Cyclic Alternating Pattern in Peripubertal Children

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Study Objectives: The aim of this study is to complement the data on the expression and characteristics of cyclic alternating pattern (CAP) events in children, specifically in the peripubertal age group of 8 to 12 years and to analyze the association of CAP events with arousals. The study of CAP and arousal is a useful tool for assessing sleep instability and fragmentation in children.

Design: Descriptive study.

Participants: Ten sex-matched healthy children, aged 8 to 12 years, underwent standard polysomnography after 1 adaptation night in the sleep laboratory. Sleep stages, CAP, and arousals were analyzed according to standard international rules.

Results: The mean CAP rate was 62.1% ± 10.8% and the mean CAP cycle duration, 24.6 ± 2.1 minutes. CAP A1 phase was the most numerous (85.5% ± 3.9%), whereas the A2 phase was 9.1% ± 4.7%, and the A3 phase as 5% ± 2.3%, (P < .01). Differences between boys and girls were detected by analysis of variance, namely increases of phase A2 and A3 subtypes in girls (P < .001). Stronger phase A1 subtype expression in slow-wave sleep was verified in both sexes. Positive correlation between electroencephalogram arousals and the sum of phase A2 and A3 subtypes was also present. The overall CAP rate is higher in this age group than the rate previously reported in children aged 6 to 10 years (62.1% ± 10.8% vs 33.4% ± 5.3%).

Conclusions: Our study provides normative data on CAP in children aged 8 to12 years and indicates that age and Tanner stages must both be considered when investigating peripubertal children.

Key Words: CAP, sleep in children, sleep instability, sleep fragmentation.

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INTRODUCTION

CYCLIC ALTERNATING PATTERN (CAP) REFERS TO ELECTROENCEPHALOGRAPHIC (EEG) ACTIVITY CHARACTERIZED BY SEQUENCES OF TRANSIENT EPISODES that differ from the activity of basal EEG and occur throughout non-rapid eye movement (NREM) sleep stages.[1] It may indicate sleep instability and/or a sleep disorder not covered by the standardized sleep fragmentation indexes using Rechtschaffen and Kales or the American Sleep Disorders Association criteria.[2-5] To enable clinical application, a consensus for rules and techniques on CAP detection has been published.[3] CAP expression is influenced by age and endogenous and exogenous features.[6-13]

Variation in CAP parameters has been described in different age groups, from the adolescent to the elderly.[14] Parrino et al[14] have suggested that, in normal healthy individuals, CAP expression shows a trend to a U-curve pattern, according to age. This assumption was based on data obtained on subjects between 10 and more than 70 years of age, subdivided in to 4 age groups. In individuals between 10 and 19 years of age, the CAP rate was 43% of NREM sleep; it was 32% in those between 20 and 39 years of age; 38% in those between 40 and 59 years of age, and 55% in those over 60 years of age. However, for the 0- to 14-age range, the pattern of the curve has not yet been clearly defined, even though lower percentages of CAP expression have been described in children aged 6 to 10 years, [15] which is lower than the values described for teenagers.[14] Also, between 10 and 19 years of age, children will go through puberty, and sleep will change significantly. We hypothesized that the expression of CAP in children aged 8 to 12 years of age may be different from that of the prepubertal children reported by Bruni et al[15] and could be different from that seen in the postpubertal age range (15-19 years). Also, the study of CAP is a useful tool to evaluate the instability and fragmentation of sleep in children and may be a valuable index in the investigation of behavioral changes, such as irritability, hyperactivity, and learning impairment.[17]

The aim of the present study was thus to complement the data on the expression and characteristics of CAP events in children with well-defined nocturnal sleep, a specific age limit, and a well-defined Tanner staging.[18]

METHODS

Subjects

Ten healthy children, aged 8 to 12 years, equally distributed according to sex, with a Tanner scale of pubertal development[18] of 2 and 3 were enrolled in the study. The mean age was 10 (± 1) years for boys and 11 (±1) years for girls. Our subject group had 3 girls and 3 boys at Tanner stage 2.

The exclusion criteria were the presence of the sleep-related complaints, general medical conditions, neurologic or psychiatric diseases, and the use of medications that influence sleep during the previous 6 months. A standard questionnaire was applied in order to screen for sleep-related symptoms and evidence of breathing disorders. The questions were answered by the children with the help of their attendant. All children were submitted to a

Disclosure Statement

This is not an industry supported study. Dr. Rosa has received a development and license fee for CAP detector with Flaga HF (Medcare); and has received free use of Somnologica Science from Medcare. Drs. Lopes, Roizenblatt, Guilleminaut, Passarelli, Tufik, and Poyares have indicated no financial conflicts of interest.

