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ARTICLE

Sleep disorder investigation might be considered to be mandatory in attention deficit/hyperactivity disorder guideline

Investigação de distúrbio do sono deve ser considerada obrigatória e incluída no manejo de distúrbios do déficit de atenção/hiperatividade

Paulo Sérgio Azeredo Henriques Filho[1,2,3]

ABSTRACT

Objective: To determine the prevalence of obstructive sleep apnea (OSA) in children with attention deficit/hyperactive disorder (ADHD) and compare amplitude and latency of the P300 potential among children with and without OSA. **Method:** Sixty-one children with ADHD underwent oddball auditory attention tests for detection of P300 (ERPs) followed by an all-night polysomnography. The children were divided in two groups, those with and without OSA. **Results:** Significant decreased amplitude of the P300 potential was observed in children with OSA when compared with children without OSA. **Conclusion:** The study showed that sleep fragmentation as a result of OSA can exacerbate the attention disorder that characterizes ADHD, and highlights the importance of assessing the presence of OSA in the differential diagnosis of children with attention deficits.

Keywords: obstructive sleep apnea; event-related potential; P300 potential; attention deficit disorder with hyperactivity.

RESUMO

Objetivo: determinar a prevalência de apneia obstrutiva do sono (AOS) em crianças com déficit de atenção / hiperatividade (TDAH) e comparar amplitude e latência do potencial P300 entre as crianças com e sem AOS. **Método:** Sessenta e uma crianças com TDAH foram submetidos a testes de atenção auditiva com o paradigma oddball para a detecção de potenciais relacionados a eventos (PREs) do tipo P300, seguidos por polissonografia de noite inteira. As crianças foram divididas em dois grupos, crianças com e sem AOS. **Resultados:** Foi observada redução significativa da amplitude do potencial P300 em crianças com AOS quando comparadas com crianças sem AOS. **Conclusão:** O estudo mostrou que a fragmentação do sono, consequente a AOS, pode exacerbar o déficit de atenção, que caracteriza o TDAH, e destacou a importância de avaliar a presença de AOS no diagnóstico diferencial de crianças com déficit de atenção.

Palavras-chave: apnéia do sono tipo obstrutiva; potencial evocado; potencial P300 ; transtorno do déficit de atenção com hiperatividade.

Attention deficit hyperactivity disorder (ADHD) is a common psychiatric disorder characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with the child's cognitive development. Its symptoms, which usually start before age 12 and must be present in two or more settings (*e.g.* at home, or school), negatively affect the child's social, academic or occupational functioning[1]. The worldwide prevalence of ADHD was estimated to be between 5% and 6% although significant regional differences exist due to still poorly-understood factors[2].

Obstructive sleep apnea (OSA) is defined as a sleep-related breathing disorder characterized by prolonged and recurrent partial (hypopneas) or complete (apneas) pauses in the airflow, attributed to the collapsibility of the upper airways, that interrupt normal ventilation, resulting in disruption of a normal sleep pattern[3]. The prevalence of OSA, diagnosed by varying criteria in different diagnostic studies, has widely ranged from 0.1% and 13%, but most studies report a figure between 1% and 4%[4]. Additionally, attention deficits have been reported in up to 95% of children with OSA, and OSA has been reported in as many as 20% to 30% of children with a full ADHD syndrome[5].

Several studies reported the association between OSA and other sleep-related breathing disorders, with neurocognitive

[1]Universidade de Brasília, Faculdade de Medicina, Programa de Graduação Ciências Médicas, Brasília DF, Brasil;

[2]Universidade de Brasília, Faculdade de Medicina, Departamento de Patologia, Laboratório Interdisciplinar de Biociências e Laboratório de Pesquisa de Imunogenética e Doenças Crônico-Degenerativas, Brasília DF, Brasil;

[3]Hospital Regional de Taguatinga, Unidade de Clínica Médica, Departamento Clínico de Neurofiologia, Taguatinga DF, Brasil.

Correspondence: Paulo Sérgio Azeredo Henriques Filho; CA 05, Bloco F, Apto 404; 71503-505 Brasília DF, Brasil; E-mail: pazeredocin@gmail.com

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symptoms and ADHD in children[6]. Therefore, the assessment of sleep disturbances remains an essential component of the evaluation of children with ADHD since sleep disturbances may result in significant attention and behavior dysregulation[6].

