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ORIGINAL ARTICLE

Sleep Disturbances in Patients with Asperger Syndrome Related to the Severity of their Symptoms

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Abstract
Patients with Asperger syndrome (AS) usually report sleep problems. The objective of this study was to compare the general sleep structure of children with Asperger syndrome to that displayed by healthy children through polysomnographic study. Sleep characteristics were compared to severity of AS symptoms. Two groups of children aged 8–12 years were studied, one group with AS patients and the other with healthy children. Results show that patients with AS had a significant increase in sleep latency, REM latency and a decrease in the number of REM sleep episodes. It was also observed that the AS patients exhibit a correlation between the fragmentation of sleep and the increase in the intensity of the AS symptoms. It is concluded that sleep latency, REM latency and number of episodes are affected in AS patients and the AS symptoms are related to sleep disturbances in patients.

Keywords Sleep · Asperger · Severity

1 Introduction

Sleep is a physiological and behavioral process that is characterized by the presence of a reversible state of unconsciousness, a diminished sensory activity and an almost absent motor activity. Some other behavioral characteristics that are present include closed eyes and a specific posture [11].

Sleep is related to fundamental processes for an adequate functioning of the organism. Among these processes are the consolidation of memory, the restoration of brain activity, the regulation of emotional states and cognitive abilities, as well as the optimal functioning of the body's immune system. Thus, an inadequate sleep causes negative consequences in the above-mentioned processes [2, 9, 11, 26].

Since sleep is a process that depends on the appropriate functioning of the central nervous system, any psychiatric or neurological disease has the potential to produce functional and structural alterations in sleep, causing a non-restorative sensation with the consequences mentioned above. Depression, anxiety, epilepsy, Parkinson's disease and neurodegenerative diseases are some of the conditions that have the greatest impact on sleep and therefore are widely studied. However, studies of sleep in patients with generalized developmental diseases (a group of conditions that include all types of autism described nowadays) have begun to yield strong data on the poor quality of sleep present in these patients [11].

In different sleep studies carried out on patients with autism, multiple disturbances such as decreased bed time, decreased total sleep time, increase in REM sleep latency, higher number of twitches, increase in wake time after sleep onset (WASO), increase in the number of phase changes, greater sleep fragmentation and higher percentage of N1 phase (light sleep) were produced. All these disturbances produce poor sleep quality [3, 6, 7, 10, 14, 15, 20, 24, 25, 27]. Although these general findings have been described by different authors, they are inconsistent and frequently contradictory, in part due to differences in the number and age of subjects used in each study and the great heterogeneity of the impairment level presented by the studied patients. Moreover, most of the autistic patients studied have not been adequately diagnosed showing different levels of disability.

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Sleep is essential for the proper development of children and adolescents due to the release of hormones, among other functions. It is also in this population where Asperger syndrome is most evident and most disabling. If therapeutic interventions are required to improve sleep in these patients, it is necessary that they be carried out from an early age and therefore it is important to study these populations in depth. This includes knowing if there are differences in the macroarchitecture of their sleep and if these parameters correlate with increases in the severity of the symptoms. The objective of this study was to carry out a comparative analysis between the severity level of patients with Asperger syndrome and their sleep characteristics.

2 Methods

2.1 Study Design

This was a cross-sectional, case–control study.

2.2 Participants

The study was done on 13 male patients with Asperger syndrome (6–12 years old; age mean 8.1 years) from the "Caritas de Amistad" foundation. They were diagnosed based on psychometric tests and neurological evaluations. There was also a health control group paired in age and sex with the participant patients. For all participants, informed consent was obtained from the parent or tutor.

The inclusion criteria were as follows:

For the AS group: having a diagnosis of AS performed by specialized psychologies in Caritas de Amistad association based on criteria from DSM-IV trough interviews with the parents and their children.

For the healthy group: sex and age matched with a member of the AS group.

The exclusion criteria were as follows:

For the AS group: the observation of any sleep disorder during the habituation night; comorbidity with attention/deficit hyperactivity disorders or intellectual disabilities.

For the healthy group: the observation of any sleep disorder on the habituation night or previously diagnosed; presence of chronic disease or health problems that will impact sleep quality or quantity; intake of medication.

Sampling for AS group participants was carried out through the voluntary participation of members of the Caritas de Amistad association, while for the typical development group, convenience sampling was carried out.

2.3 Materials and Instruments

Polysomnographic studies were performed using a Cadwell Easy II digital polygraph. In addition to the polysomnographic recordings, patients were psychometrically evaluated to compare their mental abilities with their sleep characteristics.