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physical examination; those with evidences of respiratory disorders, adenotonsillar hypertrophy, and/or breathing abnormalities detected during sleep recording were excluded.

Sleep Recording

Sleep quality in the sleep laboratory was assessed by questions designed to evaluate sleep satisfaction. The questions were answered by the children with the help of their attendant on a scale ranging from 0 (worst) to 10 (best).

After a 1-night adaptation to the sleep laboratory, sleep recording was carried out during the usual sleep time, with a minimum duration of 7.5 hours of total sleep time, using the Stellate System™, Harmonie 2.4 (Montreal, Quebec, Canada), with a sampling frequency of 200 Hz per channel. The recording included 4 channels for EEG (C3-A2, C4-A1, O1-A2, O2A1), 2 for electrooculogram (right and left), 2 for electromyogram (chin and anterior tibial), and 1 for electrocardiogram (modified V2 lead), as well as oronasal thermistors, microphone, thoracic and abdominal belts, and pulse oximetry (Ohmeda™, Helsinki, Finland).

Sleep and Visual Detection of CAP

Two investigators independently scored either sleep-wake architecture based upon Rechtschaffen and Kales criteria[4] or CAP. These investigators were blinded to demographic information. The analyzed sleep parameters were sleep-onset latency (3 consecutive epochs of stage 1 or any stage of sleep), total sleep time, sleep efficiency (total sleep time/total recording time), time awake after sleep onset, NREM sleep stages, and REM-sleep percentages of total sleep time. The arousal events were scored based on the American Sleep Disorders Association arousal definition for adults,[5] with arousal defined as abrupt EEG shift toward fast activity such as 8 to 13 Hz (alpha) or > 16 Hz (beta). In REM sleep, an increase in amplitude of the submental electromyogram was required to score an arousal event. A minimum interval of 10 seconds of continuous sleep was needed to score a new arousal.

Each sleep recording was exported in the European Data Format, and the Somnologica TM (Flaga-Medcare, Reykjavik, Iceland) program was used for visual scoring of CAP parameters, following the recommendations of the CAP Consensus Report.[3]

A CAP A phase was considered as periodic EEG activity during NREM sleep, characterized as transitory and abrupt variation in frequency and amplitude of basal EEG activity, lasting 2 to 60 seconds. A CAP B phase was described as the interval between 2 A phases, with the duration of 2 to 60 seconds, and CAP cycles were defined as the sum of A and B phases. CAP sequences, identified by repetitive clusters of stereotyped EEG features, were considered for at least 2 consecutive CAP cycles. The CAP parameters studied in NREM sleep were CAP rate (percentage of CAP sequences in total NREM sleep); CAP time, cycle count, and duration; CAP A phase count and duration; CAP B phase count and duration; and CAP sequence count and duration. An A phase was divided into 3 subtypes: subtype A1, with predominance of synchronized EEG activity, and less than 20% of desynchronization, such as delta bursts, K complex sequences, vertex waves, and polyphasic bursts (of slow and fast rhythms); subtype A2, scored in the presence of 20% to 50% of desynchronized EEG activity, with predominance of polyphasic bursts; and subtype A3, in which at least 50% of the EEG activity comprised low-amplitude fast rhythms, such as K-alpha complexes, arousals, and polyphasic bursts. A Phase A subtype index was calculated, expressed as the percentage of phase A1, or A2, or A3 per hour of NREM sleep.

Statistical Analysis

Central-tendency measures were expressed as mean ± SD. The Mann-Whitney U test for independent samples was used for identifying sex differences in sleep data, with a significance level of 5%. A 1-way analysis of variance, followed by the Tukey test, was used to describe the differences between CAP parameters during NREM sleep stages, and a 2-way analysis of variance, followed by the Tukey test, was used to detect sex differences between CAP parameters during NREM sleep stages. Correlations between sleep-architecture parameters and CAP events, as well as between arousals and phase A subtypes of CAP, were evaluated by Spearman correlation coefficient (r_S). The level of significance for the variance analyses and correlation tests was set at $P \leq .01$.