Attention deficits have been evaluated with several different tools, although the method extensively used has been the measure of visual or auditory evoked potentials (ERP) with the analysis of the P300 wave, applying the oddball paradigm. The P300 is a positive component of the ERP that peaks around 300msec after a stimulus. The P300 wave is generated from various sites of the brain including the cortical and subcortical areas, particularly the auditory cortex, hippocampus, amygdala, brain stem and thalamic structures[7]. The amplitude of the P300 wave represent the attentional resource allocated in the task[8] while its latency reflects the stimulus reaction time[9].

In children under 12 years, the classification and grading of abnormal respiratory events is different from that of adults since children have a faster respiratory rate and a lower functional residual capacity[10]. Clinical daytime manifestation of OSA in children is also different from that observed in adults since the presence of excessive daytime sleepiness is rarely observed among children, and hyperactivity or inattention is predominant among preadolescents[3].

Our working hypothesis was that the assessment of attention, through the evaluation of P300 event related potentials in children in whom ADHD was found in association with OSA, would reveal an additional increase in their already-altered P300 components. Consequently, the aim of this study was, firstly, to determine the prevalence of OSA in a group of children with ADHD and, secondly, to compare amplitude and latency of the P300 potential between groups of ADHD children with and without associated OSA.

METHODS

Study population

The study group consisted of 365 children with learning difficulties that had been previously screened by the Mental Health Unit of the State Secretariat of Education of the Federal District (Brazil). These children attended schools in the Brasilia Public Educational System and concomitantly received supplementary educational help. Exclusions from this initial group were children with a hearing disorder, developmental learning disorder, and children using drugs that could interfere with auditory functions and/or attentive or cognitive processes (*e.g.* hypnotics, sedatives, antihistamines, antidepressants, antiepileptics, etc.). After applying the exclusion criteria, 61 clinically confirmed cases of ADHD (diagnosed according to the DSM-IV[11]) were selected, and tentatively divided in two groups: children with and children without symptoms suggestive of OSA. These children, who were in low-middle income families, with similar cultural backgrounds, underwent a subset of the WISC-III[12] and all had an IQ of at least of 80. The children's parents or caregivers received information regarding the research protocol and gave written informed consent before the beginning of the study, and prior to the assessment they also agreed to the temporary discontinuation of psycho-stimulant medications. The study was conducted according to the Declaration of Helsinki on Biomedical Research involving human subjects[13] and the University of Brasilia Ethics Committee in Medical Sciences approved the protocol.

P300 evoked potential test

To verify the integrity of the auditory pathways all children underwent behavioural audiometry and brainstem auditory evoked potential (BAEP) by rarefaction click before the P300 evoked auditory potential test[14].

All P300 recordings were performed one to four hours after a meal, and no caffeine intake was allowed during the four hours preceding the test. The P300 potential was assessed using the oddball paradigm, in which occasional relevant tonal stimuli are generated among a set of frequent irrelevant stimuli. The evoked potential testing was performed in an isolated room with the child comfortably seated in an armchair, using a Medtronic Keypoint EMG Unit (Minneapolis, MN, USA). The P300 wave was considered positive when an increased amplitude in the parietal-central region, according to the international System 10-20 (position Fz, Cz, and Pz), was elicited as a prominent peak with an amplitude of approximately 300msec in response to the infrequent relevant auditory stimuli. The time elapsed between the stimulus and the onset of the potential, i.e. its latency and the amplitude of the potential, were analysed according to the normative data of the International Federation of Clinical Neurophysiology[14]. Each test of 15 minutes duration was repeated three times at 10 minute intervals. Reference values proposed by Tsai et al.[15] were used to analyse P300 wave components: amplitude of 14.8 ± 4.3 and latency of 319.1 ± 23.3, for children aged eight to nine years; amplitude of 15.9 ± 4.6 and latency of 323.9 ± 24.6 for children aged 10 to 11 years; and amplitude: 19.9 ± 5.6; latency: 327.7 ± 22.1 for children aged 12 to 13 years.

