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Cyclic alternating pattern in infants with congenital hypothyroidism

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Abstract

Congenital hypothyroidism is defined as thyroid hormone deficiency present at birth which is crucial for brain development. Recently, the cyclic alternating pattern, a rhythm present in electroencephalography recordings in non-Rapid eye movement sleep, has been related to brain development and cognition in different pediatric conditions. Therefore, we evaluated the cyclic alternating pattern rate in infants with congenital hypothyroidism, thyroxine supplementation, and healthy controls. The parameters of the cyclic alternating pattern were evaluated in 19 healthy infants (10 female, mean age 25.5 ± 15.5 months) and 21 infants diagnosed with congenital hypothyroidism (19 female, mean age 24.3 ± 19.0 months). We considered the transient electro-cortical activations (phase A of the cycle) in non-Rapid eye movement sleep and the subdivisions of the A phase in: A1, A2 and A3, based on their frequency content. All subjects were subjected to polysomnography recording in a standard laboratory setting. Sleep data were stored computer following the International 10–20 System. Data showed that congenital hypothyroidism infants exhibited higher frequency of central apnea, hypopnea, and arousals in comparison to controls. Particularly, central apnea index decreased with age in the control group but not in congenital hypothyroidism group. Regarding to cyclic alternating pattern measurements, congenital hypothyroidism infants exhibit a higher frequency in the percentage of A3 subtype (electroencephalographic desynchrony) and conversely a lower percentage of A1 subtype (electroencephalographic synchrony), than healthy infants. An important finding of this study is the positive correlation between A1 mean duration and age, which is bigger in control group than in congenital hypothyroidism group (time duration in control group (0.52 s/month) *versus* congenital hypothyroidism group (0.1 s/month). Infants with congenital hypothyroidism showed an increase of A3 subtype, of central apnea, and of arousals. The reduction of

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percentage and mean duration of A1 subtype could be a valuable indicator of sleep development in patients with congenital hypothyroidism and healthy infants.

Keywords: Cyclic alternating pattern; Congenital hypothyroidism; Polysomnography; Infants

1. Introduction

The thyroid hormone (TH) plays a major role in the late brain development [1]. Congenital hypothyroidism (CH) is defined as a deficiency in the thyroid hormone that can be induced by: problems with thyroid gland development or alteration of thyroid hormone biosynthesis (resulting in primary hypothyroidism); thyroid stimulating hormone (TSH) deficiency (inducing secondary or central hypothyroidism); or rarely, by mutations in the TSHβ subunit gene (Congenital TSH deficiency) [1]. Congenital hypothyroidism appears to be associated to a congenital malformation including neurologic abnormalities [2], that could be irreversible after birth [3]. The developing embryo and fetus is dependent on maternal supply of TH providing a protective effect, especially to the fetal brain, the adverse consequences of severe maternal TH deficiency of offsprings neurodevelopment are well established after this time as occurs in CH [1,4]. The fetal thyroid gland does not begin THs synthesis until mid gestation, recent evidence suggests that even mild forms of congenital thyroid dysfunction, particularly during early postnatal development, may have a long-lasting influence on child cognitive development and a high-risk for neurodevelopmental disorders such as mental retardation and could be irreversible after birth [3] Therefore, as other authors we agree it is important to gain a better understanding of the role of CH and its effects [5]. Sleep development is an important indicator of early development of the human central nervous system. Hayashi and cols. reported that patients with CH did not exhibit sleep-wakefulness circadian rhythm disturbances but two child showed a rapid eye movement (REM) sleep decreasing, which was reverted after L-thyroxine replacement [6]. In addition, other sleep parameters were evaluated in patients with CH in a study by Terán-Pérez and colleagues. They reported that 43% of patients displayed central apnea and 83% hypopnea in the range from 4 to 8 months of age, decreasing with the hormonal replacement therapy [7]. In that casem the changes in sleep macrostructure in patients with CH should be consider as a link between sleep disturbances and cognitive impairment reported in patients wit CH.

