A laboratory study of sleep in Asperger's syndrome

Roger Godbout,[1,3,CA] Cybèle Bergeron,[1] Élyse Limoges,[1] Emmanuel Stip[1,3] and Laurent Mottron[2,3]

[1]Centre de Recherche Fernand-Seguin, Hôpital Louis-Hippolyte Lafontaine, Montréal, Québec H1N 3V2; [2]Clinique spécialisée de l'autisme, Hôpital Rivière-des-Prairies, Montréal, Québec; [3]Département de Psychiatrie, Université de Montréal, Montréal, Québec, Canada

[CA,1]Corresponding Author and Address

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Asperger's syndrome (AS) is a pervasive developmental disorder that may fall along the autistic spectrum. We compared the sleep of eight patients with AS with that of participants matched for age and gender. Patients with AS showed decreased sleep time in the first two-thirds of the night, increased number of shifts into REM sleep from a waking epoch, and all but one patient showed signs of REM sleep disruption. EEG sleep spindles were significantly decreased while K complexes and REM sleep rapid eye movements were normal. Three patients with AS, but none of the comparison participants, showed a pathological index of periodic leg movements in sleep. These observations show that sleep disorders are associated with AS and suggest that defective sleep control systems may be associated with the clinical picture of AS. *NeuroReport* 11:127–130 © 2000 Lippincott Williams & Wilkins.

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INTRODUCTION

Asperger's syndrome (AS) is a pervasive developmental disorder whose continuity with high-functioning autism is still a matter of debate [1]. DSM-IV diagnostic criteria stipulate that individuals suspected of AS must show altered social interactions, restricted interests and repetitive and stereotyped behaviors as in autism but, contrary to the latter, should not show any significant language abnormalities and, more particularly, any delay in the acquisition of language, psychomotor or cognitive skills [2]. There are very few reports on the neuroanatomical or neurochemical basis of AS so that researchers and clinicians have to rely on studies of autism in order to further pathophysiological hypotheses. Anatomical and brain imaging studies in persons with autism have provided a list of candidate structural markers for the syndrome, including temporal/temporo-occipital systems, frontal lobes, hippocampus, and the cerebellum. However, when neurological (epilepsy, etc.) and medication status and IQ are controlled, results are far from unequivocal (for a complete review, see [3]).

Neurochemical and neuropharmacological studies have revealed some interesting results regarding serotonin. Three studies that measured plasma 5-HT found higher levels (hyperserotoninemia) in groups of children with autism than in children without autism [4–6]. More precisely, about 50% of children with autism showed high levels of plasma 5-HT, although this proved to be true only for those children with high functioning autism, i.e., patients with an IQ of $\geqslant 70$ [7]. The presence of antibodies directed against 5-HT receptors was also recently identified in the plasma of high functioning persons with autism but, again, not in those persons with intellectual handicaps (IQ <70) [5]. These results show that 5-HT neurotransmission is affected in high functioning autism, a finding that is likely true for persons with AS as well, given the resemblance between the two syndromes. However, as the two syndromes are independent clinical entities, it is also possible that they diverge in physiological, behavioral, and cognitive physiopathological measures.

The neuroanatomical and biochemical literature cited above prompted us to explore whether these etiological hypotheses could also point toward disorders of sleep or nocturnal EEG abnormalities. 5-HT is a major element in the modulation of the sleep–wake cycle and there is evidence in the literature suggesting that serotonergic neurotransmission abnormalities could be associated with sleep disorders in AS and autism [8,9]. Although there are no published reports dealing specifically with the EEG during sleep in persons with a clear diagnosis of autism, daytime waking recordings have shown that a relationship can be drawn between daytime waking EEG activity and the clinical picture [10].

Since the specific diagnostic criteria for AS were not published until very recently, only one case-study of sleep

and EEG in AS is available in the scientific literature [11]. Clinical observations suggest, however, that persons with AS may present the same sleep disorders as persons with autism, namely, difficulties in initiating and maintaining sleep, as well as disordered REM sleep [9,12–16] and nocturnal EEG abnormalities (see [11]). In the present study we investigated sleep organization and EEG phasic activity in eight patients diagnosed with AS.