RESULTS

The sleep quality was satisfactory in all subjects; the mean score at the sleep-satisfaction questionnaire administered the morning following polysomnography was 8.7 ± 1.5. Sleep parameters were within normative values[19,20] in all children (Table 1). Significantly larger CAP rates were observed in slow-wave sleep (SWS) in comparison to stage 2 and stage 1 ($P < .01$), and no difference was observed between the rate measured in stage 3 and in stage 4 NREM sleep. Mean CAP duration was longer in stage 2 followed by stage 4 sleep ($P < .01$). The number of CAP cycles varied with NREM sleep stages and was greater in stage 2, followed by stage 4, whereas CAP cycle duration was also longer in stage 2 than SWS ($P < .01$, all). The mean duration of the A phase was longer in stage 4 and B phase in stage 2 ($P < .01$, all) (Table 2). The number of CAP sequences across NREM sleep was 29.5 ± 13.4, the duration of CAP sequences was 480.6 ± 215.9 seconds, the number of cycles per CAP sequence was 20.2 ± 10.0, and finally, the percentage of cycles per CAP sequence was 98.2% ± 1.1%.

CAP A-subtypes data are shown in Table 3. Phase A1 subtype was significantly higher than phase A2 and phase A3 subtypes ($P < .01$ for both) during NREM sleep. Additionally, the index of

Table 1—Sleep Parameters in 10 Children

	Mean	SD
SL, min	13.8	9.5
TST, min	485.6	42.8
SE, %	96.1	2.2
S1, min	16.1	5.7
S2, min	253	39.7
S3, min	15.4	3.0
S4, min	84	21.9
REM, min	109	22.3
Arousal, total no.	25.3	8.8
Arousal index, no.	3.2	1.2
Arousal index in stage REM	4.0	1.7
Arousal index in stage NREM	3.1	1.5

SL refers to sleep latency; TST, total sleep time; SE, sleep efficiency; S1, stage 1 non-rapid eye movement (NREM); S2, stage 2 NREM; S3, stage 3 NREM; S4, stage 4 NREM; REM, rapid eye movement.

Table 2—Cyclic Alternating Pattern Expression During NREM Sleep

	Total NREM sleep	S1	S2	S3	S4	ANOVA $F_{3,27}$	ANOVA *P*	Significant posthoc*
CAP rate, %	62.1 ± 10.8	23.5 ± 14.5	53.5 ± 13.0	92.6 ± 7.0	88.6 ± 9.7	95.7	<.0001	S4, S3 > S2, S1
Boys	56.9 ± 6.8	22.0 ± 17.9	46.6 ± 4.9	92.9 ± 6.8	82.1 ± 9.5			
Girls	67.0 ± 12.3	25 ± 12.5	60.5 ± 15.3	92.3 ± 8.1	95.2 ± 3.8			
CAP time, min	228.8 ± 46.3	3.8 ± 2.9	130.8 ± 37.3	14.4 ± 3.3	74.1 ± 22.3	71.6	<.0001	S2, S4 > S3, S1; S2 > S4
Boys	205.2 ± 35.9	3.1 ± 2.2	112.3 ± 30.5	15.2 ± 3.3	74.7 ± 24.0			
Girls	252.3 ± 46.4	4.5 ± 3.6	149.3 ± 36.5	13.5 ± 3.4	73.6 ± 23.2			
CAP cycles, no	567.3 ± 153	9.4 ± 6.6	313.3 ± 106.1	41.3 ± 10.3	202.3 ± 8.1	50.5	<.0001	S2, S4 > S3, S1; S2 > S4
Boys	494.6 ± 98.9	8.2 ± 5.6	251.2 ± 66.9	42.6 ± 11.9	192.6 ± 81.9			
Girls	640 ± 72.3	10.6 ± 7.9	375.4 ± 105.9	40.0 ± 9.5	213 ± 87.3			
CAP cycles, sec	24.6 ± 2.1	23.2 ± 4.1	26.3 ± 1.8	21.5 ± 4.2	22.7 ± 2.8	5.1	.006	S2 > S3, S4
Boys	25 ± 1.8	21.6 ± 2.3	26.8 ± 1.5	21.9 ± 3.2	23.9 ± 1.9			
Girls	24.1 ± 2.4	24.7 ± 5.1	25.9 ± 2.2	21.5 ± 4.2	21.5 ± 0.9			
Phase A, sec	7.4 ± 1.0	6.7 ± 1.1	6.5 ± 1.0	7.4 ± 1.1	8.8 ± 1.2	19.4	<.0001	S4 > S3, S2, S1
Boys	7.4 ± 0.9	15.0 ± 2.1	20.2 ± 0 .9	15.5 ± 4.0	8.6 ± 1.4			
Girls	7.4 ± 0.8	18.1 ± 4.4	19.5 ± 1.5	12.8 ± 3.0	9.0 ± 0.9			
Phase B , sec	17.2 ± 1.7	16.5 ± 3.6	19.8 ± 1.2	14.2 ± 3.7	13.9 ± 2.8	9.9	.0001	S2 > S3, S4
Boys	17.6 ± 1.9	15 ± 2.1	20.2 ± 0.9	15.5 ± 4.0	15.3 ± 4.0			
Girls	16.7 ± 1.7	15 ± 2.1	19.5 ± 1.5	12.8 ± 3.0	12.8 ± 3.0			