Sleep study

The night following the assessment of the P300 potential, each child underwent all-night polysomnography using an Alice 5 Polysomnography Recorder Model AC02109 (Philips Healthcare, Andover, MA, USA). Four electroencephalographic (EEG) derivations were used (C3, C4, O1, and O2), which referred to the earlobes. Right and left electrooculograms (EOG) and chin electromyograms (EMG) were also recorded. Thoracic-abdominal plethysmograph, oral/nasal thermistor and nasal cannula were used to monitor respiration, and a transcutaneous finger

pulse oximeter was used to measure oxygen saturation. Respiratory events were considered significant if they lasted ≥ 2 respiratory cycles and were accompanied with a ≥ 3% SpO_2 desaturation and/or terminated by arousal[16]. Obstructive apnea was defined as the cessation/reduction of airflow to < 90% of baseline with continuing or increasing effort. Hypopnea was defined as a decrease in airflow ≥ 50% of the baseline amplitude.

Respiratory effort-related arousals, defined as respiratory efforts that generate arousals, were considered as part of the respiratory disturbance index. The nasal cannula pressure transducer was used to confirm its presence or absence. The apnea hypopnea index (AHI) was defined as the total number of apnea and or hypopnea events per hour of sleep, and was considered abnormal when greater than one event per hour. A sleep respiratory disturbance index was defined as the total number of abnormal respiratory events (apnea, hypopnea or respiratory effort-related arousals and was considered abnormal when greater than one event per hour.

Statistical analyses

To detect the interaction among the independent variables (age, gender and AHI) of the two groups (OSA+ADHD group and ADHD group) a descriptive analysis of the three P300 test results was performed. The amplitude and latency of the P300 waves were analysed utilizing the two-way ANOVA and *t*-test. Spearman correlation analysis investigated the relation between AHI and P300 variables. The Kruskal Wallis independent normality test was performed for all data sets ($p > 0.0001$).

RESULTS

Population results

Based on the results of the all night polysomnography, the initial study group of 61 children (26 girls, 35 boys, age range: 6–13 years, mean age of 10.6 ± 2.1) was divided in two groups. A group of 26 children (10 girls, 16 boys, age range: 6–13 years, mean age: 10.7 ± 2.2) in which OSA was present (OSA+ADHD group), and a group of 35 children (16 girls, 19 boys, age range: 6–12 years, mean age: 10.7 ± 2.2) in which OSA was not detected (ADHD group).

Polysomnography results

The OSA+ADHD group showed a mean AHI value of 3.1 (±1.4), while in the ADHD group, the mean AHI values were 0.44 (±0.24). The P300 wave mean amplitude values and mean latency values found in the two groups is shown in Table 1.

From the polysomnography evaluation, the analyses of the interaction among sleep variables showed that the respiratory-effort related arousals did not significantly affect the respiratory disturbance index, thus these events were not considered in subsequent analyses.

The increased AHI, observed in all the three tests of the ADHD+OSA group, showed negative correlation mainly with P300 amplitude ($F > 2.23$, $p < 0.010$), although increased latencies were observed ($F > 34.39$, $p < 0.0001$). These results were confirmed by Spearman correlation analysis, which showed a significant correlation between increased AHI and decreased P300 amplitude (test 1: $r = -0.631$, $p = 0.0001$; test 2: $r = -0.672$, $p = 0.0001$; test 3: $r = 0.651$. $p = 0.0001$). This analysis also confirmed the finding of a positive correlation between increased AHI and increased P300 latency (test 1: $r = 0.386$, $p = 0.000$; test 2: $r = 0.328$, $p = 0.000$; test 3: $r = 0.571$. $p = 0.0001$).

Analysis of the P300 wave amplitude by the Repeated Measures ANOVA detected significant differences in the three tests of OSA+ADHD group ($F = 297.57$, $p = 0.0001$), whereas no differences were observed in the ADHD group. Comparing the two groups (OSA+ADHD and ADHD) using the same test showed significant difference in the amplitude of the wave ($F = 3.661$, $p = 0.028$) but failed to show significant difference either in latency or in the covariates gender and age.