The following psychometric test was used:

• Childhood Asperger syndrome test (CAST). Dichotomous inventory of 37 items that includes statements about symptoms related to the diagnosis of Asperger syndrome, such as social relationships, language, communication, mental flexibility, behavior, fiction and imagination. The maximum score is 37 and the cutoff point is 15 for the diagnosis of AS [19, 21]. The sensitivity of the CAST, at a designated cut-point of 15, was 100%, the specificity was 97% and the positive predictive value was 50%, using the group's consensus diagnosis as the gold standard.

Regarding test–retest stability, the kappa statistic for agreement was 0.70, and 97% of children did not move across the cut-point of 15. The correlation between the two test scores was 0.83 (Spearman's rho) [21, 28].

2.4 Procedure

2.4.1 • Polysomnographic Studies

Both control and patient children underwent polysomnographic recordings for two consecutive nights during 8 consecutive hours. The recordings were carried out in the Neurosciences Laboratory of the Faculty of Psychology at the National Autonomous University of Mexico during the period of September 2013–December 2014. The first night was considered as adaptation to the recording conditions. Therefore, only the recording data from the second night were quantified.

According to the International 10–20 System, electrodes were placed to obtain the activity of the following EEG derivations: F3-M2, F4-M1, C3-M2, C4-M1, T3-M2, T4-M1, P3-M2, P4-M1, O1-M2, and O2-M1. Additional electrodes were placed to obtain the ocular (EOG) and muscular (EMG) activities, as well as the electrocardiogram (EKG).

Participant children and their caregivers were asked to be in the recording place 2 h before their usual bedtime. Once the electrodes were placed and the recording instruments were ready, children were asked to go to bed o begin the 8 h recording. The parent or tutor answered the CAST test while the children were being prepared for the study.

At the end of the recordings, the cables were disconnected, the electrodes were removed, and the patient

left the laboratory. Recordings were staged based on the Sleep Scoring Manual of the American Academy of Sleep Medicine.

After recording analysis, total sleep time was obtained and time spent in each sleep stage was calculated. The number and mean duration of REM sleep episodes were also obtained. Finally, sleep latency (time between the beginning of the recording and the sleep onset) and REM latency (time between sleep onset and the beginning REM sleep) were calculated.

2.5 Data Analysis

The statistical package SPSS was used for the analysis of the data. The data from the PSG recordings and the psychometric evaluations of the control and patient children were compared by means of the Mann–Whitney U test, while the Pearson correlation was used to determine the relationship between the sleep data and the behavioral and cognitive parameters.

3 Results

3.1 Demographic Information

The mean age of the HP group was 9.26 years with a standard deviation of 2.65, while the average age of the AS group was 9.60 years with a standard deviation of 1.84. All the participants were male. None of the participants had an additional diagnosis to Asperger's syndrome.

3.2 Sleep Parameters

As mentioned above, two nights of sleep recordings were conducted for both control and patient children and only the data from the second night were utilized for the comparative

Table 1 Polysomnographic data

	Group	Minimum	Maximum	Mean	SD	*U*	Sig.
Total sleep (min)	Control	454	528	479.50	21.30	60.50	0.735
	Experimental	396	495.5	467.86	29.33		
Latency to sleep (min)	Control	2	22.5	8.86	6.41	34.00	0.049*
	Experimental	2	89	21.36	23.96		
Percentage of N1	Control	4	14	7.54	3.72	64.00	0.901
	Experimental	3.4	12	6.58	2.28		
Percentage of N2	Control	36	54	45.81	5.60	48.50	0.280
	Experimental	34	60	48.81	7.94		
Percentage of N3	Control	16	31	25.00	3.97	51.00	0.354
	Experimental	16	33	25.90	5.73		
REM percentage	Control	16	25	20.54	3.01	37.00	0.073
	Experimental	10	25	17.90	4.30		
Total REM sleep time (min)	Control	79.5	122	101.40	15.45	36.50	0.069
	Experimental	40.5	121	85.04	22.87		
WASO (min)	Control	1.5	19	6.90	5.45	52.00	0.388
	Experimental	0	43	8	12.26		
Sleep efficiency	Control	94	99	96.36	1.80	42.00	0.136
	Experimental	81	99	93.54	5.26		
Latency to REM sleep (min)	Control	48.5	156	88.86	35.98	4.00	00.000***
	Experimental	132	211.5	176.13	25.89		
Number of awakenings per night	Control	1	18	6.63	5.39	45.50	0.204
	Experimental	0	10	3.63	2.73		
Number of REM sleep episodes	Control	4	7	5.27	.90	13.50	0.001**
	Experimental	3	5	3.81	.75		
Mean duration of REM sleep phase (min)	Control	11.4	24.4	19.77	4.37	39.00	0.096
	Experimental	*8.1*	*30.2*	*22.7*	*5.57*		

*Differences statistically significant considering a level of significance of 0.05

**Differences statistically significant considering a level of significance of 0.01

***Differences statistically significant considering a level of significance of 0.001

analysis. Tables 1 integrates the data of the patient and healthy children.