Data are represented as mean ± SD.
S1 refers to stage 1 non-rapid eye movement (NREM) sleep; S2, stage 2 NREM sleep; S3, stage 3 NREM sleep; S4, stage 4 NREM sleep.
*Posthoc comparison Tukey test, $P < .01$.

Table 3—Phase A Subtypes of Cyclic Alternating Pattern According to Sleep Stage

	Total NREM sleep	S1	S2	S3	S4	ANOVA $F_{3,27}$	ANOVA *P*	Significant Posthoc†
A1								
Duration, sec	6.7 ± 1.0	5.3 ± 1.0	5.6 ± 1.0	7.4 ± 1.2	8.4 ± 1.2	5.2	.006	S4, S3 > S2, S1
Boys	7.2 ± 7.0	5.7 ± 1.1	5.8 ± 0.6	7.3 ± 0.4	6.9 ± 4.0			
Girls	6.3 ± 6.0	4.9 ± 0.8	5.3 ± 0.6	7.5 ± 1.7	7.9 ± 1.0			
Index, %	85.5 ± 3.9	15.8 ± 11.2	47.5 ± 2.1	84.1 ± 15.2	84.5 ± 10.8	80.5	<.0001	S4, S3 > S2, S1
Boys	87.4 ± 3.3	14.8 ± 12.0	48.7 ± 2.9	78.1 ± 18.3	77.5 ± 10.5			
Girls	83.5 ± 3.6	16.7 ± 11.7	46.2 ± 11.9	90.1 ± 9.9	91.4 ± 5.6			
A2								
Duration, sec	9.5 ± 4.7	3.2 ± 4.5	8.4 ± 1.1	7.5 ± 5.5	13.3 ± 3.3	12.7	.0002	S4 > S2, S3 > S1
Boys	8.4 ± 4.4	3.6 ± 5.0	8.6 ± 0.6	11.4 ± 2.9*	15.1 ± 3.6			
Girls	10.6 ± 5.1	2.7 ± 4.5	8.3 ± 1.5	3.6 ± 3.6	11.4 ± 1.9			
Index, %	9.1 ± 1.2	1.9 ± 3.5	6.7 ± 5.6	3.6 ± 3.8	3.0 ± 2.4	3. 1	.04	NS
Boys	8.4 ± 4.4	2.9 ± 4.0	8.4 ± 3.1	2.9 ± 1.6	2.3 ± 2.6			
Girls	9.4 ± 5.4	0.8 ± 1.1	9.4 ± 6.5	4.2 ± 5.4*	3.7 ± 2.3			
A3								
Duration, sec	16.7 ± 3.3	10.1 ± 7.3	16.1 ± 3.3	3.5 ± 8. 0	22.0 ± 10.7	9.1	.002	S4, S2 > S3, S1
Boys	17.8 ± 4.0	9.3 ± 8.8	16.9 ± 4.1	0.4 ± 0.8	21.7 ± 12.9			
Girls	15.6 ± 2.1	10.9 ± 6.5	15.3 ± 2.5	0	22.4 ± 9.5			
Index, %	3.2 ± 1.4	3.5 ± 4.8	3.4 ± 1.9	0.6 ± 2.0	1.2 ± 1.2	2.8	.06	NS
Boys	2.4 ± 1.5	0.3 ± 6.6	2.0 ± 1.8	1.3 ± 2.8	1.2 ± 1.2			
Girls	3.9 ± 1.4	4.1 ± 2.8	4.7 ± 0.5 *	0	1.2 ± 1.3			

S1 refers to stage 1 non-rapid eye movement (NREM) sleep; S2, stage 2 NREM; S3, stage 3 NREM; S4, stage 4 NREM.
Data are presented as mean ± SD. Analysis of variance (ANOVA) phase A subtype characteristics and sleep stages.
*Mann-Whitney U test with $P < .05$ comparing findings between sexes.
†Posthoc Tukey test with P value < .01.

phase A1 subtype, as well as the duration of all other subtypes, was increased in stage 4 NREM sleep, particularly the duration of A3 subtype [$F_{2,18} = 77$, $P < .01$]. The mean duration of phase A3 was longer than any other subtypes [$F_{2,18} = 77$, $P < .001$], and phase A2 duration, greater than phase A1 (Tukey, $P < .01$).