DISCUSSION

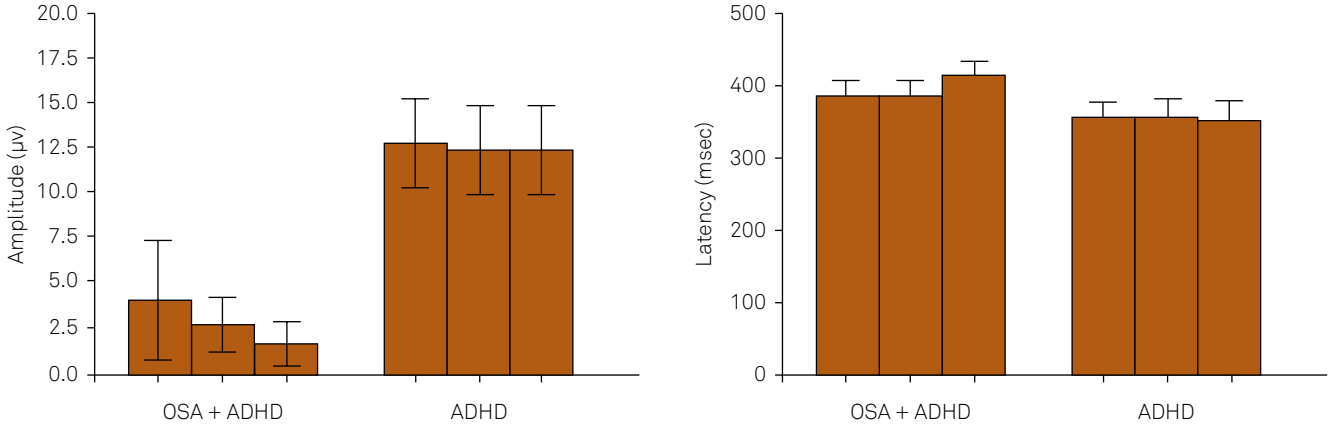
Amplitude

The comparison between the groups of patients showed that there were significant differences between the values of amplitude of P300 (Table 1, Figure 1). Both groups exhibited lower amplitude values compared to normative reference values[16]. The presence of amplitude changes of P300 potentials during the examination of the children included in this study can be considered as being related to attention deficit disorder. Changes in amplitude of this potential may also be related to

Table 1. P300 wave mean amplitude and latency values of the two groups of children (ADHD+OSA and ADHD).

Variable	Test 1	Test 2	Test 3	N
Mean amplitude values				
Group OSA + ADHD	4.1 ± 3.31	2.7 ± 3.69	1.7 ± 2.31	26
Group ADHD	12.7 ± 2.42	12.4 ± 2.41	12.3 ± 2.46	35
Mean latency values				
Group OSA + ADHD	351.6 ± 21.40	350.2 ± 26.67	349.2 ± 25.16	26
Group ADHD	380.8 ± 22.30	382.3 ± 20.43	408.71 ± 19.52	35

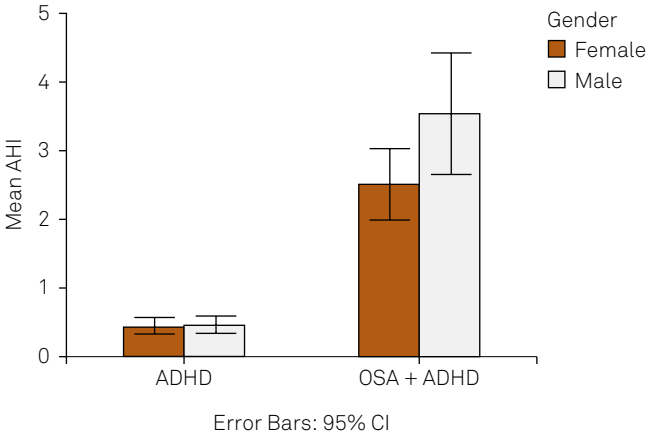
OSA: obstructive sleep apnea; ADHD: attention deficit/hyperactivity disorder.



ADHD: Attention Deficit Hiperactivity Disorder; OSA: Obstructive Sleep Disorder.