MATERIALS AND METHODS

Subjects: Patients with AS were recruited through a specialized clinic in autism. Upon approval from the Ethics Committee, the first 10 patients formally diagnosed with AS and having a full-scale IQ >80 were asked if they would agree to be recorded at the sleep laboratory. Of these 10, eight patients with AS accepted (seven male, one female; 22.6 ± 13.6 years, range 7–53 years). Patients were diagnosed by explicit checking of DSM-IV criteria for AS [2], as well as with the administration of the Autism Diagnostic Interview by a trained clinician (LM) [17]. Inclusion criteria were a score above the cut-off point in the three relevant areas (social, communication, and restricted interest and repetitive behaviors) and an absence of delay for language and of language abnormalities typical of autism (echolia, stereotyped behavior, pronoun reversal) in past or current behaviors. The patient described in the published case-study [11] is part of the present sample.

Eight right-handed participants (seven male, one female; 24.3 ± 18.7 years old, range 7–61 years) formed the group of age- and gender-matched comparison participants. Exclusion criteria for comparison participants were a past or current history of psychiatric, neurological or other medical or sleep disorders. Comparison participants were also excluded if any of their first-degree relatives had a history of primary sleep disorder or major psychiatric illness.

All participants were asked to refrain from taking any CNS-active medication for at least 14 days prior to the recording. None of the participants but two had been exposed to antidepressants or neuroleptics in the 12 months preceeding the recording and none had been taking benzodiazepines for the last 3 months. The two treated patients were unable to comply with the medication withdrawal requirements for therapeutic reasons. One patient (No. 3) continued taking 40 mg of the 5-HT reuptake blocker fluoxetine each morning, and the other (No. 7) continued taking 3.5 mg haloperidol and 20 mg trifluoperazine daily.

Sleep was recorded for two consecutive nights and scored according to standard methods using 20 s epochs [18]. Sleep onset was defined as the first occurrence of either 10 consecutive minutes of stage 1 or one epoch of stage 2, 3, 4 or REM sleep. Total sleep time was defined as the total amount of minutes spent in any of the sleep stages during the sleep period (i.e. from sleep onset to final awakening). Total sleep time was broken down into thirds of the sleep period. Anterior tibialis EMG (two nights) and respiration flow (one night) were also recorded. Periodic leg movements in sleep (PLMS) were scored according to standard criteria [19].

Three sleep phasic activities were scored. Stage 2 sleep spindles were visually identified on the C_3 lead according to the following criteria: bursts of EEG activity at 12–15 Hz and lasting 0.5–2.0 s; no amplitude criteria were applied. Stage 2 K complexes were also visually identified on the C_3 lead according to the following criteria: a negative-going biphasic wave with a sharp onset and smoother offset, lasting 0.5–1.5 s and with an amplitude $\geqslant 75\,\mu V$. REM density was defined as the number of 2 s REM sleep epochs containing at least one REM. Sleep spindle and K complex, and REM density indices were calculated by dividing the total number of events by the time (in hours) spent in stage 2 and REM sleep, respectively.

Statistical analysis: All variables except stage shifts (waking to REM sleep, stage 1 to REM sleep, and stage 2 to REM sleep) and indices of phasic events (sleep spindles, K complexes, and REMs) were compared with the Kolmogorov–Smirnov two-sample test using an alpha of 0.10 [20]. The Kolmogorov–Smirnov is a non-parametric test that assesses the hypothesis that two samples were drawn from different populations. It is sensitive to differences in the general shapes of distributions in the two samples such as dispersion, skewness, etc. Pilot work indicated that this was the case with the present two samples. Since the number of shifts between sleep stages and phasic activity were similarly distributed within both samples, the Mann-Whitney U-test was used, with an alpha of 0.05 [20].

Ethics: All participants gave informed consent to take part in the study. The experimental protocol was approved by the Ethics Committee of the Centre de recherche Fernand-Seguin, Hôpital Louis-Hippolyte Lafontaine, where the study was performed.

RESULTS

Table 1 shows that, as a group, patients with AS had less sleep in the first two-thirds of the night than did comparison participants. Those with AS also made more entries into REM sleep from a waking epoch while comparison participants made more entries into REM sleep from a stage 2 epoch. Other macrostructural REM sleep parameters were normal in the group of patients with AS.

Analysis of phasic EEG events revealed a significantly lower density of sleep spindles in patients with AS. This difference was also observed in the first and the last third of the night. The difference in the second third suggested a trend approaching statistical significance (see Fig. 1). K complexes in stage 2 were far more prevalent in patients with AS, although this difference did not reach statistical significance, perhaps due to a high variability among the comparison participants that was noted for this measure. Similar rapid eye movements in REM sleep were observed between the two groups. As a group, patients with AS showed a pathological index of PLMS (12.3 ± 7.1) while comparison participants did not. Sleep apnea syndrome was absent from all participants.