Several significant correlations were found: a positive correlation was observed between the number of EEG arousals and the sum of phases A2 and A3 subtypes (r_S=0.90; $P < .01$), but not with phase A1 subtype (r_S=-0.08; p=0.83). A positive correlation was found between SWS and the index of phase A1 subtype (r_S =0.47; $P < .01$). A positive correlation was also found between the time awake after sleep onset and the index of phase A2 subtype during sleep stage 1 (r_S =0.62; $P < .01$). Additionally, a positive correlation was also found between the number of A3 subtype events and the sleep stage-2 duration (r_S=0.72; $P < .01$).

Although no sleep-architecture difference was observed between sexes, including the number of EEG arousals (as shown in Table 3), several sex differences were seen when phase A subtypes were compared: girls showed a significant increase of index of phase A2 subtype in stage 3 ($P < .05$) and phase A3 subtype index in sleep-stage 2 [$F_{3,24} = 6.5$, $P = .02$] and boys had a longer duration of phase A2 subtype in stage 3 ($P < .01$).

DISCUSSION

The study of CAP may be a tool for evaluating instability and fragmentation of sleep in children, but it is essential to get normative data. Our children were recruited with this purpose in mind. We first verified that they not only had normal polysomnography, but also had a subjective good night sleep as indicated by their postsleep inventory questionnaire.

Normative data on CAP have been published: Bruni et al[15] found that CAP rate occupied 36% of the sleep of 6- to 10-year-old children, and Parrino et al[14] mentioned a 43% rate in teenagers. In our 8- to 12-year-old group, the CAP rate was 62% ± 11%. This rate is higher than previously reported. This difference could be related to the age group of our subjects (8 to 12 years), to the peripubertal period (children were Tanner stage 2 and 3), or to the cultural and ethnic differences (Italian Caucasian versus multiethnic Brazilian). The higher EEG frequencies involved in phases A2 and A3 explain the positive correlation observed between these events and the number of EEG arousals, whereas the slow EEG frequencies involved in subtype A1 explain the positive correlation between CAP A1 and SWS percentage.

We also found a significant difference in phase A subtypes based on sex, with a higher amount of phase A2 and A3 in stages

