 AM (including the first micturition of the day) were considered to contain aMT6s, thereby representing the night period. All aMT6s assays are creatinine-standardized to account for differences arising from variations in urine concentrations. The results were expressed as ng/mg creatinine. The aMT6s level of subjects with WBS was compared with the level of healthy subjects matched for gender and chronological age.

2.4. Statistical analysis

Comparison of the two groups was performed using the Mann-Whitney *U* test; data were expressed as the mean ± standard error of the mean (s.e.m.), and values were considered significantly different at $p < 0.05$. The results are also shown as percentages relative to total number of participants of the group. For correlation analysis between the variables, behavior, sleep, memory and aMT6s, the Pearson correlation coefficients was used at 5% significance level. In order to compare the daytime aMT6s vs nighttime aMT6s urinary content, data were expressed as the mean ± s.e.m. of three days of samples grouped in the three daytime points vs mean ± s.e.m. of the samples grouped in the nighttime point. On the other hand, to identify rhythmicity of aMT6s, data of 72 h of each individual were analyzed independently. The presence of rhythmicity, the amplitude and mesor of the rhythms were analyzed applying the Cosinor method [57].

3. Results

The results of the CBCL showed that 87% of the WBS group presented clinical score on the overall competence and total behavioral problems scales. The most common behavioral problems were thinking, emotional problems and anxiety. More than 50% of individuals with WBS presented clinical score of activities, school, social problems, attention problems, internalizing or externalizing problems and attention deficit and hyperactivity (ADH) (Table 1).

The results in the auditory sequential memory test showed that 100% of individuals with WBS presented performance lower (from 1

Table 2
Sleep disorders in SWB children according to SDSC.

	DIMS	SBD	DA	SWTD	DES	SHY	TS
Mean	14.04	5.82	4.13	10.78	10.16	4.87	48.91
Standard error	1.02	0.62	0.36	0.87	1.03	0.69	2.72
Cut off	>21	>6	>11	>23	>19	>7	>52
Pathological (%)	20.0	40.0	0	0	0	27.0	33.3

DIMS - disorders of initiating and maintaining sleep; SBD - sleep-breathing disorders; DA - disorders of arousal; SWTD - sleep–wake transition disorders; DES - disorders of excessive somnolence; SHY - sleep hyperhidrosis; TS - overall score.