3.3 Comparative Analysis Between Groups

As observed in Table 1, the comparative analysis of the findings obtained from the sleep recordings, show that the number of REM sleep episodes was significantly greater in control children, while sleep latency and REM latency were significantly longer in the AS group.

3.4 General Descriptive Data from CAST Test

As observed in Table 2, patients presented CAST scores higher than the control group. Score range in patient children varied from 20 to 32, while in control group it did from 7 to 16.

3.5 Relationship Between Sleep Parameters and CAST Score

The comparison of CAST questionnaire scores of patients with their sleep parameters Table 3 showed a statistically significant negative correlation with decrease in N3 sleep stage ($p = 0.014$) as well as in the sleep efficiency ($p = 0.024$). In contrast, it was a statistically significant positive correlation in WASO (p 0.026).

Table 2 Descriptive data of the CAST questionnaire scores

	Minimum score	Maximum score	Average	Standard deviation
Experimental group	20	32	25.20	3.61
Control group	7	16	10	3.28

4 Discussion

Patients with Asperger syndrome have neurophysiological and neuroanatomical differences expressed as functional deficiencies in the frontal and temporal lobes, reduction in the volume of the cingulated gyrus, as well as anatomical abnormalities in the cerebellum [8, 17]. In addition, the earlier polysomnographic studies carried out in patients with Asperger syndrome evidenced some significant differences between the sleep structure of patients and the healthy subjects [1, 3, 6, 14, 15, 24].

There are numerous reports related to sleep in ASD patients which did not consider the severity level of participant patients. This omission has resulted frequently in contradictory findings because the severity level may affect differentially the sleep characteristics. In this context, relatively few studies have been carried out in chosen homogenous samples of patients with Asperger syndrome, considered in the last version of the DSM (2013) as level 1 of the ASD.

Comparative analysis of the sleep latency show statistically significant differences between healthy children and children with problems. Children in the AS group took longer to sleep compared to the HP group. These differences may be due to the hypervigilance, anxiety and mood disorders that these patients usually present and contribute to the presence of insomnia [23]. However, values of sleep latency showed by both groups fell within the reported ranges considered as normal [13].

REM sleep latency was statistically significantly longer ($p < 0.001$) in patients (176.13 min) than in healthy

Table 3 Pearson correlation comparing sleep parameters with the total of the score CAST test obtained by the patients

Sleep parameter	Pearson coefficient	Significance
Total sleep (min)	− 0.414	0.268
Latency to sleep (min)	0.415	0.267
Percentage of N1	0.267	0.487
Percentage of N2	0.601	0.087
Percentage of N3	− 0.814	0.014*
REM percentage	0.028	0.944
Total duration of REM (min)	− 0.027	0.945
WASO (min)	0.769	0.026*
Sleep efficiency	− 0.775	0.024*
Latency to REM sleep (min)	− 0.252	0.513
Number of awakenings per night	0.770	0.025*
Number of REM sleep episodes	0.016	0.967
Mean duration of REM sleep phase (min)	− 0.188	0.580

*Statistically significant correlation with the level of significance of 0.05

**Statistically significant correlation with the level of significance of 0.01

children (88.86 min), whose value is similar to that considered as the standard value for REM sleep latency [11].

The REM sleep latency of patients overpass the time where this phase usually is presented, instead it coincides in the time presentation of the second REM sleep phase in healthy participants. There is an elongation in the time spent in the N3 sleep phase that probably overshadows the appearance of the first REM sleep episode [11].

The increase in latency of this sleep phase could be directly related with the immaturity of the brain in these patients. Since this latency finding is similar to that described by Tanguay et al. [22], when compared with REM sleep of autistic children with that in healthy children 18 months younger, whose brain is more immature.

The reduction in the number in REM sleep episodes observed in patients was directly related to the increased latency to their REM sleep. However, no significant differences were found in the proportion of the REM phase in relation to the total sleep of the patients; these data indicate that there is REM sleep compensation throughout the night; otherwise the percentage of REM sleep would be lower in relation to the control group.