Cyclic alternating pattern (CAP) is a rhythm present in electroencephalography (EEG) recordings in non-Rapid eye movement (NREM) sleep characterized by periodic bursts of transient EEG activations (phase A of the cycle) different from the background activity [8]. The sequences are repeated several times, specially at first cycles of sleep during the night, and interrupted by presence of stable sleep without oscillations called non-CAP phase. There are three main EEG patterns (also called phases) described according to the prevalence of EEG synchrony (subtype A1), prevalence of EEG desynchronization (subtype A3), or a combination of both (subtype A2) [9]. During the first year of life the progressive increase in CAP rate with deepness of sleep, and with age, is associated to maturation of slow-wave activity [9].

The lower percentage of A1 phase with an increase of A2 is considered a reflect of higher NREM sleep instability [10] and the alterations in CAP parameters are reported in children disease related to cognitive deficits including Asperger syndrome, dyslexia, epilepsy, Down syndrome, Dravet syndrome, overweight, sleep enuresis, in children born to depressed mothers, catathrenia and bruxism in 10 years old patients [11–19].

Although evidence suggest that CAP is an important factor that correlates with neurophysiological aspects of sleep and cognition in children [20–22], there are no previous reports that analyse the CAP in infants with CH. As a consequence our objective was to investigate the CAP features in infants diagnosed and treated for CH.

2. Material and methods

2.1. Participants

Nineteen healthy subjects (10 female, [53%]; mean age 25.5 ± 15.5 months) were recruited for this study after a neurodevelopmental assessment and the confirmation of no aggregated illness. Twenty one-CH infants born in Mexico City (19 female, [90%] mean age 24.3 ± 19.0 months) detected using the mandatory national screening for CH, were recruited at the National Institute of Pediatrics with complete follow-up study. The hormonal replacement treatment started immediately after the patient's identification and the treatment onset was usually between 1.3 and 7.7 months of age. Infants with CH were studied at the laboratory of neurodevelopment and the thyroid hormone replacement dosage was established following the guidelines of the American

Academy of Pediatrics. All the infants diagnosed with CH had normal thyroid hormonal levels and within range accepted for laboratory standards at the time of the study (Thyroid stimulant hormone: $x = 2.1 \pm 1.9$ μIU/dL; T3: $x = 170 \pm 31.3$ ng/dL; T4: $x = 11.1 \pm 1.8$ μg/dL). The infants displaying a concurrent illness were excluded from the study, particularly those displaying macroglossia or severe alterations of the oropharynx. The research and ethics committees of the participants institutions approved the study and parents signed an informed consent letter after a wide explanation of the objectives of the study following recommendations of Declaration of Helsinki.

2.2. Polysomnographic study

The polysomnographic recordings were performed at the clinic of sleep disorders in which all infants were scheduled for a polysomnographic study in the morning, at home, and were brought to the sleep laboratory. Silver plate electrodes for electroencephalographic (EEG) recording were placed in scalp following the International 10–20 System [23]. Other electrodes were used to study eye movement, electromyography (EMG), nasal thermistor and thoracic and abdominal belts for respiratory activity. Infants were allowed to sleep for recordings of at least 2 h. This procedure allowed to us the acquiring at least two sleep cycles. Polysomnographic recordings in all infants started between 8 and 8:30 and usually lasted until 10:30 and 11:00 h. The scoring of each sleep stage was blindly done following the international guidelines used for infants and children [24,25]. Sleep architecture was classified in three NREM sleep stages: N1, N2, and N3; and REM sleep. The following variables were studied: total sleep recording, total awake time, total sleep time, total time in REM sleep, total time in NREM sleep, total time in N1 + N2 sleep, and total time in N3 sleep. We also evaluated: apnea/hypopnea index, oxygen saturation, and arousal index.