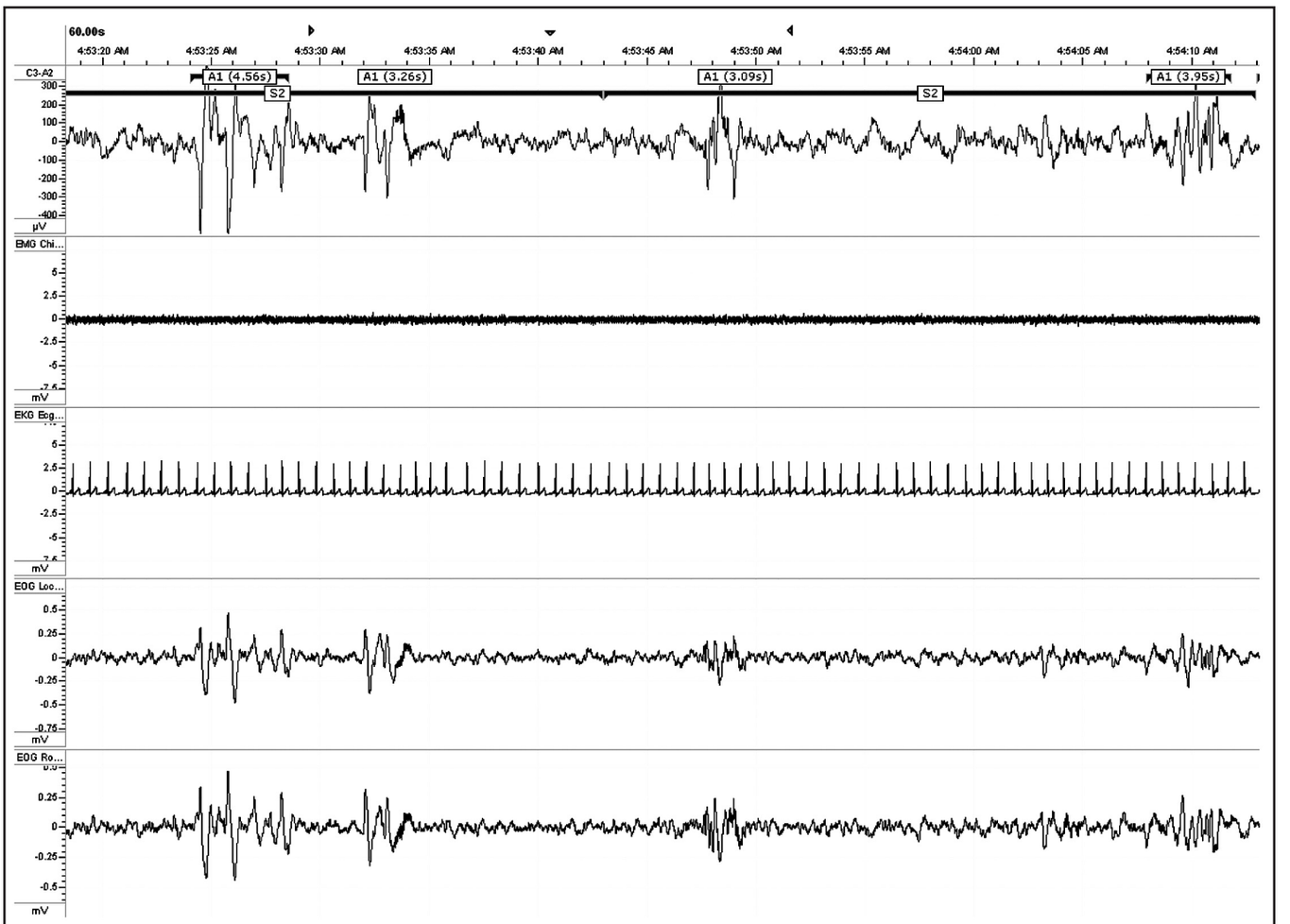

Figure 1—Example of A1 subtype of cyclic alternating pattern (CAP) expression in 60 seconds of stage 2 of non-rapid eye movement (NREM) sleep in 9-year-old girl (Tanner stage 2); the CAP rate was 66.7% in NREM sleep. As can be seen in this figure, A1 subtype in children exhibits prominent delta synchronism and relatively small duration. Channels are from top to bottom: C3-A2 (electroencephalogram lead); EMG (chin electromyogram), EKG (electrocardiogram); EOG Loc and EOG Roc (left and right electrooculogram).

2 and 3 NREM sleep in girls, suggesting a greater NREM sleep instability in this sex. But these last data should be interpreted with caution as these A2 and A3 phase sex differences could be related to the older age of the girls, despite the fact that boys and girls were matched for Tanner stages.

Overall, a predominance of phase A1 subtypes was found in both sexes (see Figure 1). Phase A1 subtype has a predominance of delta EEG frequencies and, therefore, could be associated with a lower arousability; also, the increase of phase A1 subtypes in SWS could be a marker of the NREM-sleep stability in the school-aged children before the onset of puberty. Similarly to Parrino et al,[21] in adults, positive correlations were detected between phase A2 and A3 subtypes and American Sleep Disorders Association EEG arousals in NREM sleep. The correlation between phase A2 and A3 subtypes and amounts of stages 1 and 2 supports the concept of the presence of a lighter sleep when these subtypes are recorded.

The presence of EEG arousals was within the expected normal range. However, the mean total group arousal index was 3.2 events per hour of total sleep time, which is a lower index than that previously reported in normal children.[15,20,22] This might be due to peculiarities of these populations.

Collection of more data during childhood is needed to map the normal evolution of CAP over time with the integration of the puberty-related hormone changes in this evolution. We acknowledge that, as in many normative studies on CAP, the number of subjects presented here is relatively small, and, subsequently, conclusions have to be limited. However, we balanced our group and studied an equal number of boys and girls and we carefully matched them for Tanner stages. The girls were slightly older than the boys; this difference could partially explain the sleep-EEG variations expressed by CAP analysis noted between sexes. But additionally, by using a more-limited age range than used in previous studies, we found that the reported U-shape pattern of CAP expression over time may not be as clear cut as published.[14] These discrepancies emphasize the need for investigation of more children with a more-limited age span.

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