Individual data of the patients with AS are presented in Table 2. All patients but one (No. 5) displayed at least one of the following disruptions of REM sleep: a short REM sleep latency (patients 1, 7, 8), a long REM sleep latency (patients 2, 3, 6), or dissociated REM sleep (patients 2, 3, 4, 7). REM sleep dissociation took the form either of increased EMG levels during otherwise typical REM sleep (scored as

Table 1. Sleep organization in patients with Asperger's syndrome and control subjects

	Asperger's syndrome	Controls	*p*
Total sleep time (min)	390.2 ± 7.2	401.4 ± 8.4	ns
Sleep time 1/3 (min)	127.8 ± 4.7	135.9 ± 4.0	*
Sleep time 2/3 (min)	132.5 ± 1.3	137.7 ± 1.3	*
Sleep time 3/3 (min)	129.8 ± 1.6	127.7 ± 6.2	ns
Sleep latency (min)	25.5 ± 9.1	14.2 ± 3.0	ns
SWS latency (min)	20.3 ± 12.1	21.7 ± 4.9	ns
REM sleep latency (min)	110.8 ± 26.8	93.5 ± 12.1	ns
Sleep efficiency (%)	93.6 ± 1.7	93.8 ± 1.6	ns
REM sleep efficiency (%)	89.0 ± 3.3	85.7 ± 3.1	ns
Stage shifts			
Waking to REM sleep (no.)	4.1 ± 1.3	1.3 ± 0.4	*
Stage 1 to REM sleep (no.)	4.5 ± 0.7	7.5 ± 2.3	ns
Stage 2 to REM sleep (no.)	2.6 ± 6.8	5.4 ± 0.9	*
Stage 1 (%)	20.4 ± 6.8	10.5 ± 1.9	ns
Stage 2 (%)	43.7 ± 6.6	56.9 ± 3.2	ns
Stage 3 (%)	9.6 ± 1.9	10.5 ± 3.5	ns
Stage 4 (%)	7.0 ± 3.4	7.6 ± 1.9	ns
REM sleep (%)	19.3 ± 2.1	18.6 ± 1.5	ns
Sleep spindle index (no./h stage 2)	141.8 ± 39.6	282.4 ± 44.4	*
K complex index (no./h stage 2)	109.1 ± 16.0	65.0 ± 20.0	ns
REM index (no./h REM sleep)	288.1 ± 55.5	305.8 ± 40.6	ns

*Statistically significant differences; see Materials and Methods for tests and alpha levels used.

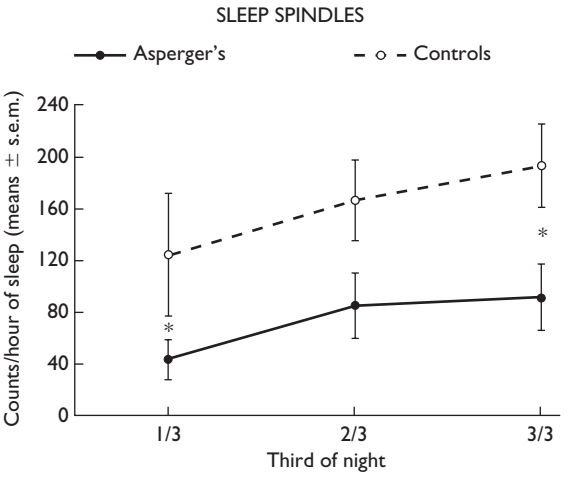

Fig. 1. Evolution of sleep spindles through the night in Asperger's syndrome and comparison participants. Stars indicate a statistically significant difference between the two groups.

stage 1) or of rapid eye movements during otherwise typical stage 2 sleep (scored as stage 2). Moreover, three patients (1, 4, 6) presented a pathological PLMS index.

Patients 3 and 7 were taking CNS-active medications at the time of recording. Their individual polysomnographic results, however, are well within the range of the other patients (see Table 2).