2.3. Cyclic alternating pattern (CAP) scoring

The CAP is defined as a rhythm present in NREM sleep characterized by EEG activity with sequences of transient electro-cortical activations (phase A of the cycle) different from EEG background activity (phase B of the cycle). These sequences are repeated several times during night in a cyclic pattern interrupted by stable sleep without oscillations, called non-CAP phase longer than 60 s. The A phases of the CAP were subdivided in different subtypes: A1, A2 and A3, based on their frequency content. Subtype A1 was composed predominantly by slow waves (EEG synchrony), subtype A3 with prevalence of fast EEG activities (EEG desynchrony), and subtype A2 presenting a combination of both. CAP scoring was manually blindly performed by two qualified neurophysiologists, based on the Atlas of qualification of Terzano [26], using the Somnium program, center-occipital areas were evaluated only to mark the CAP A phase subtypes and phase B [27]. CAP parameters studied were as follows: CAP rate, CAP time, index of each CAP subtype, percentage of each subtype, mean duration of each subtype, and CAP sequences.

2.4. Statistical analysis

The CAP parameters as well as polysomnographic, arousal and respiratory data were summarized by mean and standard deviation for each of two groups: infants diagnosed with CH and controls infants. Student's *t* test was used for unadjusted between-group comparison. Homoscedasticity of the distribution in each variable was evaluated by Levene's test. For the lack of homoscedasticity, statistical difference was determined by Welch two-sample *t* test. For all of unadjusted comparison the effect size was showed by Cohen's d and η^2. To determine the effect of CH on CAP parameters, controlling the age effect, we performed analysis of covariance (ANCOVA). Main effect was interpreted when the interaction between CH and age was discarded. If the interaction effect was presented, single linear regression model was interpreted separately for each of CH group and control group. The R^2 was given to show effect size in each model. For recognize the statistical significance we used as critical value of $p < 0.2$ for interaction effect and $p < 0.05$ for main effect. As we had to perform multiple statistical test, the statistical significant level was determined according to Holm-Bonferroni method considering the polysomnography, the arousal and the respiratory as one family and CAP parameters variables as another one for multiple comparison. All statistical analysis was done with JMP11 of SAS Institute, Inc.

3. Results

In the present study, a total of 19 control infants and 21 infants with CH participed. No differences were observed in the age at time study between control and CH groups. The percentage of females in the group of CH was higher compared to control group (53%, $p = 0.006$). No differences were detected in sleep architecture parameters in polysomnographic variables between control infants and infants with CH (Table 1). Respiratory events including apnea/hypopnea index, central apnea index, NREM sleep duration, arousal index, arousal index in REM sleep, and in NREM sleep were higher in infants with CH in comparison to healthy infants.

Table 2 shows CAP features between control infants and infants with CH. The CAP rate, CAP time, A1

Table 1
Polysomnography, arousal and respiratory data from controls and patients with congenital hypothyroidism (CH).

	Control (n = 19)	CH (n = 21)	η^2	*P*-value[¶]
Total recording time (min)	121 (63, 142)	120 (88, 133)	0.01	0.456
Total awake time (min)	6 (0, 20)	3 (0, 16)	0.07	0.082
Total sleep time (min)	114 (57, 135)	111 (83, 119)	0.02	0.424
Total REM sleep time (min)	23 (13, 40)	25 (9, 67)	0.02	0.371
Total no-REM sleep time (min)	92 (39, 104)	82 (42, 101)	0.03	0.279
N1 + N2 sleep time (min)	6 (0, 21)	14 (0, 30)	0.07	0.097
N3 sleep time (min)	84 (35, 102)	72 (42, 88)	0.08	0.067
AWN, no./h	1.4 (0, 9.3)	1.0 (0.0, 7.6)	0.07	0.644
Arousal Index, no. /h	6.0 (1.3, 10.5)	11.1 (2.9, 32.4)	0.27	0.001[*]
AHI (no./h)	4.2 (1.0, 7.3)	17.4 (3.7, 98.3)	0.53	<0.001[*]
OAI (no./h)	0.1 (0, 1.4)	0 (0.0, 4)	0.01	0.467
HI (no./h)	0 (0, 3.6)	1.1 (0.0, 23.3)	0.36	<0.001[*]
MAI (no./h)	0 (0, 0.6)	0.0 (0.0, 13.6)	0.05	0.172
CAI (no./h)	4 (0, 6.3)	13.6 (2.6, 77.1)	0.30	<0.001[*]
Mean SpO_2 (%)	91.4 (85.6, 94.4)	91.4 (84.3, 97.1)[*]	0.01	0.560

min = minutes. no. = number. h = hour. REM = Rapid eye movements. Mean (minimum, maximum).
[¶] Statistical test by Wilcoxon rank sum test.
[*] Statistically significant according to Holm–Bonferroni method.