As a summary of this first part of the analysis, there are statistically significant differences in three of the sleep parameters registered through the polysomnographic study: sleep latency, REM latency and the number of REM episodes per night. Both REM parameters are related, since the increase in latency to REM sleep by itself explains the reduction in the number of REM episodes.

Although the other sleep parameters do not present statistically significant differences, a tendency of patients to have more fragmented sleep can be observed. In contrast, the control children tend to have a greater number of awakenings. However, they are brief and do not reflect an increase in WASO and/or sleep deficiency. In patients these values tend to be longer, followed by elongated sleep conciliation.

The results obtained in this research are, in general, consistent with other polysomnographic studies conducted on children with autism. Elia et al. [6] and Buckley et al. [4] found a significant elongation in REM sleep latency in autistic children. Elia et al. also found significant differences in other sleep parameters, such as a higher percentage of the N1 phase and a lower total sleep time. These parameters did not have significant differences in Buckley's study or in the present study, although a trend toward shorter total sleep time was observed. On the other hand, Buckley et al. found a decrement in the percentage of REM sleep in relation to the total sleep time, which was not observed in the present study. However, a significant decrease in the number of REM episodes was observed, which could have severe consequences in the development and the functioning of the brain in children with Asperger.

Differences in REM sleep latency between patients and those in the control children have been related to abnormalities in cholinergic mechanisms in the cerebral cortex of patients with autism in early stages of their development [16]. In addition, the main neurotransmitter responsible for the beginning and the maintenance of the REM sleep is acetylcholine, so deficiencies in this system of neurotransmission where the nicotinic receptors are involved will generate changes to delay the triggering of REM sleep and reduction in the number of episodes as observed in this study.

A decrement in the synthesis of melatonin in patients within the autistic spectrum disorder has been described [18]. This hormone plays an important role in the maintenance of biological cycles within the organism, including the distribution of REM sleep that appears approximately every 90 min alternating with SWS throughout the sleep period. Melatonin also participates in the consolidation and continuity of REM sleep [12], although no changes have been identified specifically on the latency to REM sleep after its administration. This may explain the decrement in the number of REM sleep episodes in this study.

In addition, Buckley et al. [4] suggest that the ponto–thalamic–cortical circuits that are activated during the REM sleep phase are necessary for the development of neuronal connections in the brain of developing children. Therefore, newborn infants have significantly more percentage of REM sleep that influences their brain maturation. Thus, any impairment in the parameters of REM sleep could negatively impact the development of nervous system functions, for example cognitive and behavioral deficiencies as described in individuals that do not have adequate REM sleep. In rats, it is observed that the deprivation of REM sleep in early stages of life is related to social deficiencies that appear later in its development [4].

On the other hand, the sleep disturbances identified in the studied patients are correlated to the severity of their autistic symptomatology constituted by impairment of social interaction, imagination, verbal and non-verbal communication, psychomotor development and flexibility of thought.

The negative correlation between the percentage of the N3 phase of sleep and the CAST test indicates that the lower percentage displayed by this phase is related to a greater symptomatology of Asperger syndrome. Also, the significant correlations between sleep efficiency, WASO and the amount of awakenings with the CAST test are directly related to sleep fragmentation and poor quality of sleep.

It has long been known that sleep deprivation has negative consequences on people's diurnal functioning. These consequences include fatigue, excessive daytime sleepiness, attention and memory problems and also a decrease in health and quality of life in general [11]. It has also been described that the lack of a good quality of sleep induces irritability, low tolerance to frustration and difficulty modulating

impulses and emotions [5]. These processes are mainly regulated by the prefrontal lobes, so any functional alteration in these lobes caused by sleep disturbances may explain the appearance of these behavioral disorders. The relationship between poor sleep quality (lower sleep efficiency, higher WASO and greater number of awakenings) found in this study and the increase in the severity of symptoms related to cognitive inflexibility, problems with socialization and non-verbal communication can also be explained by the functional affection of the prefrontal lobes by the sleep disturbances, since most of the processes that are affected in patients with Asperger syndrome are regulated by the frontal lobes [8, 17].

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Compliance with Ethical Standards

Conflict of interest The present paper does not have any conflict of interest.

Ethical approval The research has complied with all relevant federal guidelines and institutional policies in the use of human participants.

Informed consent The caretakers of every participant signed an informed consent disclosing the use of personal information.

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