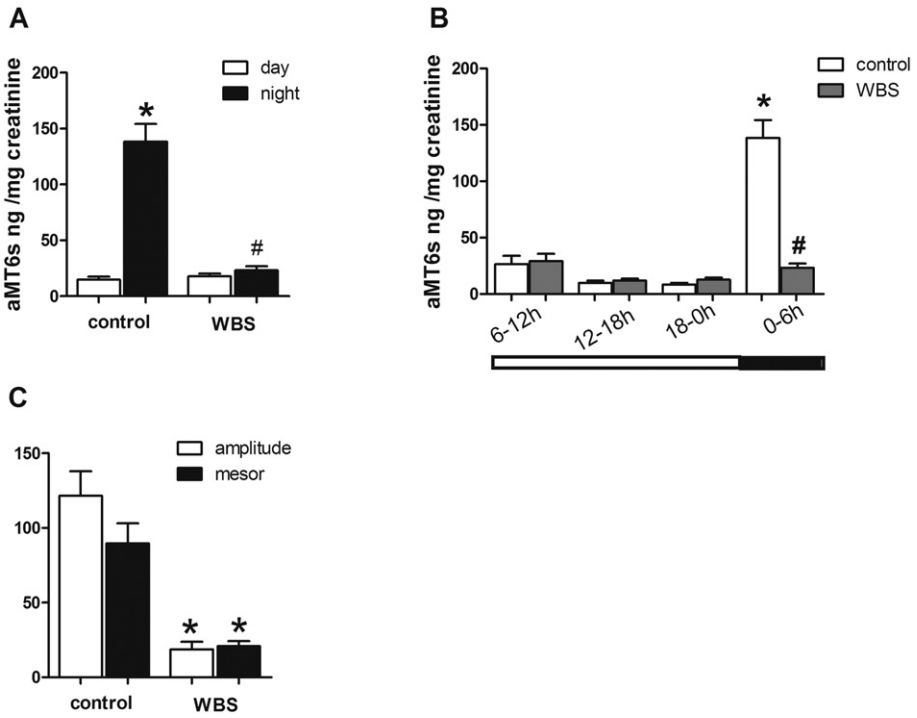

Fig. 1. Williams-Beuren syndrome (WBS) daily excretion of 6-sulfatoxymelatonin (aMT6s). In A, diurnal and nocturnal urinary levels of 6-sulfatoxymelatonin (aMT6s) (ng/mg creatinine) in control and Williams-Beuren syndrome (WBS) subjects. In B, pattern of aMT6s rhythm of controls (control) or individuals with Williams-Beuren syndrome (WBS) in four periods (06:00–12:00 h, 12:00–18:00 h, 18:00–24:00 h, 24:00–06:00 h) of three consecutive days. In C, amplitude and mesor of the aMT6s rhythm of controls (Control) and Williams-Beuren syndrome (WBS). The data are expressed as the mean ± s.e.m. of the aMT6s excretion rates, N = 20 subjects in control, and 15 in WBS group, $^{*}p < 0.05$ day ≠ night; $^{\#}p < 0.05$ control ≠ WBS.

to 6) than expected for its chronological age (10 ± 3), indicating difficulty in the immediate recall of auditory stimuli. The visual sequential memory test showed that 47% of individuals with WBS presented lower performance (15–26) than expected for chronological age (36 ± 6).

The evaluation of sleep shows that 65% of the WBS group displayed at least one sleep disorder. The most common disorders were SDB (40%), TS (33%), SHY (27%) and DIMS (20%) (Table 2).

The analysis of aMT6s levels (ng/mg creatinine) showed no daytime/nighttime changes (17.9 ± 2.3/23.2 ± 3.7) in the WBS group (Fig. 1A), and no changes in contents in each period (6:00–12:00 h; 12:00–18:00 h; 18:00–00:00 h, 00:00–06:00 h) were observed throughout the 24 h (Fig. 1B). Conversely, the control group showed difference ($p < 0.0001$) between the aMT6s contents during the daytime (14.9 ± 2.7) and nighttime (138.4 ± 15.9) (Fig. 1A). The Cosinor test showed that 26% of the WBS group presented circadian rhythmicity in aMT6s content with peak at nighttime; 21% showed delayed rhythm (peak of aMT6s excretion rates at daytime), and 53% showed absent circadian rhythm in aMT6s excretion rates. The amplitude (18.6 ± 5.1) and mesor (20.8 ± 3.3) of the aMT6s rhythm in the WBS group were lower than in the control group (amplitude 121.7 ± 16.2, mesor 89.6 ± 13.4) (Fig. 1C).

Finally, the investigation of correlation between behavioral findings, auditory sequential memory, visual sequential memory, sleep disturbances and aMT6s showed that aMT6s levels are related with DIMS ($r = -0.63$, $p < 0.05$) (Fig. 2A), and total sleep disorders (TS) are related with auditory memory ($r = -0.47$, $p < 0.05$) (Fig. 2B).

4. Discussion

Our behavioral investigation demonstrated that individuals with WBS presented high frequency of social and behavioral competence problems. Among the most common problems were thought, affective, attention, hyperactivity and anxiety, which have also been reported in previous studies [28,38,42,53].

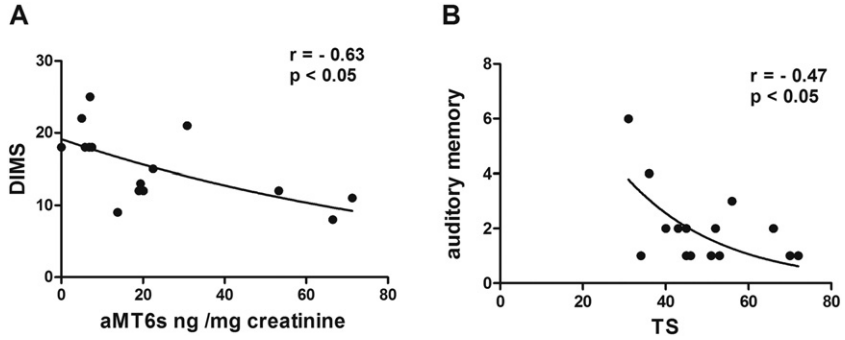

Fig. 2. Correlation between sleep disturbances (scores of Disturbance Scale for Children (SDSC)), the content of nocturnal 6-sulfatoxymelatonin (aMT6s) (ng/mg creatinine) excretion rates, and auditory memory observed in Williams-Beuren syndrome (WBS) group. In A, correlation between aMT6s nocturnal and disorder of initiating and maintaining sleep (DIMS). In B, correlation between overall score of sleep disturbance (TS) and auditory memory (N = 15).