Figure 1. (A) shows significant progressive decline of the P300 wave mean amplitude in the ADHD+OSA group across the three tests, while only a slight decline can be observed in the ADHD group. Conversely, (B) shows a slight increase of the P300 wave mean latency in the OSA+ADHD while the latencies of the ADHD group are relatively stable. Considering the presence of OSA as a risk factor and correlating it with the three tests of each group, the ADHD+OSA showed lower amplitudes (r = 0.79, r = 0.77 and r = 0.81, p = 0.000) and more prolonged latencies (r = 0.60; r = 0:57; r = 0.76, p = 0.000).

disorders that compromise the maintenance of working memory; however, sleep restriction (Table 2 and Figure 2) may attenuate the amplitude as well[17,18]. This attenuation phenomenon related to sleep disorders is also observed in other sensory modalities. A study that investigated the effect of sleep restriction over pain-related evoked potentials in adults showed a significant interaction between attentional focus and sleep condition with reduction of the amplitude, making the attentional focusing less distinctive, but preserving the intensity discriminative skill and enhancing the pain perception. These opposite effects of minor amplitudes and overreaction to the stimuli were interpreted by the author as a lack of control by the descendent inhibitory pathways, based on findings by Tiede et al.[19] Similar processes might be involved in auditory processing disorders and should be considered in further studies.



ADHD: Attention Deficit Hiperactivity Disorder; OSA: Obstructive Sleep Disorder.

Figure 2. Boxplot of apnea and hypopnea index (AHI) and gender for the ADHD and OSA+ADHD groups. Error bars represent 95% of confidence interval.

Latency

The values of latencies of P300 potentials were higher than the reference values[16] for both groups and showed significant variation between the groups (Table 1 and Figure 1). Therefore, it seems that the presence of OSA causes alterations in latency, prolonging it, with a cascade effect on brain areas used for abstraction, including the frontal (Fz), central (Cz) and parietal (Pz). The same was observed by Huang et al.[20] Another possible explanation is related to the fact that attention disorder can also cause abnormalities in working memory, which uses attention to follow its function[21,22]. A study focusing on an analysis of working memory related to attention could better define the relationship between attention deficit and sleep disorders, and changes in working memory due to altered latencies.

OSA and P300

In our study we observed that apnea and its consequent desaturation of oxyhemoglobin produces sleep fragmentation (Table 2), but there a strong direct association between higher AHI and prolongation of latency with amplitude reduction (Tables 1, 2 and Figures 1, 2). Ours results differ from Sforza and Haba-Rubio[23] who found no direct relationship between elements and fragmenting sleep, or prolonged latency and reduced amplitude, although they found a correlation between sleep disorders such as insomnia and sleep breathing disorders and cognitive abnormalities of evoked potentials. Over the years it has been confirmed that chronic and intermittent interruption of sleep, regardless of cause, is responsible for harmful effects on cognitive performance[24], which could explain a direct relationship between rates of sleep fragmentation and quantitative alterations of cognitive evoked potentials like P300[23,25]. Quantitative changes of cognitive evoked potentials observed in our study could be explained by neuronal alterations caused by nocturnal hypoxemia secondary to apneas.

Table 2. Polysomnographic parameters in 61 children, in a group of 26 children with OSA+ADHD and in 35 control children with ADHD without symptoms of OSA.

Parameters	ADHD (n = 35)	OSA+ADHD (n = 26)	P
Sleep latency (minute)	27.2 ± 19.1	14.1 ± 12.7	< 0.01
REM latency (minute)	121.3 ± 21.5	114.9 ± 32.9	NS
TST (hour)	8.8 ± 0.3	8.1 ± 0.4	NS
Sleep efficiency (%)	93.7 ± 5.3	89.2 ± 4.2	NS
Stage 1 (%)	7.1–4.5	9.0–5.0	NS
Stage 2 (%)	46.9–5.4	53.1–7.3	< 0.05
Slow-wave sleep (%)	23.8–4.9	18.0–4.5	< 0.01
REM sleep (%)	27.2–4.8	13.6–6.5	< 0.005
Spontaneous arousal index per hour of TST	7.9–2.1	4.1–4.0	< 0.01
Respiratory arousal index per hour of TST	0.9 –0.0	4.9–0.9	< 0.001
AHI per hour of TST	0.0–0.0	12.9–2.2	< 0.00001
AI per hour of TST	0.0–0.0	3.9–0.5	< 0.00001
Spo_2 (mean)	98.8–0.8	95.2–1.4	NS
Spo_2 nadir	95.1–0.2	79.4–1.9	< 0.00001
TST / Spo_2 <90 (%)	0.0–0.0	2.7–0.9	< 0.00001

Values are mean ± standard deviation of the mean; n: number of participants; ±: standard deviation; OSA:obstructive sleep apnea ; ADHD:attention deficit hiperactivity disorder ;REM: rapid eye movement; TST: total sleep time; AHI: obstructive apnea/hypopnea index; AI: obstructive apnea index; Spo_2: peripheral capillary oxygen saturation; NS: non significant.