DISCUSSION

Apart from a case-study [11], this report is the first to objectively document sleep organization in AS. As a group, the patients with AS had difficulty initiating and maintain-

Table 2. Sleep organization in eight patients with Asperger's syndrome

ID (sex)	Age	Sleep latency (min)	Latency SWS (min)	Latency REM (min)	Total sleep time (min)	Sleep efficency[a]	No. awakenings	No. REM periods	Mean REM cycle length (min)	REM efficiency[b]	Stage 1 (%)	Stage 2 (%)	SWS (%)	REM (%)	PLMS index
1 (M)	53	85.7	103.3	48.0	372.0	88.7	61	5	81.9	90.9	63.4	11.1	0.4	25.1	47.3
2 (M)	20	26.7	16.3	139.3	403.8	97.1	19	3	108.9	85.8	8.4	61.9	8.2	21.5	0
3 (M)	15	10.3	5.7	134.7	399.7	96.1	30	4	100.1	92.6	8.2	47.5	21.3	23.1	2.4
4 (M)	7	6.3	1.7	80.7	401.7	96.9	20	4	99.8	96.1	18.2	21.0	42.2	18.6	35.3
5 (M)	25	14.3	18.0	87.0	365.0	89.3	45	4	97.2	91.4	19.1	57.4	5.1	18.4	0
6 (M)	22	30	0.3	277.7	361.7	86.0	32	2	175.5	67.6	24.2	46.9	13.3	6.5	13.6
7 (M)	16	11.3	7.7	48.7	410.3	97.6	20	5	72.3	97.4	7.6	49.6	18.3	24.6	0
8 (F)	22	19.0	9.7	70.7	407.3	96.9	23	5	83.8	90.9	11.1	53.4	18.1	17.2	0
Mean	22.5	25.5	20.3	110.8	390.2	93.6	31.3	4	102.4	89.1	20.0	43.6	15.9	19.4	12.3
s.e.m.	4.8	9.1	12.1	26.8	7.2	1.7	5.3	0.4	11.3	3.3	6.6	6.3	4.9	2.1	7.1

[a]sleep efficiency = [(total sleep time/total sleep time + waking time after sleep onset) × 100]
[b]REM efficiency = [(min REM sleep in REM periods/total REM period time) × 100]

ing sleep, as evidenced by the low amount of sleeping time in the first two-thirds of the night. Sleep latency, sleep efficiency and the proportion of stage 1 were, however, within the normal range. More striking than this limited sleep disruption, two interesting characteristics were observed in the present group of patients with AS: low incidence of sleep spindles and abnormalities of REM sleep.

Sleep spindles are thought to represent a sleep protective mechanism by which access of inputs to the brain (and their processing) are diminished through a deactivation of the thalamo-cortical loops [21]. Recent results have suggested that EEG sleep spindle density significantly correlates with selective attention in young, healthy human participants [22]. This is congruent with present results since persons with high functioning autism (and patients with AS) have selective attention atypicalities, namely difficulty switching attentional focus, enhanced visual search, and locally-oriented perceptual processing [23]. Decreased EEG sleep spindles could therefore reflect an abnormality in the capacity of the thalamo-cortical loop to contribute to the filtering of inputs, including of the perceptual type [21].

The REM sleep abnormalities found in seven of the eight patients may also be related to daytime cognitive difficulties in AS. It has been long known that REM sleep is related to daytime cognitive functioning [24]. The relationship between this sleep stage and daytime cognitive functioning in AS deserves further investigation.

Contrary to two previous studies which quantified oculomotor activity during REM sleep in patients with autism and reported either increased [12] or decreased [15] REM density, we did not find differences between patients with AS and comparison participants in terms of their REM density. While it is possible that patients with AS and those with autism may differ on oculomotor activity measures, the divergent findings are more likely explained by the present use of stringent diagnostic criteria, including IQ.

Finally, patients with AS, as a group, displayed a pathological index of PLMS; three patients contributed to this effect, including a 7-year-old child. It is still to be determined whether AS presents a particular susceptibility to this dopamine-dependent sleep disorder [19] and/or if it has a particular impact on daytime functioning in these patients. It is noteworthy however that PLMS has been frequently observed in Gilles de la Tourette Syndrome [25], a neuro-developmental disorder that shows co-morbidity with AS.

CONCLUSION

Sleep in AS presents with a variety of disturbances: sleep time in early night was low, sleep spindles were decreased, REM sleep was disrupted and PLMS was prevalent. Some of these features have also been reported in autism and most of them can be related to hyperserotoninemia [11]. The relevance of this instability of the sleep process to the clinical picture in AS needs to be systematically investigated.

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