Table 2
Cyclic alternating pattern (CAP) parameters from control group and infants with congenital hypothyroidism (CH).

	Control (n = 19)	CH group (n = 21)	η^2	*P*-value[¶]
CAP Rate %	70 (28, 94)	50 (5, 81)	0.17	0.009[*]
CAP time (min)	50 (19, 82)	42 (2, 72)	0.10	0.051
A1 %	79 (49, 90)	72 (16, 84)	0.16	0.011[*]
A2 %	9 (3, 16)	9 (0, 14)	<0.01	0.914
A3 %	11 (4, 34)	22 (9, 84)	0.19	0.005[*]
A1 Index, no./h	70.4 (21.3, 95.7)	54.9 (5.8, 101.1)	0.18	0.008[*]
A2 Index, no./h	7.0 (2.5, 13.8)	5.7 (0.0, 16.2)	0.23	0.151
A3 Index, no./h	9.2 (4.4, 23.1)	13.7 (6.5, 58.7)	0.15	0.016[*]
A mean duration, s	8 (5, 16)	6 (5, 11)	0.17	0.009[*]
B mean duration, s	20 (17, 31)	24 (18, 29)	0.08	0.083
Isolated A phase, no.	13 (4, 29)	19 (8, 25)	0.09	0.054
Sequence mean duration (min)	10 (6, 18)	6 (5, 12)	0.25	0.002[*]

[¶] Statistical test by Wilcoxon rank sum test. Mean (minimum, maximum).
[*] Statistically significant according to Holm–Bonferroni method.

percentage, A1 index, A1 mean duration, A phase mean duration, and CAP sequences mean duration were reduced in infants with CH compared to control group. Conversely, we found significant higher values in A3 subtype percentage and in number of isolated A phase in infants with CH compared to control group (see Table 2). A crucial finding was the correlation positive correlation between the A1 mean duration and the age (first 2 years of life) in the control group ($p < 0.001$) in which there are an increase of 0.52 s per month ($R^2 = 0.77$, $p < 0.001$) meanwhile in the CH group it increase just 0.1 s ($R^2 = 0.65$, $p < 0.001$) (Fig. 1).

4. Discussion

This is the first study to evaluate CAP parameters in infants with CH. We found a high prevalence of female infants with CH and an increase in central apnea, arousal index, and CAI. These data corroborate previous findings that indicate that CH is associated with the presence od central sleep apnea [7].

In addition, we reported for first time that CAP is altered in infants with CH characterized by the higher percentage of A3 subtype in CH children that is similar to findings in children with autism [13] suggesting NREM sleep disruption [28]. In contrast, we found a A1 subtypes reduction, the A1 subtypes are indicative of neuronal mechanism for NREM sleep maintenance [28] and the decrease in this phases may reflect the poor maturation of arousability [29]. The reduction in the central apnea index correlates with the age in the control group but not in CH group despite an adequate endocrine supplementation (Fig. 2). Our data suggest that child with CH are at high-risk for sleep respiratory disturbances such as central apnea. Although several sleep macro-architecture parameters comparison showed no