These alterations may be caused by abnormal neuronal metabolism in the hippocampus and frontal cortex. This can be associated with cognitive deficits other than those described above and changes in IQ[26]. The functional impairment of the frontal cortex can cause low performance of superior mental executive functions and lack of behavioural inhibition, which are essential for the development of other mental functions such as verbal and nonverbal memory, self-regulation of affect and motivation[22].

Imaging studies are other sources of evidence that suggest the possibility of neuronal damage in patients with apnea and hypoxemia, as was observed in our study. The neuronal damage caused by nocturnal hypoxemia was probably linked to increased inflammatory activity[27]. In addition to the assumptions described above of the greater involvement of the P300 potential of our 26 individuals with attention deficit obstructive apnea, there is further scientific evidence suggesting that the functional impairment of the frontal region is related to changes in cerebral blood flow[27,28]. These changes could be related to chronic or intermittent hypoxia, as in that caused by obstructive apnea, which has been suggested as possible evidence of impaired oxygen delivery to brain regions by raising blood flow velocity, and this could cause functional impairment of cortical regions such as the prefrontal, generating cognitive disorders flow[27,28].

OSA and ADHD

In this study 42.6% of children with ADHD also had OSA (Table 1, 2 and Figure 2). A similar finding was reported by Schechter[16], which described 42% of an early case series sample with OSA that also had hyperactivity symptoms as well as sleepiness, behaviour disturbance and decreased school performance[16]. Also, snoring was found in 33% of children diagnosed as ADHD. Additionally, in one study, altered P300 in children with OSA was only found in children with severe OSA associated with sleep deprivation and forced awakeness, suggesting that the larger impact of OSA over P300 features may also be linked in young people[29].

Perspectives

Several risk factors that can predict the developmental course of ADHD and its possible future persistence have been identified as family history of ADHD, adverse pregnancy and birth conditions, maternal stress, psychosocial adversity, and parenting practices during preschool years. These factors are important intervention targets as they determine the degree of impairment and predict outcome. Treatments such as tonsillectomy or adenotonsillectomy seem to drastically reduce aggressive, inattentive, and hyperactive behaviours, improving attention and vigilance in children with OSA and even in children with ADHD and OSA compared to those treated only with methylphenidate, but these need to be validated in more accurate studies[16,30]. The need for continued treatment and effective follow-up should be emphasized as it has been shown that results of pharmacological and psychosocial interventions are generally short lived[30].

This study indicates that the association between attention deficit disorder and obstructive sleep apnea may be included as a risk factor for major changes, both in latency

and in the P300 amplitude (Figure 1). A repeat series of the P300 test appears to potentiate the effect of attention deficit in the OSA+ADHD group of individuals. P300 amplitude differentiates the groups, but latency does not, as we found increased latency in both the OSA and ADHD groups, but not significantly so (Figure 1). ADHD is known to affect more males and, in this study, this gender also showed a higher prevalence of OSA (61.5% of the sample). The boys varied greatly showing more and stronger effects of OSA over P300 markers, whereas the girls were homogeneous and had less impact at P300 markers, but the effect was still significant (Figure 2).

Given the strong effect found in P300 features in this study, we can suggest that a better examination of sleep quality be done in children under investigation for ADHD diagnosis. Even if not for differential diagnosis, OSA must be considered as, at least, an attention and working memory disorder along with behavioural disturbance. Our findings reinforce the advice from Huang et al.[30], which states that clinicians should become familiar with sleep apnea as a life-threatening condition with overlapping symptoms including ADHD. Given this scenario, sleep disorder investigation might be considered to be mandatory in ADHD guidelines, as OSA or snoring can act as a cause or contributing factor needing to be investigated.

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