Despite the known sociality and affectivity, these individuals have difficulties in organization of thought, and the vast majority of parents report the presence of several fears, obsessions and extreme anxiety [42]; according to Achenbach and Edelbrock [2], these are the three essential characteristics for the condition of internalizing nature of change, which justifies the fact that we found a high percentage of clinical scores for internalizing scale in the present study.

In the present study, the intellectual performance of the sample ranged from borderline to moderate intellectual disability similar to that reported in the literature [61]. In fact, the low intellectual functioning in WBS appears to be related to the greater awareness of problems related to the organization of thought, as referenced by teachers of these individuals [40].

The performance in the auditory and visual sequential memory of individuals with WBS was lower than expected for the age, similar to findings by Rossi et al. [60], thereby creating the context of executive function impairments in this syndrome [20,51].

The sleep quality of the WBS group was altered, which was indicated by DIMS, STWD and DES, which is corroborated by subjective or objective findings of sleep disorders in this population; this showed increased sleep latency, increased wake and moving time, and sleep fragmentation [6,11,32,66].

In the present study, nocturnal levels of aMT6s were lower in the WBS group than in controls. The absence of nocturnal melatonin peak in the WBS group opens perspective for a future investigation about the possible causes for this blockage in melatonin production. The pathway of melatonin synthesis involves the signaling of environmental light-dark alternations in the pineal gland. The retina on receiving the photic information synchronizes the hypothalamic suprachiasmatic nuclei (SCN) through retinohypothalamic tract. From the SCN, this information projects throughout a poly synaptic pathway that reaches the pineal gland [39]. In the absence of light, serotonin is acetylated in the pineal gland by the action of arylalkyl-amine-*N*-acetyltransferase enzyme (AA-NAT). The resulting *N*-acetylserotonin (NAS) is then methylated by *N*-acetylserotonin *O*-methyltransferase (ASMT or HIOMT) at 5-methoxy-*N*-acetyltryptamine or melatonin. Changes in this pathway may lead to a blockage on the production of melatonin, e.g., reduced expression of the enzymes AA-NAT or ASMT by genetic factors [37,46] or by the presence of inflammatory cytokines [55]. Furthermore, peripheral or central abnormalities in serotonin physiology resulting from genetic factors could affect melatonin production [3,71].

To our knowledge, no previously published study had examined the possible causality of sleep problems via an analysis of endocrine rhythm of aMT6S in the urine of children with WBS. Thus, this study demonstrated, for the first time, that more than 50% of the WBS population has no circadian rhythm in the aMT6s content.

Under normal conditions, the melatonin levels in plasma begin to increase before night-time sleep and reach a maximum between 3:00 and 4:00 AM [19]. Recently, it was demonstrated that there was no significant difference between levels of salivary melatonin in the afternoon and bedtime in WBS children [66]. Although, in this previous study, samples had been collected in only one day at three time points: 4–6 PM, at bedtime, and immediately after awakening. The results are in agreement with the present study that also indicated a lack of nocturnal peak of melatonin.

The negative correlation between aMT6s and DIMS reinforces the idea that, as in others pathologies, the lack of melatonin can exert a negative influence on sleep quality [22]. In fact, melatonin release into the bloodstream and cerebrospinal fluid indicates the role of darkness in these two important distribution compartments [43]. Thus, the lack of day/night melatonin variation can contribute to sleep disturbances, because the body loses an important biomarker of the dark, which contributes to a poorer quality of sleep [22]. Moreover, melatonin supports a nocturnal decrease in the core body temperature, which, in turn, facilitates sleep [5].

The results also showed correlation between the sleep and auditory memory performance data. These data corroborate previous findings that show that disturbed sleep in neurodevelopmental disorders is associated with poor daytime function and behavior [27,76].

It is believed that the poor performance in memory tasks, in addition to alterations of behavior, are factors that can significantly influence learning difficulties and lead to academic failure for these individuals. Additionally, melatonin can be an endocrine factor that is responsible for sleep problems in this population, and both factors in combination must be further investigated.

Although we recognize that it is a study with a restricted population, the results reported here open perspectives to discussing the viability of new therapies to improving the quality of sleep and consequently behavior and cognition in this population.

5. Conclusions

In summary, this study reinforces that individuals with WBS presented thinking, attention and emotional problems, anxiety, social and school behavioral problems, and poor performance on tests of auditory and visual memories. The presence of sleep disorders and their relationship to memory reinforces the idea that sleep investigation should be included in the clinical evaluation of children with WBS. This study also indicates that abnormalities in the melatonin rhythm may contribute to sleep problems in WBS and the consequential behavior problems.

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