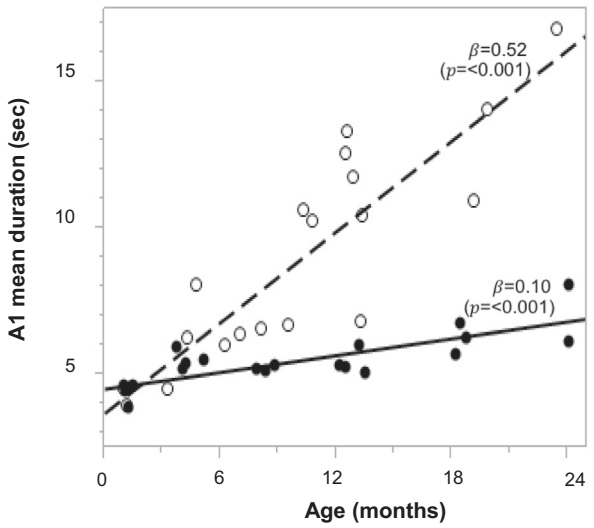

Fig. 1. Linear regression analysis of A1 mean duration and age in the control group (open circles) and CH group (dark circles). Both groups exhibit an increase in A1 mean time but with a different time increase per month: control group = 0.52 s per month ($R^2 = 0.77$, $p < 0.001$), CH group = 0.1 s per month ($R^2 = 0.65$, $p < 0.001$).

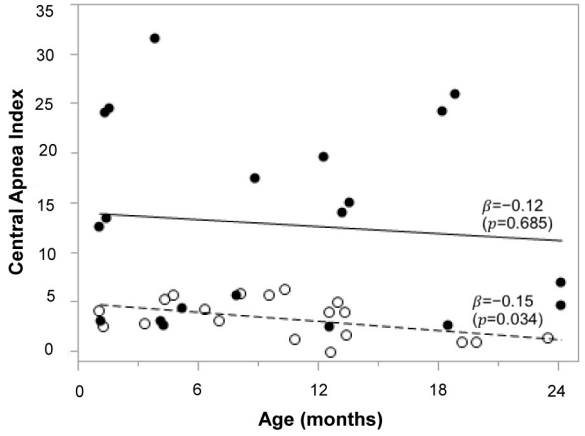

Fig. 2. Simple linear regression analysis of age (months) and Central Apnea Index (number of events per hour) in the control group (open circles) and CH group (dark circles). Note the negative correlation between age and Central Apnea Index in control group ($\beta = 0.15$, $R^2 = 0.24$, $p = 0.034$) but not in CH group ($\beta = 0.12$, $R^2 < 0.01$, $p = 0.685$).

differences between control infants and infants with CH, almost all CAP parameters showed significant differences between groups, underlining importance of CAP in neurodevelopmental disorders.

The reduction of A1 subtype percentage and in the time of mean duration is reduced in CH infants and the increase of A3 percentage. Above mentioned indicate unstable sleep meanwhile the decrease in A1 subtype is reported in other pathological conditions including autism, attention deficit hyperactivity disorder, infants with apparent life-threatening events, Down syndrome, and fragile X syndrome [21,29,30]. The increasing in the CAP rate, mainly to the significant difference in the mean duration of A1 (cortical synchronization), might be related to the dysfunction in the neural network of sleep subserving to the sleep control in children with CH despite hormone treatment. Thereby, we suggest that polysomnographic recording must be performed in infants diagnosed with CH to detect those who are at high-risk for neurodevelopmental alterations [31].

Some limitations should be acknowledged. The small number of subjects and the daytime recording of sleep could not give as a complete picture of the sleep structure of the infants. Despite above mentioned limitations, this is the first study that report CAP alterations in infants diagnosed with CH and thyroxine supplementation. In addition, these data strongly contribute to the proposal regarding to the CAP measurement is an indicator of sleep development related to brain maturation, particularly the A1 and A3 subtypes. More studies are needed for the fine understanding of thyroid hormone and its relationship with CAP structure and development.

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Authors' contributions

R. Santana-Miranda took part in the conception and design of the work, performed polysomnographic studies in infants, evaluated sleep parameters and CAP, and took primary responsibility of writing the manuscript. C. Murata performed the statistic analysis and critically revised the paper. A. Rosa, C.A. Castillo Montoya, J.A. Rojas Zamorano, A. Poblano and E. Esqueda León analysed polysomnografic data to identify CAP parameters and critically revised the paper. G.A. Alvarado Ruiz followed the neurodevelopment in infants included in the study. O. Bruni and E. and Dominguez-Salazar took part in the conception of the final manuscript vesion and critically revised the manuscript. J. Velazquez-Moctezuma took part in the design of study and critically revised the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that there are no competing interests.

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